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ON THE MECHANISM OF THE PRIMARY PHOTODISSOCIATION OF ORGANIC MOLECULES*

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I. INTRODUCTION

Photodecomposition of molecules may be investigated by two different methods. *Preparative* photochemical experiments establish facts as to the end-products of a reaction produced by light, the primary process remaining a matter of deduction. *Spectroscopical* experiments are concerned with the undisrupted molecule and therefore may establish facts as to the primary process, secondary reaction, or end-products remaining uninvestigated. Obviously a general theory can be evolved only by a combination of both methods. This paper is mainly concerned with the absorption spectra of organic molecules. Comparison of the data thus obtained with thermochemical calculations gives a certain insight into the primary processes of photodecomposition. The conclusions may be checked by purely photochemical evidence. As they are based on certain features of the Heitler-London pair-bond theory of valency, we believe that our extension of this theory will contribute to a more general understanding of photochemical processes.

So far, the primary photolytic process in irradiated organic molecules has generally been assumed to consist in the fission of one of the bonds, *i.e.* in the formation of two free valencies per photolyzed molecule. Only in a few cases, the simultaneous rupture of two bonds has been considered, *e.g.* for the photolysis of molecules containing a double bond, like carbon disulfide and ketene (1) or for the photodecomposition of inorganic halides of the stannic iodide type (2). For other molecules, like aldehydes and ketenes, it has been discussed as a possibility, but has been abandoned later (3).

For a number of inorganic substances, one of the present authors (4, 5) has shown that splitting of a single bond occurs only when the central atom does not exhibit its maximal valency, *i.e.* as long as the bonds are formed by the outside p-electrons only of the central atom, as these—with the exception of the rare gases—do not form closed groups (^1S term),

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but represent free valencies of the unexcited atom. As soon as the two electrons of the closed s^2 group are involved and thereby the state of maximal valency is reached, the photodecomposition does not follow the above assumption. In such a case the photolysis does not lead to two particles possessing free valencies, but one of the primary products is a "saturated" molecule of lower valency of the central atom, while the others only are unexcited radicals or atoms. To this result the Heitler-London theory of valency gives the theoretical foundation. The s^2 electrons of a molecule of lower valency have no bonding power as long as they form a closed group, *i.e.* as long as they are on the same orbital with antiparallel spin; such a molecule ($SnCl_2$, PCl_3, SO_2) in such a $^1\Sigma$ ground term is therefore chemically inert. Hence the approach of the radicals or atoms to such a molecule does not induce the formation of a higher molecule.[1] This occurs only when the molecule has been excited from its $^1\Sigma$ ground term to a higher electronic level by the splitting of the s^2 group of electrons. For the final molecule (maximal valency of the central atom, $SnCl_4$, PCl_5, SO_3), the system made up of two unexcited atoms or radicals plus the unexcited molecule of lower valency in its $^1\Sigma$ ground term (*e.g.* $PCl_3 + 2Cl$), forms a repulsive electronic level which often is the first excited electronic state of the final molecule (*e.g.* PCl_5); the energy difference between the completed molecule and the corresponding one of lower valency is usually relatively small, *i.e.* smaller than a true single bond energy. The process of light absorption in such cases, therefore, represents the excitation of the final molecule from its ground level to this repulsive (non-bonding) state. Hence, photolysis of this type involves simultaneous liberation of two atoms or radicals—corresponding to the existence of two 's' electrons, and the energy required has no bearing on a "single bond energy." The view that fissure of the s^2 group of electrons is indispensable for their chemical activation, is supported by the formation of a diamagnetic ground-term of such molecules as SO_3 by combination of a diamagnetic molecule (SO_2) and the paramagnetic oxygen atom.

The present paper applies this theory to organic molecules. The analogy between carbon and the elements dealt with above, is complete. It is generally accepted that the unexcited carbon atom, in its ground level ($2s^2\ 2p^2\ ^3P$) is bivalent and that the formation of the "normal" organic molecules involves splitting of the s^2 group and transition to a term of the configuration $2s\ 2p^3$ or $2p^4$. As a matter of fact, it has been shown before (5) that in the absorption spectra of halogenated methanes, the number of maxima, the energy differences of these maxima, and the comparison of the beginning of the various absorption regions with thermochemical

[1] At small intermolecular distances the system of course may change from one potential curve to the other by means of energy of activation.

data, point to a photoreaction of the type $CX_4 + h\nu \rightarrow CX_2(^1\Sigma) + 2X(^2P)$. These molecules show not two, but three regions of continuous absorption with energy differences similar to the excitation energy of the halogen atom, and no other interpretation appears to account for this except the simultaneous liberation of two atoms.

The present paper deals with the aldehydes, aliphatic ketones, acids, and their derivatives. The spectra have been measured in an apparatus and by a method similar to those described before (4, 5).

Absorption leading to a photodecomposition corresponds to a transition to a repulsive curve. Such a curve is indicated either by a region of true continuous absorption or, in a band spectrum, by a point of predissociation followed by diffuse bands. Both features can be recognized in the gaseous state only. In solutions, even in non-polar solvents, the envelope of a band-spectrum is often misinterpreted as a continuous absorption, [for acetone, see (6)], and in some cases obvious theoretical difficulties have been caused by such a misinterpretation.[2] Only when the absorption spectra for vapor state and solution coincide may the same photochemical process be postulated for the solution also.

Our view does not involve the assumption that all photochemical processes take place in accordance with the above scheme. On the contrary, it is necessarily to be expected, that in other regions of the spectrum processes of other types take place. But it so happens that in most cases the repulsive curve involving a saturated molecule of minor valency is the lowest one, and hence the theory put forward here applies to many processes produced by light of the visible and near-ultraviolet regions. A case in point discussed at greater length below is the photodissociation of acetone. There, some misunderstanding has recently been caused by the fact that ethane and $CO(^1\Sigma)$ is produced by light of the well-known near-ultraviolet absorption spectrum, and methyl and acetyl radicals by wave lengths belonging to the second region of absorption which, beginning at 2300 Å, has its maximum in the near Schumann region.

II. SOME GENERAL REMARKS ON METHODS

Some remarks appear necessary concerning the values used in the following sections for: (a) calculating single bond energies from thermo-

[2] Thus, *e.g.* the characteristic "ethylene band" in solution at short wave lengths (roughly 2000 Å) is the envelope of a true band-spectrum, and probably represents a process of activation, but not of photodissociation. Even in the gaseous state, vibrational bands may be so closely packed that they cannot be resolved, and give rise to a pseudo-continuous spectrum. A case in point is acetone, where the fluorescence shows the true nature of the spectrum. A truly continuous absorption spectrum, however, means always the breaking up of a molecule.

chemical data, and (b) finding the long-wave limits of continuous spectra.

(a) The heat of formation of a substance, *e.g.* formaldehyde, from the atoms (D) is obtained by calculating the heat of formation from the elements (24.5 kcal) from the heat of combustion and applying Born's cycle. All the D values used have been obtained by this method.[3] [For $D(H_2)$, $D(O_2)$, etc., see foregoing paper (5)[4].] In the classical way, these D values may be divided into contributions (d) of individual bonds. Starting from methane, a quarter of the total D is ascribed to each of the C–H bonds. According to Rossini's (8) most recent measurements, $D(CH_4)$ amounts to 379.9 kcal/mole, hence d(C–H) = 95 kcal/mole. These d values are fundamentally different from the so-called "single bond energies." In the system C + 4H, only the energy differences between the ground level of the molecule CH_4 and the level of the separated unexcited atom (carbon bivalent) is represented by D, but adiabatic dissociation of methane, which, according to the terminology used here, measures the "single bond energies," leads to a level in which the carbon atom is excited and therefore tetravalent.

The energy of excitation of the C atom to the term $sp^3\ ^5S$ is 4.3 e.v. = 100 kcal/mole (9). Of the configuration sp^3 this is the lowest term, and the other ones will not be much higher. For each C–H bond, $\frac{100}{4}$ = 25 kcal/mole have to be added to the d value, giving 120 kcal/mole for the bond energy of C^{IV}–H. It should be understood that this is a rough mean value for the single bond energy of C–H, and the energy of any bond will vary somewhat in different molecules and radicals. In a similar way, two other fundamental values, *viz.* for the C–C and the C–O bond, may be obtained from ethane and ether respectively:[5] d(C–C) = 75, d(C–O) = 76, hence the true bond energies for C^{IV}–C^{IV} and C^{IV}–O become 125 and 101 kcal/mole, as in the latter case the excitation of one, in the former that of two carbon atoms must be taken into account. Analogously the energy of the bond C^{II}–C^{IV} is 100 kcal/mole. For $D(C^{II}–H)$ an extrapolation from the comparison between $D(SnCl_2)$ and $D(SnCl_4)$, both known thermochemically, has given 114 kcal/mole in a previous paper (5). This value is 6 kcal/mole less than $D(C^{IV}–H)$, and although such an extra-

[3] The figures for the heats of combustion have been taken from the International Critical Tables or from Landolt Boernstein's Tables, if not stated.

[4] For the dissociation energy of carbon monoxide and the sublimation energy of carbon, we use the values D(CO) = 241.4 and S(C) = 156.2 kcal/mole, respectively. *Cf.* footnote 6.

[5] $d(C–C) = D(C_2H_6) - 6d(C–H) = 644.1 - 569.4 = 74.7$
$2d(C–O) = D(C_4H_{10}O) - 2d(C_2H_5) = 1250.3 - 1098.4 = 151.9$, d(C–O) = 76.
(These figures differ slightly from earlier calculations by Euken, Fajans, *et al.*, on account of more recent spectroscopic values for $D(H_2)$, $D(O_2)$, etc.)

polation cannot be expected to give accurate results, it shows nevertheless that the C^{II}–H bond will be slightly weaker.

Finally, D(O–H) has been calculated in the following manner. The heat of formation for water is 57.8, $D(H_2O) = 218.7$. D(O–H) has been calculated by Sponer (7) on the basis of a sensitized photoreaction $H_2O = H + OH + 117.8$. As we are not dealing with OH radicals but with OH groups attached to C atoms, the present calculations have been carried out with a mean value of $\frac{1}{2}D(H_2O) = 109$ kcal/mole; as in the parallel case of H_2S we have no means yet to correct similarly the mean value for $D(S–H) = \frac{1}{2}D(H_2S) = 81.9$ (see below). But we have the impression that still better agreement could have been obtained in some cases with the higher value 117.8 for D(OH). In that case, the O–H value would be almost independent of whether the hydroxyl group is connected with a second hydrogen or with a carbon atom, a conclusion which appears quite reasonable. Values between 114 and 118 kcal/mole have been deduced by various authors, and recently Fox and Martin (10) derived a value between 106 and 115 kcal/mole for the O–H bond in alcoholic hydroxyls from infra-red measurements.

(b) The beginning of a continuous absorption, *i.e.* the threshold value of the photodecomposition of a vibrationless molecule, is not clearly defined, but depends on experimental conditions. With higher temperature, higher pressure, or greater length of the absorbing layer, it may be shifted toward longer waves in rather wide limits. All these conditions tend to increase the number of molecules with higher energy content *i.e.* of higher vibrational levels of the ground state. This problem has recently been discussed at greater length (5), and it has been shown that agreement with thermochemical data obtains, if by low pressure and temperatures and by short cells, the absorption due to molecules with excited vibrational levels is sufficiently suppressed. A repetition here of the experimental and theoretical arguments favoring this view appears to be unnecessary, the more so as they agree with our experience on band spectra. Moreover, this view is readily confirmed for all continuous spectra showing two or more connected maxima. In such a spectrum the first long-wave limit should have a difference from the second and the following ones comparable to the difference of the maxima themselves. As the second long-wave limit and the subsequent ones are marked by the points of retransmission, it can be seen that a satisfactory value for the first long-wave limit obtains only under the above experimental conditions. It might be added that similar conditions also obtain for the point of predissociation. The energy difference between the intersecting repulsive state and the ground term is lessened for the excited vibrational levels of the latter. A shift of the point of predissociation obtains toward longer

waves and is recorded by the photographic plate, the greater the number of molecules populating the levels with $v'' > 0$. Exactly as in the case of a continuous spectrum, this shift becomes more marked with increased temperature (11). In formaldehyde vapor, *e.g.*, predissociation has been observed by Henri and Schou (12) at λ 2670 (= 107.0 kcal/mole) at room temperature and at λ 2750 (= 103.6 kcal/mole) at 220°. According to the vibrational analysis, the latter involves at least two vibrational levels of the electronic ground state while, *e.g.*, for bromine vapor, more than five can be found even with very small layers and pressures. In order to determine the long-wave limit of a continuous spectrum or the predissociation point in a band system corresponding to the vibrationless molecule, it is necessary therefore to use low pressures and short layers for measurements in the gaseous state. With regard to solutions, it follows further, that one has to take a wave length for which the value of the absorption coefficient (K) is not much lower than the maximum of the absorption curve. Experience has shown that a wave length corresponding to a K value identical with that of the following minimum gives a reasonable value for the long-wave length limit as well for gases as for solutions. For the latter, this corresponds to a value of K which normally equals about $\frac{1}{10}$ of K max.

III. PHOTOLYSIS OF FORMALDEHYDE

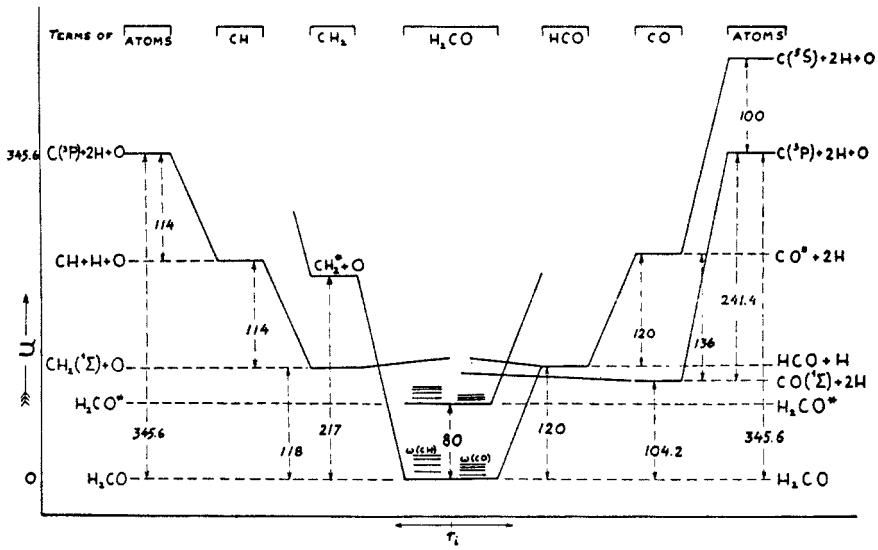
In order to give an example, we will apply the considerations developed so far to the much-discussed case of formaldehyde.

Formaldehyde possesses a band spectrum (12, 13), therefore a non-repulsive bonding excited term above the ground state. The energy difference between these two electronic levels is about 80 kcal/mole for the vibrationless molecule. The band spectrum shows a point of predissociation between λ 2670 and 2750 (107.0–103.6 kcal/mole). The final products of photolysis are hydrogen and carbon monoxide (3a).

The following scheme of the electronic energy levels of the system, which may be considered as a simplified Franck-Condon diagram, shows the possibilities of building up formaldehyde from the single atoms and the ways of its decomposition. The molecule may be built up either from CO + 2H or from CH_2 + O, which possibilities are indicated by the right and the left side of the diagram, respectively. From the system C + 2H + O on the left side, CH_2 + O is formed in two steps (*via* CH + H + O). The heat of combustion, measured thermochemically, being 134 kcal/mole, 345.6 kcal obtains for the atomic energy of formation D. The term $CH_2(^1\Sigma)$ + O is placed at $D(CH_2O) - 2D(C^{II}\text{–}H) = 346 - 2 \times 114 = 118$ kcal/mole above the ground level of formaldehyde. When the oxygen atom approaches the molecule $CH_2(^1\Sigma)$, no combination

takes place, and the repulsive curve arises. The molecule $CH_2(^1\Sigma)$ has to be excited and the original s^2 group to be split in order to bring about the formation of CH_2O in this way. We have placed this level rather arbitrarily at 217 kcal above the ground level, *i.e.*, d(CO) + half the excitation energy of ^5S.

From the system C + 2H + O another two-step reaction leads on the right-hand side of the diagram to the formaldehyde molecule. The first involves formation of carbon monoxide in its unexcited ($^1\Sigma$) state, in



Scheme of electronic levels of formaldehyde.

(Vibrational levels are indicated for the two stable levels of the completed molecule.) U represents the potential energy, the various r_i represent the internuclear distances. From the ground state of the molecule in the middle of the diagram, dissociation takes place towards the right side according to the sequence: $H_2CO \rightarrow H + HCO \rightarrow 2H + CO \rightarrow 2H + C + O$, and towards the left side according to: $H_2CO \rightarrow O + CH_2 \rightarrow O + H + CH \rightarrow O + 2H + C$.

which it does not possess free valencies. We take 241.4 kcal/mole as the spectroscopic value (14) for the energy of formation of CO.[6] The approach

[6] The value of D(CO) is not yet definitely known, but is of the order of 10 e.v. = 230 kcal/mole. Slightly different values are possible at present according to the accuracy ascribed to predissociation data, which always include a certain amount of kinetic energy, as can be seen from the discrepancy of the values of *e.g.*, $D(S_2)$ taken from predissociation and convergence point (14). Herzberg, in his recent review on this subject [*Chem. Rev.*, **20**, 145 (1937)], favors a lower value of 210 kcal/mole. Some values of S(C) have been deduced recently under the assump-

of two H atoms to $CO(^1\Sigma)$ does not induce molecule formation, but this becomes possible after the CO is excited to a higher term.[7] Therefore, we have again a repulsive curve, $D(CH_2O) - D(CO) = 345.6 - 241.4 = 104.2$ kcal/mole above the ground level of the formaldehyde molecule. On the basis of a true single bond energy of 120 kcal/mole per each C^{IV}–H bond, the position of the bonding triplet term of CO would be $240 - 104 = 136$ kcal/mole (= 5.9 e.v.) above its ground state $(X)^1\Sigma$.

The band spectrum indicates another term 80 kcal/mole higher, exhibiting vibrational levels, which accordingly is not a repulsive, but a stable term. Such spectra, and therefore such terms, are found for all molecules containing the carbonyl group. Mulliken (16) ascribed this stable level to the excitation of a certain π(p)-electron in this group. This is, however, immaterial for our purpose; the level is an excited level of the whole system, and the products of photodissociation are not determined by the stable, but by the intersecting repulsive curve.

By light absorption the formaldehyde molecule is at first excited to this lowest level at 80 kcal/mole. The "origin" of the corresponding band spectrum lies at 80 kcal/mole, but it extends to shorter and longer waves on account of the various transitions between the higher vibrational levels

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tion that the spectroscopical known CN is identical with the chemical radical C≡N. As a matter of fact, the ground level of the former probably is C=N. *Cf.* Asundi and Samuel, *Proc. Indian Acad. Sci.*, **5**, 244 (1937).

In our calculations D(CO) is used twice. It is deducted from the atomic energy of formation, whereas the sublimation energy of carbon, added to the heat of combustion, is directly derived from it. The actual value of D(CO) is therefore immaterial for our results, with the exception of the three molecules for which CS takes the place of CO. The corresponding figures might be slightly incorrect, but the error cannot be great, because also D(CS) is taken from a vibrational extrapolation and therefore probably again slightly too high.

Norrish [*Nature*, **141**, 1138 (1938)] doubts the correlation of the maxima of the CX_4 type molecules in the preceding paper (5) on the grounds of the uncertainty of S(C). But again both the values $D(CX_4)$ and $D(CX_2)$ depend on it and their difference therefore is much less affected. Assuming the true value of S(C) to be 30 kcal/mole lower, this difference will be lower by about 10 kcal/mole, and while the agreement of observed and calculated values becomes slightly less in cases like CI_4, it would be actually slightly improved in others like CBr_4.

[7] Burton and Rollefson (15) have recently introduced into the discussion the principle of "microscopic reversibility". It expresses the assumption that elementary processes as those discussed here, can only take a path which is reversible. We do not intend to discuss this principle in general, but it must be pointed out that the decomposition of formaldehyde into $CO(^1\Sigma)$ and hydrogen certainly represents an elementary process which is not reversible, as formation of the aldehydes from particles is not possible, except after previous excitation of the $CO(^1\Sigma)$. Furthermore the equilibrium in question would be that of 2H + CO and *excited* H_2CO. For these reasons the mechanism suggested here cannot be excluded *a priori* on these grounds.

of the two electronic states. If the absorbing molecule is already in some excited vibrational state of the ground term, less energy than 80 kcal/mole may be required, and if excitation leads from the ground level to a higher vibrational level of the excited electronic term at 80 kcal/mole, such a transition needs more than 80 kcal/mole. The 104 kcal calculated above as difference between $D(H_2CO)$ and $D(CO)$ are in agreement with the observed value of 107.0 to 103.6 kcal/mole for the point of predissociation. Predissociation therefore appears to occur at the intersection of the lowest repulsive curve $[CO(^1\Sigma) + 2H]$ with the vibrational levels of the higher stable electronic term, and predissociation always indicates the existence of such an intersection, while continuous absorption corresponds to the existence of an unstable state only. Formaldehyde is decomposed into CO + 2H, by absorbing light of 103 kcal or more (2750 Å or less).

This mechanism of photodissociation is very nearly related to that proposed earlier by Norrish. The main difference appears to be that we picture the dissociation process as a single elementary process, *i.e.* a simple transition to the repulsive curve produced by the non-bonding s^2 group of electrons. Therefore the dissociation energy is not related to the bond energies, and the two H atoms are indeed split off simultaneously. It is obvious that formally the process can be represented by the scheme: $CH_2O \rightarrow CO + H_2$, but this cannot be the real primary process, as the hydrogen has to be set free in form of atoms, most of which will recombine under ordinary experimental conditions, but will not always do so.

According to Norrish and Kirkbride (3a) [for acetaldehyde, *cf.* (1a)], photodecomposition of formaldehyde begins already at λ 3300 (86 kcal/mole), *i.e.*, on irradiating formaldehyde with wave lengths belonging to the region of banded structure below the point of predissociation. This is due to bands involving excited vibrational levels of the ground term. A similar suggestion has already been put forward by Herzberg (17). As each C–H vibration means 8 and each C–O vibration 5 kcal/mole, this amount of energy is not to be neglected. This view is well supported by the experiments of Leermakers (18) in the identical case of acetone, who found that the quantum yield increases with temperature, from 0.4 at 67° to 1.0 at 167°; *i.e.* with the increase in population of the excited vibrational levels. Similar results have been obtained for acetaldehyde and propionaldehyde by Smith (19) and by Leighton and Blacet (20). Norrish's result, therefore, is easily explained by the fact that his experiments were conducted at 100°.

The above representation therefore indicates two essential conclusions:

(a) The repulsive curve $CO(^1\Sigma) + 2H$ is the lowest of all repulsive states, even lower than that involving H + CHO. For molecules, which do *not* possess a low excited *stable* state such as is associated with the low

excitation energy of the electrons of the carbonyl group, this repulsive curve will form the very lowest excited level of the molecule.

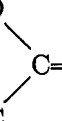
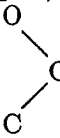
(b) In a case of predissociation, in which besides the repulsive also a stable excited state must be taken into consideration, the dissociation-products are in the same way determined by the unstable and not by the stable term. No special mechanism is required for transferring to other parts of the molecule energy stored by excitation inside the carbonyl group. The intersection of the excited carbonyl term with another unstable one provides this mechanism.

IV. ACIDS AND THIO ACIDS

A number of acids and esters have been investigated by previous authors with regard to their absorption spectra and the products of their photolysis. We shall show that the accumulated data, and also new data presented here, fit very well into the above interpretation.

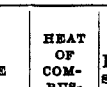
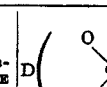
Measurements for acetic and formic acid vapor (and the vapors of their esters) we owe to Scheibe (21), but a certain difficulty arises in comparing them with measurements on the same substances in solution. The first beginning of absorption, measured in the vapor state does not coincide with the wave length for a K value of $\frac{1}{10}$ of the maximum. Inspection of Scheibe's curves shows that he used too low a pressure in order to extend the spectrum into the Schumann region. In fact, the value of K at the beginning of his curves is even higher than at the next minimum. This conclusion has been confirmed by a re-investigation of ethyl acetate vapor.

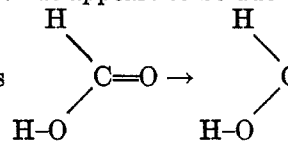
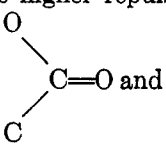
In a tube of 10 cm. length and at a pressure of a few mm. of mercury, the beginning of the absorption lies between λλ2630 and 2420, corresponding to 108–117 kcal/mole. The maximum lies at 2130 Å which is in fair agreement with the measurements of other authors in the vapor state (21) and in solution (22).

In order to compare spectroscopical and thermochemical data, we calculate from the heat of combustion of liquid ethyl acetate (539.1) $D(CH_3 \cdot CO \cdot OC_2H_5) = 1259.4$ and subtract the contributions d of eight C–H, one C–C, and one C–O bonds. The value as obtained for the group  is 349.1 kcal/mole. On deduction of D(CO) = 241.4 from this figure, 107.7 kcal/mole obtain as the energy required to convert the group  into —O, C— and the carbon monoxide molecule $CO(^1\Sigma)$.

As this value corresponds satisfactorily with the value observed spectroscopically, our assumption is justified, the essential photochemical process is formation of CO and the radicals CH_3 and OC_2H_5.

The following table includes (23) the corresponding data for two other representatives of the same group:

SUBSTANCE	HEAT OF COMBUSTION	D SUBSTANCE	D()	SUGGESTED DISSOC.-PRODUCTS	D() − D(CO)	OBSERVED	
						λ	*kcal/mole*
HCOOH	62.9 (gas)	475.1	365.7	$CO(^1\Sigma) + H + OH$	124.3	Vap. 2170 Sol. 2360	131 121
CH_3COOH	207.1 (gas)	752.7	358.6	$CO(^1\Sigma) + CH_3 + OH$	117.2	Vap. 2125 Sol. 2320	134 122
$CH_3COOC_2H_5$	539.1 (liq.)	1259.4	349.1	$CO(^1\Sigma) + OC_2H_5 + CH_3$	107.7	Vap. 2630-2420	108-117

A second absorption region has been observed for these substances beginning at a minimum in the Schumann region of λ1900 (149 kcal/mole) for formic acid, λ1845 (153 kcal/mole) for acetic acid, and λ1870 (152 kcal/mole) for ethyl acetate, respectively (21). From the present point of view an interpretation of this second absorption region may be advanced tentatively. It appears to be due to the second repulsive curve involving the process  As in the case of methane halides, also the molecule R_2C does not possess free valencies on its ground state $^1\Sigma$, but produces a repulsive curve on the approach of an oxygen atom. The position of this higher repulsive curve is to be obtained by subtracting from the groups  the true bond energies $(C^{II}–C^{IV}) + (C^{II}–O)$ and $(C^{II}–H) + (C^{II}–O)$ respectively.[8] From D(HCO·O) we therefore deduct 114 + 101 = 215, and from D(C·CO·O) 100 + 101 = 201.

[8] As the value $(C^{II}–O)$ is unknown, we are using the value $(C^{IV}–O)$ instead; the difference between $(C^{II}–H)$ and $(C^{IV}–H)$ does not exceed about 5% and we expect a similar deviation only in our case.

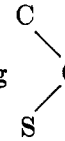
SUBSTANCE	HEAT OF COMBUSTION	D SUBSTANCE	D(O, C=O, [H]C)	SUGGESTED DISSOC.-PRODUCT	D(O, C=O, [H]C) − D(CX₂)	OBSERVED	
						λ	*kcal/mole*
HCOOH	62.9 (gas)	475.1	365.7	H, HO, C(¹Σ) + O	151	1900	149
CH_3COOH	207.1 (gas)	752.7	358.6	CH_3, HO, C(¹Σ) + O	158	1845	153
$CH_3COOC_2H_5$	539.1 (liq.)	1259.4	349.1	CH_3, C_2H_5O, C(¹Σ) + O	148	1850	152

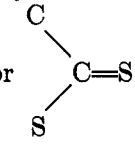
In order to support this view, the spectra of some thio derivatives of this group have been measured, mainly for the following reasons: (a) The absorption spectra of these substances lie at longer waves and are more easily accessible. (b) For such calculations the atomic energy of formation of the saturated molecule of lower valency produced in the photolytic process is essential. This heat of formation of $CS(^1\Sigma)$ is independently known from its band spectrum (24) to be 7.7 e.v. = 178 kcal/mole according to vibrational extrapolation. This value is an upper limit and agrees well, *e.g.*, with the predissociation data of CS_2 (1b). (c) Agreement between expected and observed values in this new case would exclude the possibility that with the carboxyl (and carbonyl) compounds the observed and calculated values coincide fortuitously. The spectra of the following compounds have been measured: thioacetic acid, CH_3COSH; dithioacetic acid, CH_3CSSH; and thiourea, NH_2CSNH_2. Of these only the heat of combustion of thiourea is known (345.8 kcal/mole) and therefore leads to $D(NH_2)_2CS = 595.5$.[9]

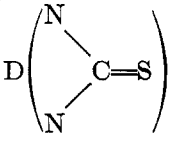
In order to obtain $D(CH_3COSH)$, we assumed, as is customary in thermochemical extrapolations, that the difference $D(CH_3COOH) - D(CH_3COSH)$ equals the difference $D(CH_3OH) - D(CH_3SH)$ or $D(C_2H_5OH) - D(C_2H_5SH)$. The mean value of these differences is 53.5,

[9] This calculation of D involves the energy of dissociation of S_2 for which a value of 44 kcal/gram-atom has been deduced from the convergence point of the band spectrum recently (14), further the heat of sublimation and polymerization of sulfur, both together 15 kcal/gram-atom (25). In his recent monograph, Olsson points out that the convergence point in reality might be situated slightly more towards shorter waves. In this case our value would be one-tenth or two-tenths of an e.v. too low.

hence $D(CH_3COSH) = 752.7 - 53.5 = 699.2$. Equally, $D(CH_3CSSH)$ has been calculated from the equation $D(CH_3COSH) - D(CH_3CSSH) = D(NH_2CONH_2) - D(NH_2CSNH_2)$. $D(NH_2CONH_2)$ being 666.5, the difference on the right side of this equation is 71.7 kcal/mole. For $D(CH_3CSSH)$, 628 kcal/mole obtains.

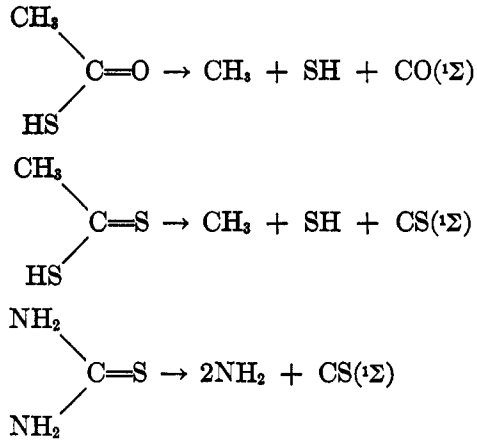
Thioacetic acid (26) has been measured in the vapor state and in chloroform solution. For experimental reasons the maximum could not be traced exactly; the beginning of absorption lies in the vapor state, between λ2960 and λ2820 (96–101 kcal/mole). The maximum apparently lies at wave lengths not much shorter than λ2550, which was the last wave length we could reach experimentally in this case. From $D(CH_3COSH)$ we subtract $d(CH_3 = 3 \times 94.9 = 284.7$ kcal/mole and $d(S–H) = \frac{1}{2}D(H_2S) =$ 81.9. For the grouping  , D = 332.6 thus obtains. Subtraction of D(CO) = 241.4 leaves 91.2, in satisfactory agreement with the observed value.

Dithioacetic acid (27) exhibits a maximum at 2820 Å for the vapor state, at 2910 Å in chloroform solution. The very beginning of the absorption could be located rather sharply at 3010 Å (94 kcal/mole) in the vapor state, in solution for $K = \frac{1}{10}$ of K_{max}, λ is higher, *viz.* 3360 Å (84 kcal/mole). Besides that, a minimum, *i.e.* the beginning of a second absorption region has been observed, in solution at λ2570 (= 110 kcal/mole) and in the vapor state at λ2440 (= 116.5 kcal/mole). Taking the K value of this second minimum in solution as that of the true beginning of the first absorption region, the first long-wave limit had to be placed at λ3200 (89 kcal/mole). The true value therefore lies between the limits of 84 and 94 kcal/mole, probably near to the mean value of 89. By subtraction of $d(CH_3)$ and d(S–H) from $D(CH_3CSSH)$, we obtain for  D = 261.5. Subtraction of D(CS) = 178, leaves 84 kcal/mole.

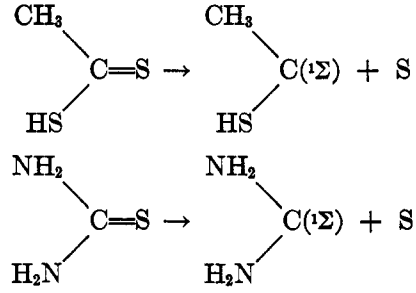
Thiourea has been measured in the vapor state. It exhibits a first region of absorption with a long-wave limit between λλ3300 and 3000 (86–94 kcal/mole) and a maximum at λ2530. This is followed by a minimum at λ2370 (119.5 kcal/mole). From $D(NH_2CSNH_2)$ we subtract 4 d(NH) according to $d(NH) = \frac{1}{3}D(NH_3) = \frac{249.9}{3} = 83.3$. D 

therefore is 262.2. Deducting D(CS) = 178, 84 kcal/mole obtains as against the observed value of 86–94 kcal/mole.

The primary photochemical processes in these three compounds therefore are:



The second absorption regions, measured for dithioacetic acid and thiourea, respectively, may be due to the processes:



which both correspond to a second, higher repulsive curve, but no numerical evidence can be put forward at present.

V. ALDEHYDES AND KETONES

The absorption spectra of many aldehydes and ketones have been thoroughly investigated before. The theoretical treatment of these measurements, parallel to that of formaldehyde, is summarized in the following table; it shows that again our view explains the spectral position of the region of continuous absorption or of the point of predissociation. In the vapor state the spectra have been investigated by Henri *et al.* (28); the points of predissociation have been taken mainly from their measurements. The ensuing region of continuous absorption has also been observed in the vapor state; but its intensity, *i.e.* the position of the maxima and minima

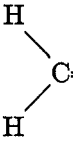
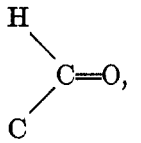
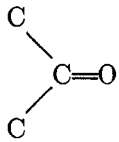
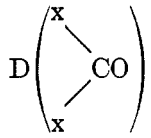
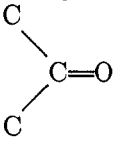
of continuous absorption hardly have been measured quantitatively. In some cases, we have taken as the beginning of a second continuous absorption in the vapor state the corresponding minimum of the absorption curve in solution [for acetaldehyde *cf.* (29)].

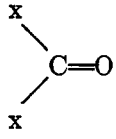
With regard to the calculation, one general remark should be made: It has been known for some time that on dividing the atomic dissociation energies D into individual bond contributions, a different value of d(C=O) is obtained from the carbonyl and the carboxyl groups. Hence we have replaced for the following calculations the value of 184 kcal/mole used above for the carboxyl group, by d(C=O) = 167 kcal/mole, obtained empirically from acetone. It differs again and for the same reasons slightly from earlier calculations (see footnote 6). The agreement between the observed points of predissociation and the figures calculated on the basis of this value shows that this well-known difference between carboxylic and carbonylic CO is not purely formal, but a real variation of the energy contents which has to be located in these groups. This difference is certainly due to the presence in the carboxyl group of the second oxygen atom and may be substantiated on lines similar to those used already by Marsden and Sutton (30).

SUBSTANCE	HEAT OF COMBUSTION	D SUBSTANCE	D([H]C, C=O, [H]C)	SUGGESTED DISSOC.-PRODUCTS	D([H]C, C=O, [H]C) − D(CO)	OBSERVED	
						λ	*kcal/mole*
Formaldehyde	134.1 (gas)	345.6	345.6	$2H + CO(^1\Sigma)$	104.2	2750	103 (PrD)
Acetaldehyde	278.6 (liq.)	617.0	332.3	$H + CH_3 + CO(^1\Sigma)$	90.9	2800 3300–2730 3120	102 (LWL) 86–104 (PrD) 91 (Sol)
Propionaldehyde	440.7 (gas)	882.8	333.6	$H + C_2H_5 + CO(^1\Sigma)$	92.2	3250	88 (PrD)
Acetone	437.3 (gas)	885.7	316.3	$2CH_3 + CO(^1\Sigma)$	74.9	3500	81 (PrD)
Acetylacetone	—[10]	1401	325	$CH_3 + CH_2CO\text{-}OH_3 + CO(^1\Sigma)$	84	3290–2935 3100	85–97 (LWL) 91 (Sol)
Diacetyl	504.0	1118	306	$CH_3CO + CH_3 + CO(^1\Sigma)$	66	4395	64.5 (PrD)

[PrD = Predissociation point, vapor. LWL = long-wave limit, vapor. Sol = LWL in hexane solution.]

[10] Calculated from the heat of combustion of $CH_3COCH(CH_3)COCH_3$ = 793 (mean value) deducting 2d(C–H) + d(C–C), as that of $CH_3COCH_2COCH_3$ is not known.

Acetylacetone has been measured anew in the vapor state. It exhibits two regions of absorption with long-wave limits between λ3292 and λ2935 (85–97 kcal/mole) and at λ2457 (116 kcal/mole) respectively. The first maximum lies at λ2690, the second, belonging to the Schumann region, could not be traced. Acetylacetone and diacetyl have been included in the above table, as the two possible photolytic processes occurring at the two carbonyl groups (see below) give the same dissociation-products. It is worthy of note that the energy contents decrease in the series  ,  ,  and that this decrease is actually exhibited in the shift of the point of predissociation to longer waves. The underlying reason for this good agreement is that in the present interpretation the constant value of D(CO) has to be subtracted from the varying values of  . Even the enormous shift of the point of predissociation from *e.g.* λ2750 (formaldehyde) into the visible part of the spectrum at λ4395 (diacetyl) is represented by the theory automatically. This is obviously due to the lower energy content of the group  in diacetyl with respect to the same group in, *e.g.*, acetone.

The present interpretation and its agreement with the shift of the predissociation point permit to locate the known decrease of the energy contents in the  group. Unfortunately, our results are inconclusive for glyoxal; its predissociation lies at λ3200 (83 kcal/mole), while calculation for processes similar to the above give 104 kcal/mole. This discrepancy is probably due to the fact that the above reaction occurs with glyoxal only to an extent of 1.5% of the total change, as reported by Norrish and Griffiths (31), while the main reaction takes a different course.

The interpretation of the various regions of selective absorption at shorter waves is more difficult for these molecules than for the acids and their derivatives. The lack of experimental data concerning the vapor state has been mentioned above and only in a few instances can it be overcome by resorting to the absorption curve of hexane solution. On the other hand, the margin between various possible theoretical values becomes very small for this region, and makes it extremely difficult to decide between them. As with formaldehyde, the ketones also possess three repulsive states near the ground level. Two of them correspond to a dissociation process involving the formation of a molecule of lower valency, *i.e.* the processes (a) $R_2CO \rightarrow 2R + CO(^1\Sigma)$ and (b) $R_2CO \rightarrow R_2C(^1\Sigma) + O$. This interpretation of the Schumann spectrum has already been suggested by Price (32). The third represents the splitting of a true single bond, *i.e.* the process (c) $R_2CO \rightarrow R + R-CO$, producing two free valencies

per photolyzed molecule. For acetone, to take this as an example, the energy of process (a) has already been calculated to 74.9 kcal/mole. From $D(C\text{–}CO\text{–}C) - 2D(C^{II}\text{–}C^{IV}) = 316 - 200$, a value of 116 kcal/mole obtains for process (b), whereas the energy needed by process (c), *i.e.*, the true single bond energy $C^{IV}\text{–}C^{IV}$ has been evaluated to 125 kcal/mole. The two latter figures are indeed very close to each other. In acetone vapor the diffuse bands change into a continuous spectrum at λ2700 (= 106 kcal/mole). Fortunately the spectrum of the solution in hexane has been traced into the Schumann region (33) and a second region of strong selective absorption has been found. Its maximum lies at about λ1800, its long-wave limit between λ2300 and λ2000; the mean, *i.e.* λ2150 corresponds to 130 kcal/mole. This figure indicates process (c) as responsible for the short-wave continuum, and the results of preparative work discussed below support this view. But we are unable to decide whether the continuous region beginning at 106 kcal/mole should be identified with process (b) or whether it is overlapped by that of process (c). On the one hand, the energies of the various C–C bonds have been evaluated in a very rough manner only, and the observed value of 106 is, therefore, still consistent with the calculated one of 116 kcal/mole. On the other hand it is quite possible that the continuum at longer waves is due to the very first repulsive state. It may be due to transitions from the ground level at such internuclear distances where the vibrational levels of the stable excited state cannot be observed any longer. This would agree with the fact that in a first investigation of the Schumann region, Norrish and Noyes (34) were unable to find evidence for a primary dissociation of formaldehyde into methylene molecules and oxygen atoms.

The short-wave spectrum of diacetyl, however, offers no difficulties at all. On account of the decreased energy contents the margin between the energies of processes (b) and (c) is much larger and makes it easy to correlate the two long-wave limits with the corresponding dissociation processes. The beginning of a continuous absorption has been observed in the vapor at λ2800 (= 102 kcal/mole), and the absorption curve in hexane solution shows a clear point of inflection at the same wave length, which marks the limit of the envelope of the diffuse bands and the point at which this continuous absorption develops. This curve, however, also shows the beginning of the ascent to a further strong absorption maximum which clearly lies in the Schumann region and probably corresponds to that found in acetone. Its long-wave limit lies approximately at the point where this ascent becomes marked, *i.e.*, at λ2350 (= 121 kcal/mole). Deducting from $D\begin{pmatrix} C \\ \diagdown \\ \quad CO \\ \diagup \\ C \end{pmatrix} = 306$ the value of $D\begin{pmatrix} C \\ \diagdown \\ \quad C \\ \diagup \\ C \end{pmatrix} = 200$, a value of 106 kcal/mole) obtained for process (b), whereas the fissure of a C–C bond maintains its value of 125 kcal/mole. In the case of diacetyl, therefore, it may well be that the first continuous spectrum must be identified with process (b), the second with (c).

It appears, therefore, reasonable to identify the continuous absorption with a long-wave limit at about λ2200 to λ2300, observed in the vapor state (acetaldehyde) or in hexane solution (acetone, acetaldehyde, propionaldehyde, diacetyl) with the fissure of a single C–C bond and not with our scheme. The continuous spectrum, however, which generally follows closely the first point of predissociation and the diffuse bands, and whose long-wave limit varies, may be due to a dissociation process in which an O atom is liberated and a stable molecule of lower valency of the type $H_2C(^1\Sigma)$ is formed.

VI. KETO ACIDS

It is very gratifying that the present theory applies equally well to substances which contain two of the discussed functional groups, namely keto acids. The observed regions of absorption can be satisfactorily ascribed to the two possible photolytic processes, as occurring on one of the two present groups. They possess two regions of selective absorption. The first one at longer waves corresponds to that of the aldehydes and ketones, the second one to that of the carboxylic acids and their esters. The thermochemical calculations are included in the following table.

SUBSTANCE	HEAT OF COMBUSTION	D SUBSTANCE	SUGGESTED DISSOC.-PRODUCTS	$D\left(\begin{matrix}X\\ \diagdown\\ C{=}O\\ \diagup\\ X\end{matrix}\right) - D(CO)$	OBSERVED	
					λ	*kcal/mole*
Ethyl acetoacetate	753.6 (liq.)	1770	$CH_3 + CH_2COOC_2H_5 + CO(^1\Sigma)$	335 − 241 = 94	2596	109 (LWL)
					2850	99 (Sol) (35)
			$CH_3{\cdot}CO{\cdot}CH_3 + OC_2H_5 + CO(^1\Sigma)$	354 − 241 = 113	2225	127 (LWL)
					2175	131 (Sol)
Pyruvic acid	279.2 (liq.)	976	$CH_3 + COOH + CO(^1\Sigma)$	322 − 241 = 81	3700	77 (Sol)
			$CH_3CO + OH + CO(^1\Sigma)$	340 − 241 = 99	2850	99 (Sol) (36)

Of the substances included in the above table, ethyl acetoacetate has been investigated anew in the vapor state. It showed two separate regions of absorption, characterized by long-wave limits at λ2596 (109.5 kcal/mole) and λ2225 (127 kcal/mole), respectively. The maximum of the first region was found at λ2368, that of the second part, lying in the Schumann region, has not been traced experimentally.

VII. PREPARATIVE RESULTS OF PHOTOCHEMICAL REACTIONS

The results of preparative treatment of photochemical reactions of the above discussed type, have not always an immediate bearing on the primary processes, as many stabilization reactions may occur between the particles formed in the primary processes. The two steps, "primary photolysis" and "end-products" can often be correlated only with difficulty. In the main, there are two reasons for this unsatisfactory state of affairs, first, we are not well informed about the possible reactions between the simple particles produced by primary photodissociation, second, for preparative reasons many of the investigations have been carried out with solutions and not with vapors of low pressures. Obviously, there are two ways in which the solvent can interfere with photodissociation-products: it can react chemically—and even the so-called inert solvents as hexane or cyclohexane have been shown to be sufficiently reactive for this purpose (37)—and moreover as Franck and Rabinowitsch (38) have pointed out, a high rate of primary recombination is produced by the mere physical presence of the solvent molecules, which act like a diluent gas under extremely high pressure. The number of reactions for which spectroscopical data are known and which have been investigated in the vapor phase, and which therefore permit discussion of the primary process, is not very large; still there are certain cases where the preparative results are in complete agreement with the simplest expectations of the theory, especially those of carbon tetraiodide and of ketene. Carbon tetraiodide, on irradia-

tion, gives iodine and tetraiodoethylene (39). The primary photolytic process is $CI_4 \rightarrow 2I + CI_2(^1\Sigma)$. The two iodine atoms will recombine to form an iodide molecule, and two CI_2 molecules on collision give tetraiodoethylene, C_2I_4. In this way, the CI_4 case is fully analogous to that of SnI_4, which according to Terenin's results (2) must be represented by the equations: $SnI_4 \rightarrow SnI_2(^1\Sigma) + 2I$, and $2I \rightarrow I_2$. The observed emission of the visible iodine bands has been shown to be due to the recombination of the iodine atoms. Terenin originally tried to dispense with the formation of free atoms, but the three absorption maxima of such molecules cannot be explained otherwise (5). Besides, it is only natural that the iodine is released from the SnI_4 molecule as atoms which, however, recombine very quickly. This is easily understood from the following considerations:

The distance between two iodine atoms is 4.3 Å in the SnI_4 molecule. As the stable minimum of the potential curve of the excited term $B^3\Pi$ of I_2 lies at 3.0 Å, we are already in that region of the Franck-Condon diagram where the attraction enables the iodine atoms to recombine directly without any side reactions, *e.g.* with the SnI_2 molecule formed. In fact, the sphere of attraction of an excited and an unexcited iodine atom extends to about 5 Å, and a certain percentage of liberated atoms will therefore combine immediately to form excited iodine molecules.

Ketene, according to Norrish and co-workers (1c), gives carbon monoxide and ethylene, on irradiation. Norrish had formulated the processes involved in the following way: $CH_2{=}C{=}O \rightarrow CH_2 + CO(^1\Sigma)$; $CH_2 + CH_2{=}C{=}O \rightarrow C_2H_4 + CO$.[11] For aldehydes and ketones, Norrish and his co-workers (41) have detected preparatively two sets of reactions, which may be represented here for the case of dipropyl ketone:

$$\begin{array}{lll} CH_3CH_2CH_2 & & \text{(I) } CO + C_6H_{14}\ (37\%) \\ & \diagdown\ \diagup\ \diagup & \\ & CO & \\ & \diagup\ \diagdown\ \diagdown & \\ CH_3CH_2CH_2 & & \text{(II) } CH_3COCH_2CH_2CH_3 + CH_2{=}CH_2\ (63\%) \end{array}$$

The situation with regard to the first type of reaction (I) is relatively clear. The two formed radicals stabilize in pairs, either symmetrically or unsymmetrically. In the above case, obviously, only hexane can be formed, but for methyl ethyl ketone, *e.g.*, nearly equimolecular amounts of ethane, propane, and butane have been isolated. With aldehydes, mainly the combination of unlike radicals *i.e.* formation of RH has been observed, that is, combination of radicals belonging originally to the same molecule.

[11] Ross and Kistiakowsky (40) suggest a secondary reaction of the type $CH_2 + CH_2 = C_2H_4$. *Cf.* Norrish, Crone, and Saltmarsh, *J. Am. Chem. Soc.*, **56**, 1644 (1934).

This is easily understood for formaldehyde, where detailed figures are known. The immediate combination of the hydrogen atoms is prompted by the fact that the distance between them is 1.88 Å in the formaldehyde molecule, whereas the sphere of attraction extends to more than 2.5 Å in the ground state of the hydrogen molecule—and similar reasons may apply to other aldehydes too. More recently, it has been reported that acetaldehyde (42) and propionaldehyde (43) give also molecular hydrogen —in the latter case its quantity increases with decreasing wave length— so that obviously symmetrical stabilization of the primary particles occurs, too, but the corresponding R_2 molecules (ethane, butane) have not been detected. It is difficult to say whether this is due to the inaccuracy of our analytical methods or to reactions of the R groups other than dimerization. For acetaldehyde, Blacet and Volman (42) have drawn attention to the presence of resinous matter in the reaction-products. These facts, in any case do not contradict the theory put forward here; on the contrary, it is well understood that the formation of molecular hydrogen will increase with decreasing wave length, *i.e.*, increasing kinetic energy of the primary photodissociation-products.[12]

It may be pointed out here that the stabilization reactions of the primary radicals depend largely on the experimental conditions, and actually an increase in pressure produced by addition of a foreign gas or by raising the temperature has been shown in many cases to cause different and more complicated secondary reactions. This can easily be understood from our point of view: The combination of the liberated radicals, which normally takes place, is disturbed by more frequent collisions. This supports our view which considers the combination of the radicals to be only a secondary process and their simultaneous liberation the true primary step. Thus in the sequence of reactions $\begin{matrix} & & \mathrm{H} & & \\ & \diagdown & & & \\ \mathrm{CO} & & \rightarrow \mathrm{H} + \mathrm{H} + \mathrm{CO} & \rightarrow \mathrm{H_2} + \mathrm{CO} \\ & \diagup & & & \\ & & \mathrm{H} & & \end{matrix}$ the first plays an essential part and the second is only one among several possibilities. In different molecules or under different experimental conditions, not the immediate recombination of the two liberated radicals, but quite different reactions will occur with highest probability.

The second type of reaction (II) seems, at present, not to fit into any scheme which involves a *true* decomposition under the action of light. We would rather suggest a process of activation, *i.e.*, excitation of the molecule into its next stable term, whose existence is shown by the existence of a band spectrum. One would assume that this activation takes place in the

[12] Butyraldehyde and isobutyraldehyde apparently do not form hydrogen (44).

carbonyl group but is dissipated through the aliphatic chain. We know from the fundamental work of Sutton (45) that the intensity of such an activation wanders through the chain in a zig-zag line of continuously decreasing amplitude. It is strongest in the α, β-position to the carbonyl group, and here actually fissure takes place. Similar reactions have been observed with aldehydes (44) and fatty acids, too.

The photolysis of acetone itself has been discussed above. According to its spectrum, it dissociates into $CO(^1\Sigma)$ and two methyl radicals ($\sim$ethane) with an energy of 74.9 kcal/mole (λ3500) or more, and into two radicals, methyl and acetal with the (C^{IV}–C^{IV}) single bond energy of 125 kcal/mole (λ2200). Preparative work of Norrish *et al.* (41) bears out the first process, while this interpretation of the second absorption region agrees with and explains the new results of Spence and Wild (46), which point definitely to the formation of methyl and acetyl radicals. Spence and Wild observed that the ratio C_2H_6/CO for the photolysis of acetone is only equal to unity at $\lambda\sim3000$, while at short wave lengths this ratio changes and at the same time diacetyl appears, due to a pair-wise combination of acetyl radicals.[13]

With cyclic ketones of the cyclohexanone type, the same reactions occur. The interesting observations of Bamford and Norrish (47) prove that again $CO(^1\Sigma)$ is set free, and the remainder of the molecule undergoes the reactions which can be expected of a divalent radical —$CH_2CH_2CH_2CH_2CH_2$—.

With regard to acids, the situation is more complicated. That hydroxyl radicals are formed has been experimentally proved by Terenin for the photolysis of gaseous formic and acetic acids. The observed products (48) CO_2, CH_4, C_2H_6, and some H_2 (besides CO) from acetic acid prove, at any rate, that the reactions stabilizing the primary products indicated spectroscopically, *viz.* CH_3, OH, CO, are not at all simple, and occur with high velocity as shown by the recent results of Burton (49), who was unable to detect free methyl groups by the usual methods.

Attention finally may be directed to the decomposition of mercury dimethyl, recently investigated by Linnet and Thompson (50). The atoms of the second group of the Periodic Table are of particular interest in this connection, as the two electrons of the s^2 group are the only valency electrons these elements possess. This accounts for certain peculiarities in their chemical behavior. According to the Heitler-London theory, these atoms are chemically inert in their ground state s^2 ^1S. On approach of two methyl radicals to such a mercury atom, a repulsive curve only results, whereas adiabatic dissociation of the ground level of the mercury dimethyl

[13] The filter used by them in these latter experiments was transparent for the short wave end of the ultraviolet region and probably also for part of the Schumann region, where it could not be tested.

molecule involves an excited mercury atom. In other words, the mercury atom in its ground state (valency 0) entirely takes the place of a saturated molecule with lower valency in our above considerations, and photodissociation should follow the equation: $Hg(CH_3)_2 \rightarrow 2CH_3 + Hg(^1S)$. This is actually the case. At normal temperatures the two radicals combine to ethane to the extent of 93%; at higher temperatures this immediate combination becomes less frequent on account of the greater number of collisions, chain reactions are started by the free radicals, and the quantum yield is increased. The experimental results appear entirely to agree with this point of view.

REHOVOTH, PALESTINE
HAIFA, PALESTINE

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

BENZIMIDAZOLE STUDIES. I. THE MECHANISM OF BENZIMIDAZOLE FORMATION FROM *O*-PHENYLENEDIAMINE

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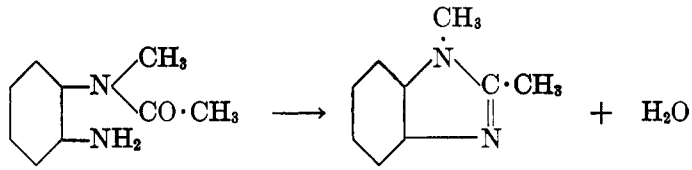
Although benzimidazoles have been known for a long time, the mechanism of the reaction by which they are formed from *o*-phenylenediamine has not been clearly established. Phillips (1) carried out a series of reactions which were intended to throw some light on this question. He concluded that the monoacyl derivative of *o*-phenylenediamine was the necessary intermediate for the reaction. Monoacyl-*o*-phenylenediamines when heated with 4 *N* hydrochloric acid passed readily into the corresponding benzimidazoles. He also noted that the diacyl-*o*-phenylenediamines yielded benzimidazoles, when treated under the same conditions. He concluded that the latter action involved, as the first step, the formation of the monoacyl derivative which subsequently underwent ring closure with the splitting out of a molecule of water. The fact that it was difficult to obtain any 2-methylbenzimidazole when *o*-phenylenediamine was heated with excess acetic anhydride served to confirm his conclusion that the diacyl derivative did not yield the benzimidazole directly.

Phillips further noted the formation of 1,2-dimethylbenzimidazole when *o*-amino-N-methylacetanilide was heated with dilute hydrochloric acid.

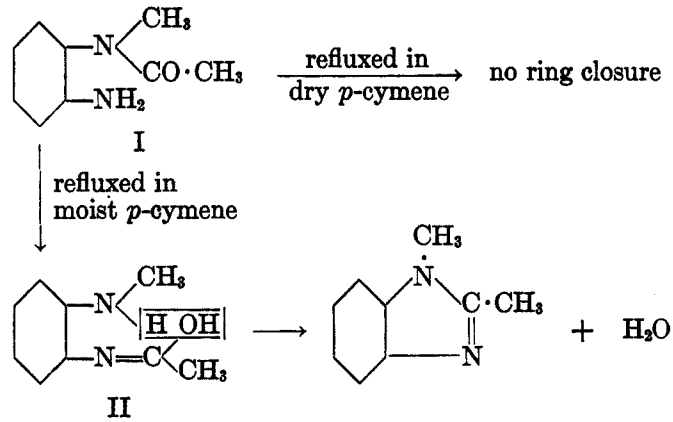


He did not draw any definite conclusions from this reaction, but it seemed that the reaction might be explained in one of two ways. It might be inferred that the ring closure proceeded by the splitting out of water with both hydrogen atoms coming from the same nitrogen atom. However it might be assumed that the aqueous medium used first hydrolyzed the acetyl derivative. Reacetylation might then occur on the other nitrogen atom, followed by ring closure. In this case the two hydrogens would have come from the adjacent nitrogen atoms.

In order to study this ring closure more carefully, it was decided to carry out a series of reactions in dry organic solvents, thereby eliminating the possibility that hydrolysis might play a part in the reactions. These reactions were designed for two purposes: (A) to test Phillips' conclusion that the monoacyl derivative was the necessary intermediate; and (B) to determine the source of the two hydrogen atoms which split out to form water. The experimental conditions used to effect ring closure were similar to those described by Chatterjee (2).

N,N'-Diacetyl-*o*-phenylenediamine was refluxed in dry xylene (b.p. 140°) and also in dry *p*-cymene. No trace of 2-methylbenzimidazole was found in either case. In comparison with the behavior of the diacyl compound, it was found that the monoacetyl-*o*-phenylenediamine gave a quantitative yield of 2-methylbenzimidazole when refluxed in dry xylene. These results were in agreement with Phillips' conclusions.

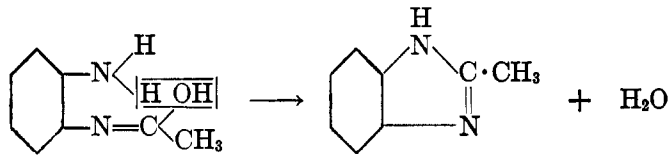
The starting compounds for the second phase of the work were *o*-amino-N-methylacetanilide (I) and N-methyl-N'-acetyl-*o*-phenylenediamine (II). When pure samples of I were refluxed in dry xylene or in dry *p*-cymene, only the starting material could be recovered. Under fairly vigorous conditions (temperatures of 140° and 176° respectively) this compound showed no tendency to undergo ring closure. It was noted that when the sample was refluxed with moist *p*-cymene, a small amount of 1,2-dimethylbenzimidazole was formed. This can be explained only on the assumption that some hydrolysis occurred, followed by acetylation of the other nitrogen atom. The latter derivative, having hydrogen attached to each of the nitrogen atoms, then underwent ring closure to form the benzimidazole.



In contrast to the behavior of I, the isomeric form N-methyl-N'-acetyl-*o*-phenylenediamine (II) was found to undergo ring closure very readily. When refluxed in dry xylene, it gave quantitative yields of the correspond-

ing benzimidazole. Ring closure was observed to occur at temperatures far below that of boiling xylene. When the compound was dried at 50–60°, ring closure slowly took place. Accurate melting point determination was found to be impossible because of this change. Melting started at a low temperature but complete melting occurred only near the melting point of the dimethylbenzimidazole, except in those cases where the melting point was rapidly determined.

The results of these experiments showed that the ring closure produced by the action of organic acids on *o*-phenylenediamine proceeds through the monoacyl derivative. The latter then probably splits out water by losing the oxygen of the acyl group and one hydrogen from each of the two nitrogen atoms. The reaction for the ring closure, involving the monoacyl-*o*-phenylenediamine, may be formulated as follows:



This mechanism, if extended, should be useful in determining the orientation of the imidazole ring relative to the aromatic ring. This work is being continued by Day and co-workers.

EXPERIMENTAL

I. *Preparation of starting compounds*

Diacetyl-o-phenylenediamine. *o*-Phenylenediamine (10.8 g., 0.1 mole) was dissolved in 3 *N* hydrochloric acid (0.2+ mole) and the solution diluted to 250 cc. Acetic anhydride (23.6 cc., 0.25 mole) and 34 g. (0.25 mole) of sodium acetate were added. When all of the sodium acetate had dissolved, the mixture was cooled and the product removed by filtration. Yield 15.36 g. (80%), m.p. 188.2–188.7° (corr.).

o-Aminoacetanilide. *o*-Nitroaniline (55.25 g., 0.4 mole) and 75.5 cc. (0.8 mole) of acetic anhydride were refluxed for 2 hours. The solution was slowly poured into water and after cooling the acetylated product was removed by filtration. It was recrystallized from hot water. Yield 97%, m.p. 93° (corr.).

Ten grams of *o*-nitroacetanilide was dissolved in 200 cc. of alcohol, 3 g. of 10% palladium on charcoal was added and the mixture shaken in an atmosphere of hydrogen until the theoretical amount was absorbed. The catalyst was removed and the filtrate evaporated under reduced pressure. The crude *o*-aminoacetanilide was recrystallized from benzene, m.p. 132.8–133.5° (corr.). This method was superior to that used by Phillips who reduced the acetylated nitroaniline with iron and acetic acid. The latter method was tried several times, but yielded mostly 2-methylbenzimidazole. To avoid the formation of benzimidazole, the reduction should be carried out under neutral conditions and preferably at room temperature.

o-Amino-N-methylacetanilide. N-*o*-Nitrophenyl-*p*-toluene sulfonamide was prepared by the method of Usherwood and Whitely (3). A solution of 250 g. (1.8 moles)

of *o*-nitroaniline and 345 g. (1.8 moles) of *p*-toluenesulfonyl chloride in 246 cc. of pyridine was heated on the water-bath for 5 hours. The mixture was poured into water and stirred until crystallization occurred. The product was recrystallized from alcohol. Yield 413.7 g. (78%), m.p. 111–113° (corr.).

This compound was methylated by the method of Usherwood and Whitely as modified by Phillips. Four hundred and ten grams (1.4 moles) was suspended in 342 cc. of 4 *N* sodium hydroxide and 103 cc. (1.08 moles) of methyl sulfate added. The mixture was boiled gently and alkalinity to phenolphthalein was maintained by adding 10 *N* sodium hydroxide as needed. More methyl sulfate (153 cc.; 1.61 moles) was then added and the above treatment repeated. This mixture was cooled and filtered. The crude N-*o*-nitrophenyl-N-methyl-*p*-toluenesulfonamide was recrystallized from alcohol. Yield 387 g. (90%), m.p. 131.7–132.8° (corr.).

o-Nitromethylaniline was obtained by heating the above product with a mixture of glacial acetic acid (193.6 cc.) and concentrated sulfuric acid (436.4 cc.) on the water-bath for 1½ hours (method of Usherwood and Whitely). The solution was poured into water and allowed to stand overnight. The product was recrystallized from warm alcohol. Yield 89%, m.p. 33–34.5° (corr.).

The *o*-nitromethylaniline was acetylated by a modification of Phillips' method. Forty-nine grams (0.32 mole) was suspended in 98.5 cc. of acetic anhydride and 0.2 cc. of concentrated sulfuric acid was added. The mixture was warmed until solution was complete and then poured slowly into water. The acetylated product did not separate, as reported by Phillips, even on long standing. The solution was almost neutralized with ammonium hydroxide and extracted with benzene. The *o*-nitro-*N*-methylacetanilide was isolated by evaporation of the benzene extract. Yield 36 g. (73%), m.p. 71.2–71.4° (corr.).

o-Amino-N-methylacetanilide was prepared by the catalytic hydrogenation of the above nitro compound, by the same procedure used for *o*-aminoacetanilide; m.p. 149.9–150.3° (corr.). Phillips reported the melting point 67–68° for this compound.

Anal. Calc'd for $C_9H_{12}N_2O$: N, 17.06. Found: N, 17.03.

N-Methyl-N'-acetyl-o-phenylenediamine. Ten grams (0.065 mole) of *o*-nitromethylaniline was dissolved in alcohol containing 12 cc. of concentrated hydrochloric acid. Hydrogenation was carried out as previously described. The crude *o*-aminomethylaniline dihydrochloride was recrystallized from alcohol and ether. Yield 92%, m.p. 177° (corr.).

The acetylation of *o*-aminomethylaniline proved to be troublesome because of the tendency of the acetylated product to pass into the corresponding benzimidazole. The acylation was first attempted by the method which Hempel (4) used for acetylating *o*-aminoethylaniline. *o*-Aminomethylaniline dihydrochloride (8.57 g.; 0.044 mole) was placed in a separatory funnel and covered with water and ether. The free base was liberated by the addition of sodium hydroxide and the ether extract dried over sodium hydroxide. To the dry ether solution was added 3.9 cc. of acetic anhydride and the solution was allowed to stand overnight. On evaporation of the ether under reduced pressure, 8.67 g. of a white solid was obtained. This proved to be the acetate of 1,2-dimethylbenzimidazole. It was converted to the free base by treatment with dilute ammonium hydroxide and recrystallized from water; m.p. 111.4–111.8° (corr.).

Anal. Calc'd for $C_9H_{10}N_2$: N, 19.16. Found: N, 19.12.

The acetylation was finally effected by slowly adding the acetic anhydride in dry ether to the dry ether solution of the free base, in the presence of sodium bicarbonate and with constant stirring. The mixture was allowed to stand for 1½ hours, filtered, and the ether removed under reduced pressure. The residue was then extracted twice with 200 cc. of petroleum ether at room temperature. The extracts were evaporated to small volume by bubbling nitrogen through the solution. An almost colorless crystalline product was obtained. Yield 20%, m.p. 71.5–79.5° (corr.).

Anal. Calc'd for $C_9H_{12}N_2O$: N, 17.06. Found: N, 17.37.

II. *Ring Closure*

Five grams of diacetyl-*o*-phenylenediamine was refluxed for 4 hours in 80 cc. of dry xylene. The diacetyl derivative was recovered quantitatively, m.p. 188–188.7° (corr.).

One gram of the diacetyl compound was refluxed for 2 hours in 30 cc. of dry *p*-cymene. Recovery of the starting material was practically quantitative, m.p. 188–188.7° (corr.).

One gram of *o*-aminoacetanilide was refluxed for 2 hours in 30 cc. of dry xylene. The solution was cooled and filtered. Yield 0.88 g. of 2-methylbenzimidazole. It was recrystallized from water, m.p. 175.9–176.9° (corr.).

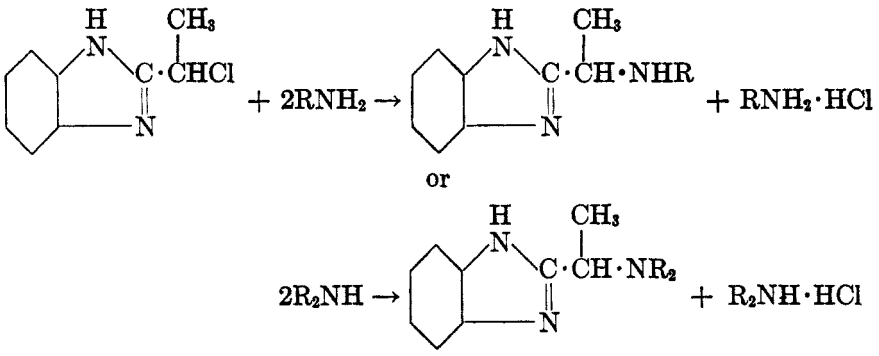
One gram of *o*-amino-N-methylacetanilide was refluxed in 30 cc. of dry xylene for 2 hours. The material recovered from the solution weighed 0.99 g. and melted at 149–149.4° (corr.), indicating that ring closure had not occurred. Another sample was refluxed in dry *p*-cymene, but again only the starting material was recovered.

Samples (0.25 g.) of N-methyl-N′-acetyl-*o*-phenylenediamine were refluxed in dry xylene (8 cc.) for 2 hours. The 1,2-dimethylbenzimidazole was precipitated from the warm solution by the addition of petroleum ether, and recrystallized from water, m.p. 111.5–111.9° (corr.). The conversions were practically quantitative.

II. PREPARATION OF 2-(α-ALKYLAMINOETHYL)-BENZIMIDAZOLES

Recent work (5) in the field of 2-substituted benzimidazoles has shown that 2-alkylaminomethyl benzimidazoles possess interesting local anesthetic properties. For example a 0.5% solution of the dihydrochloride of 2-(di-*n*-butylaminomethyl)benzimidazole was tested for corneal anesthesia and found to be about as effective as 1% cocaine solution. Similarly a 1% solution was found to be as effective as a 1% procaine solution in producing intradermal anesthesia. The compounds in this series, however, possessed some undesirable properties. The free bases were insoluble in water and their dihydrochlorides were too acidic in solution to be practical as local anesthetics. Attempts were made to prepare the monohydrochlorides but only the dihydrochlorides could be isolated.

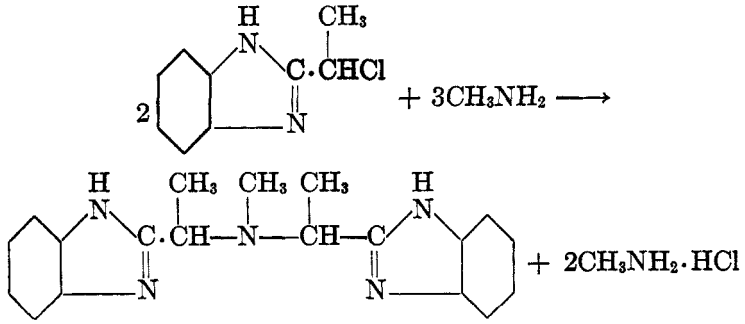
It was therefore considered advisable to extend this work in the hope of eliminating the undesirable properties. 2-(α-Chloroethyl)benzimidazole, prepared by Phillips' method (6) from *o*-phenylenediamine, was condensed with a series of primary and secondary amines.



The conditions for the condensations varied considerably depending on the particular amine which was used.

The condensations with secondary amines were normal in all cases, yielding the corresponding 2-(α-dialkylaminoethyl)benzimidazoles. Two of the latter were appreciably soluble in water at room temperature, the morpholine derivative dissolving to the extent of 2% and the dimethylamine derivative about 1%. These benzimidazoles formed only dihydrochlorides when treated with hydrogen chloride under various conditions. The 2% aqueous solutions of these dihydrochlorides were quite acidic (pH about 3).

The condensations with primary amines, above methylamine, yielded 2-(α-alkylaminoethyl)benzimidazoles. These compounds formed monohydrochlorides on treatment with hydrogen chloride. The aqueous solutions of the hydrochlorides were much less acidic (pH 6–7) than the dihydrochloride solutions noted above. When ammonia or methylamine was used, two moles of the chloroethylbenzimidazole reacted with one of the base to yield disubstituted derivatives.



These compounds formed only dihydrochlorides when treated with hydrogen chloride. This might indicate that the aliphatic nitrogen atom present in the molecule did not take part in salt formation, either through lack of

basicity or due to steric hindrance. The aqueous solutions of these salts were weakly acidic (pH 5).

From the chemical standpoint, the aims of this work have been realized. Benzimidazole derivatives, similar in structure to those known to possess local anesthetic activity but lacking their undesirable properties, have been prepared. They are being pharmacologically tested and the results of these tests will be reported later.

EXPERIMENTAL

Analyses. The semi-micro Kjeldahl method was used for the determination of nitrogen in all cases, except for the piperidine derivatives. For the latter the semi-micro Dumas method was used. The chlorine analyses were carried out by the Volhard method. The chloroethyl compound was decomposed for chlorine analysis by sodium peroxide fusion in a Parr bomb.

Melting points. The melting points recorded are corrected values. Most of the dihydrochlorides melted over a wide range. This is accounted for by the fact that they lose hydrogen chloride when heated. In order to achieve uniformity the melting points were taken with the temperature rising about 1 degree per minute.

I. *2-(α-Chloroethyl)benzimidazole.* *o*-Phenylenediamine (21.63 g., 0.2 mole) and 32.56 g. (0.3 mole) of α-chloropropionic acid were refluxed in 200 cc. of 5 *N* hydrochloric acid for 3 hours. The solution was allowed to stand overnight, filtered, and the filtrate cooled by the addition of ice. It was then neutralized by the careful addition of solid sodium bicarbonate with stirring. The product was removed by filtration, washed with water and dried. Yields 61–64%. It was found advisable to recrystallize the crude product from benzene before using it in the subsequent condensations. The recovery was 70–80%. The product was obtained as colorless needles from hot benzene, using decolorizing carbon, m.p. 134.7–135.4°.

Anal. Calc'd for $C_9H_9ClN_2$: C, 59.83; H, 5.02; Cl, 19.63; N, 15.51.
Found: C, 59.68; H, 5.04; Cl, 19.55; N, 15.46.

A series of reactions was carried out to determine the best conditions for the preparation of this compound. The best yields were obtained in 4 *N* to 6 *N* hydrochloric acid when refluxed for 3 hours. Above 6 *N* or below 4 *N* the yields dropped rapidly. The yields also dropped when the refluxing period was reduced to 1–2 hours. These facts suggested that the reaction might be reversible. Consequently samples of pure 2-(α-chloroethyl)benzimidazole were refluxed with hydrochloric acid, but no evidence was obtained which indicated that this compound was hydrolyzed under the experimental conditions used.

Reactions of 2-(α-chloroethyl)-benzimidazole with amines. One equivalent of the chloroethyl derivative was added gradually to a cold, dry alcohol or alcohol-ether solution containing 2 equivalents of the amine. After heating on the water-bath, the amine hydrochloride was precipitated by the addition of dry ether and removed by filtration. The amine hydrochlorides were recovered in yields varying from 73 to 98%. The benzimidazole derivatives could not all be isolated by the same general method from the alcohol-ether filtrates. The derivatives of the secondary amines (II to VII) and of two of the primary amines (IX and XII) were isolated by evaporating the filtrates to small volume. The solids obtained were broken up, stirred with water, and filtered. The dried products were then recrystallized from suitable solvents. The free bases were converted into the corresponding hydrochlorides by treating their cold ether or alcohol-ether solutions with dry hydrogen chloride. The

salts were filtered and recrystallized from suitable solvents. The hydrochlorides of these bases could also be obtained by treating the cold filtrates from the original reaction-mixtures with dry hydrogen chloride.

Two of the primary amine derivatives (X and XI) were most readily isolated by treating the cold filtrates from the original reaction-mixture with dry hydrogen chloride. The precipitated hydrochlorides were recrystallized from alcohol and acetone until pure. The free bases were obtained by adding sodium hydroxide pellets or solid sodium bicarbonate to aqueous solutions of the hydrochlorides. They were then recrystallized from suitable solvents.

The product formed by the interaction of the chloroethylbenzimidazole and ammonia was worked up by a third method. The filtrate from the reaction-mixture was evaporated almost to dryness. The solid residue was dissolved in concentrated hydrochloric acid and the hydrochloride precipitated by the addition of water.

The following experimental conditions include only those which gave the best yields. In every case several preliminary runs were made to determine the optimum conditions.

II. *2 - (α - Dimethylaminoethyl)benzimidazole.* 2 - (α - Chloroethyl)benzimidazole (5.91 g.; 0.032 mole) was added to 15 cc. of dry alcohol containing 2.95 g. (0.065 mole) of dimethylamine. After standing overnight, the solution was heated on the water-bath for 1½ hours. Sixty cubic centimeters of dry ether was added to the cold solution and the dimethylamine hydrochloride removed by filtration. The product can be isolated from the filtrate by the general method described above. Due to the solubility of this compound in water, it was simpler to recrystallize, from hot water in the presence of decolorizing carbon, the residue from the original filtrate; colorless plates, yield 66%, m.p. 208–210° (decomp.).

Anal. Calc'd for $C_{11}H_{15}N_3$: C, 69.80; H, 7.98; N, 22.20.
Found: C, 69.67; H, 8.06; N, 22.15.

The dihydrochloride was prepared from a dry alcohol-ether solution of the base. Recrystallization from 95% alcohol and acetone gave colorless prisms of the monohydrate, m.p. (range) 125.5–191°.

Anal. Calc'd for $C_{11}H_{15}N_3 \cdot 2HCl \cdot H_2O$: N, 15.00; Cl, 25.31.
Found: N, 15.01; Cl, 25.22.

III. *2-(α-Diethylaminoethyl)benzimidazole.* Five grams (0.027 mole) of 2-(α-chloroethyl)benzimidazole was added to a solution of 4.5 g. (0.06 mole) of diethylamine in 6 cc. of dry alcohol and 5 cc. of dry ether. The solution was refluxed for 3 hours, cooled, diluted with 10 cc. of dry ether, and filtered. The condensation-product, obtained in 88.7% yield from the filtrate, was recrystallized from ligroin, m.p. 177.5–178°. This compound formed very light greenish-yellow plates.

Anal. Calc'd for $C_{13}H_{19}N_3$: C, 71.85; H, 8.81; N, 19.34.
Found: C, 71.81; H, 8.84; N, 19.40.

The dihydrochloride was prepared from a dry alcohol-ether solution of the base and recrystallized from dry alcohol and ether; colorless prisms, m.p. (range) 137.5–185°.

Anal. Calc'd for $C_{13}H_{19}N_3 \cdot 2HCl$: N, 14.48; Cl, 24.43.
Found: N, 14.49; Cl, 24.45.

IV. *2-(α-Di-n-butylaminoethyl)benzimidazole.* 2-(α-Chloroethyl)benzimidazole (4.72 g., 0.026 mole) was added to a solution of 6.75 g., (0.052 mole) of di-*n*-butylamine in 25 cc. of dry alcohol. The solution was refluxed for 1 hour, cooled, diluted with 25 cc. of dry ether, and filtered. The filtrate gave a 75.5% yield of the product. It was recrystallized from acetone and water; colorless needles, m.p. 139.1–139.3°.

Anal. Calc'd for $C_{17}H_{27}N_3$: C, 74.67; H, 9.94; N, 15.37.
Found: C, 74.49; H, 10.08; N, 15.30.

The dihydrochloride was prepared from a dry ether solution of the base and recrystallized from dry alcohol and acetone; colorless prisms, m.p. (range) 132.5–175°.

Anal. Calc'd for $C_{17}H_{27}N_3 \cdot 2HCl$: N, 12.13; Cl, 20.48.
Found: N, 12.08; Cl, 20.45.

V. *2-(α-Dibenzylaminoethyl)benzimidazole.* Five grams (0.027 mole) of 2-(α-chloroethyl)benzimidazole was added to a solution of 10.92 g. (0.055 mole) of dibenzylamine in 25 cc. of dry alcohol. The solution was refluxed for 3 hours, cooled, diluted with 75 cc. of dry ether, and filtered. In this case most of the condensation-product precipitated with the benzylamine hydrochloride. A small amount of solid recovered from the filtrate was added to the first precipitate, and the total solid extracted twice with water and dried. The residue was recrystallized from acetone and water; colorless needles, yield 65.4%, m.p. 222.3–223.2°.

Anal. Calc'd for $C_{23}H_{23}N_3$: C, 80.90; H, 6.78; N, 12.31.
Found: C, 80.71; H, 6.70; N, 12.23.

The dihydrochloride was obtained from a dry alcohol-ether solution of the base and recrystallized from alcohol and water; colorless prisms, m.p. (range) 183.3–208°.

Anal. Calc'd for $C_{23}H_{23}N_3 \cdot 2HCl$: N, 10.14; Cl, 17.11.
Found: N, 10.02; Cl, 16.95.

VI. *2-(α-Morpholinoethyl)benzimidazole.* 2-(α-Chloroethyl)benzimidazole (10.8 g., 0.06 mole) was added to a solution of 10.42 g. (0.12 mole) of morpholine in 40 cc. of dry alcohol. The solution was allowed to stand overnight, diluted with 145 cc. of dry ether and filtered. The product isolated from the filtrate was recrystallized from water (use of decolorizing carbon was necessary in some cases); colorless plates, yields 55–64%, m.p. 196.8–197°.

Anal. Calc'd for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.40; N, 18.17.
Found: C, 67.34; H, 7.50; N, 18.3.

The dihydrochloride, obtained from a dry alcohol-ether solution of the base, was recrystallized from dry alcohol and ether; colorless prisms, m.p. (range) 140–214°.

Anal. Calc'd for $C_{13}H_{17}N_3O \cdot 2HCl$: N, 13.81; Cl, 23.31.
Found: N, 13.72; Cl, 23.21.

VII. *2-(α-Piperidinoethyl)benzimidazole.* Five grams (0.027 mole) of 2-(α-chloroethyl)benzimidazole was added to a solution of 4.71 g. (0.055 mole) of piperidine in 6 cc. of dry alcohol and 10 cc. of dry ether. The solution was refluxed for 2 hours, cooled, diluted with 75 cc. of dry ether, and filtered. The product was isolated from the filtrate in the usual way; yield 84%. It was recrystallized from ligroin; colorless needles, m.p. 167–167.2°.

Anal. Calc'd for $C_{14}H_{19}N_3$: C, 73.32; H, 8.35; N, 18.33.
Found: C, 73.34; H, 8.21; N, 18.29.

The dihydrochloride was prepared from a dry alcohol-ether solution of the base and recrystallized from dry alcohol and ether (or acetone); colorless prisms, m.p. (range) 168.5–214°.

Anal. Calc'd for $C_{14}H_{19}N_3 \cdot 2HCl$: N, 13.90; Cl, 23.46.
Found: N, 13.92; Cl, 23.43.

VIII. *Di-(α-benzimidazolylethyl)amine.* Dry ammonia was passed into a cooled solution of 6.11 g. (0.033 mole) of 2-(α-chloroethyl)benzimidazole in 22 cc. of dry alcohol and 22 cc. of dry ether. The mixture was allowed to stand for 2 days, cooled, and the ammonium chloride removed by filtration. The solid product, obtained

from the filtrate, was dissolved in concentrated hydrochloric acid and the dihydrochloride precipitated by the careful addition of water. The addition of too much water caused the precipitate to redissolve. The salt was purified by repeating the above treatment or by dissolving in water and reprecipitating it by the addition of concentrated hydrochloric acid until precipitation appeared to be complete; colorless needles, yields 36–42%, m.p. (range) 236–270°. Although this condensation was carried out under various conditions, only the disubstituted derivative could be isolated.

Anal. Calc'd for $C_{18}H_{19}N_5 \cdot 2HCl$: N, 18.51; Cl, 18.75.
Found: N, 18.50; Cl, 18.84.

The free base was prepared by neutralizing an aqueous solution of the hydrochloride with ammonium hydroxide. The base was dissolved in a mixture of benzene and acetone. The solution was evaporated to small volume and the product precipitated by the addition of ligroin; colorless prisms, m.p. 206.8–210.2°.

Anal. Calc'd for $C_{18}H_{19}N_5$: C, 70.79; H, 6.27; N, 22.94.
Found: C, 70.64; H, 6.43; N, 22.51.

IX. *Di-(α-benzimidazolylethyl)methylamine.* 2-(α-Chloroethyl)benzimidazole (5.64 g., 0.031 mole) was added to a solution of 1.94 g. (0.062 mole) of methylamine in 12 cc. of dry alcohol. The solution was refluxed for 1½ hours, cooled, diluted with 60 cc. of dry ether, and filtered. The product was obtained from the filtrate in yields of 81–90%. It was recrystallized from acetone and benzene; colorless needles, m.p. 205.1–205.9°. Even when a larger excess of methylamine was used, only the disubstituted product could be isolated.

Anal. Calc'd for $C_{19}H_{21}N_5$: C, 71.44; H, 6.62; N, 21.93.
Found: C, 71.28; H, 6.41; N, 21.87.

The dihydrochloride was prepared from a dry alcohol-ether solution of the base by treatment with dry hydrogen chloride. It was recrystallized from dry alcohol and acetone; colorless prisms, m.p. 234–237°.

Anal. Calc'd for $C_{19}H_{21}N_5 \cdot 2HCl$: N, 17.85; Cl, 18.08.
Found: N, 17.92; Cl, 18.23.

X. *2-(α-Ethylaminoethyl)benzimidazole.* 2-(α-Chloroethyl)benzimidazole (10.26 g., 0.057 mole) was added to a solution of 5.2 g. (0.11 mole) of ethylamine in 20 cc. of dry alcohol and 10 cc. of dry ether. The solution was refluxed for 3 hours, cooled, diluted with 60 cc. of dry ether, and filtered. The cold filtrate was treated with dry hydrogen chloride and filtered. The crude monohydrochloride was recrystallized from dry alcohol and acetone; colorless needles, yields 40–44%, m.p. 225.7–226°.

Anal. Calc'd for $C_{11}H_{15}N_3 \cdot HCl$: N, 18.62; Cl, 15.71.
Found: N, 18.68; Cl, 15.71.

The free base was liberated from an aqueous solution of the hydrochloride by the addition of sodium hydroxide and extracted with benzene. The benzene solution was evaporated and the product recrystallized from benzene and ligroin; colorless plates, m.p. 149–149.3°.

Anal. Calc'd for $C_{11}H_{15}N_3$: C, 69.80; H, 7.98; N, 22.20.
Found: C, 69.68; H, 8.18; N, 22.21.

XI. *2-(α-n-Butylaminoethyl)benzimidazole.* Five grams (0.027 mole) of 2-(α-chloroethyl)benzimidazole in 10 cc. of dry alcohol was added to 4.05 g. (0.055 mole) of *n*-butylamine. The solution was allowed to stand overnight. It was then heated on the water-bath for 6 hours, cooled, diluted with 105 cc. of dry ether, and filtered. The monohydrochloride was obtained from the cold filtrate, as in the case of compound X; yield 91%. It was recrystallized from dry alcohol and acetone; colorless needles, m.p. 171.8–172.7°.

Anal. Calc'd for $C_{13}H_{13}N_3 \cdot HCl$: N, 16.56; Cl, 13.97.
Found: N, 16.62; Cl, 14.00.

The free base, obtained by adding sodium hydroxide to an aqueous solution of the hydrochloride, was recrystallized from ligroin; colorless needles, m.p. 120.3–121.7°.

Anal. Calc'd for $C_{13}H_{13}N_3$: C, 71.84; H, 8.81; N, 19.34.
Found: C, 71.75; H, 8.67; N, 19.32.

XII. *2-(α-Benzylaminoethyl)benzimidazole.* Five grams (0.027 mole) of 2-(α-chloroethyl)benzimidazole was added to a solution of 5.93 g. (0.055 mole) of benzylamine in 12 cc. of dry alcohol. The solution was refluxed for 3 hours, cooled, diluted with 60 cc. of dry ether, and filtered. A 92% yield of the product was obtained from the filtrate. It was recrystallized from acetone and water; colorless prisms, m.p. 155.5–156°.

Anal. Calc'd for $C_{16}H_{17}N_3$: C, 76.46; H, 6.81; N, 16.72.
Found: C, 76.31; H, 6.93; N, 16.59.

The monohydrochloride, obtained from a dry alcohol-ether solution of the base, was recrystallized from dry alcohol; colorless prisms, m.p. 218–220°.

Anal. Calc'd for $C_{16}H_{17}N_3 \cdot HCl$: N, 14.60; Cl, 12.32.
Found: N, 14.64; Cl, 12.38.

SUMMARY

1. Phillips' statement that the monoacyl-*o*-phenylenediamines were the necessary intermediates in the formation of benzimidazoles from *o*-phenylenediamine has been confirmed.

2. It has been shown that the monoacyl-*o*-phenylenediamines do not yield benzimidazoles, under anhydrous conditions, unless there is at least one hydrogen atom on each of the two nitrogen atoms.

3. 2-(α-Chloroethyl)benzimidazole has been prepared and the optimum conditions for the ring closure involved have been established.

4. 2-(α-Chloroethyl)benzimidazole has been condensed with six secondary amines to yield the corresponding 2-(α-dialkylaminoethyl)-benzimidazoles. The latter formed only dihydrochlorides.

5. 2-(α-Chloroethyl)benzimidazole has been condensed with three primary amines, above methylamine, to yield the corresponding 2-(α-alkylaminoethyl)benzimidazoles. These bases formed only monohydrochlorides. The condensation with ammonia and methylamine resulted in the formation of disubstituted derivatives which formed dihydrochlorides.

PHILADELPHIA, PA.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE SYNTHESIS OF 7,9,10-TRIMETHYL-1,2-BENZANTHRACENE AND 8,9,10-TRIMETHYL-1,2-BENZANTHRACENE[1]

W. E. BACHMANN AND J. M. CHEMERDA

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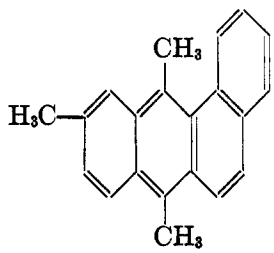
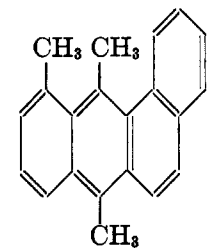
In view of the rapid production of tumors by 9,10-dimethyl-1,2-benzanthracene (1) when applied to the skin of mice, it appeared desirable to prepare additional derivatives of this hydrocarbon. We have now prepared 7,9,10-trimethyl-1,2-benzanthracene (I) and 8,9,10-trimethyl-1,2-benzanthracene (II) from 7-methyl-1,2-benzanthraquinone (III) and 8-methyl-1,2-benzanthraquinone (IV) by the method previously employed



I



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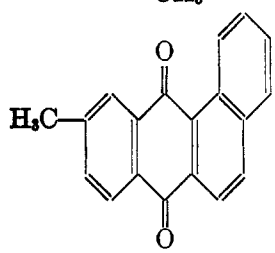

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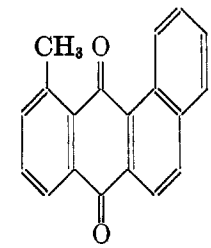
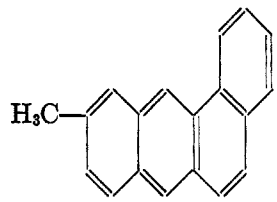


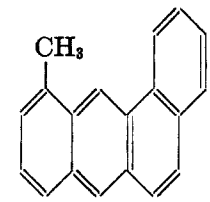
IV

for the synthesis of 9,10-dimethyl-1,2-benzanthracene (2). Briefly, the method is as follows: the quinone was treated with methylmagnesium iodide to give a diol, the diol was methylated by means of methanol containing a small amount of sulfuric acid, and the diol dimethyl ether was converted to the meso dimethyl-1,2-benzanthracene by reaction with two equivalents of sodium. The quinones required for these reactions were obtained by oxidation of the hydrocarbons, 7-methyl-1,2-benzanthracene (V) and 8-methyl-1,2-benzanthracene (VI) for which new syntheses are now reported.

[1] Aided by a grant from the Anna Fuller Fund.

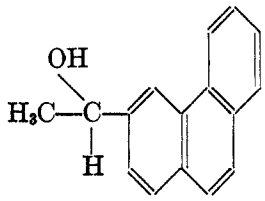


V

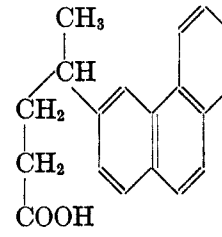


VI

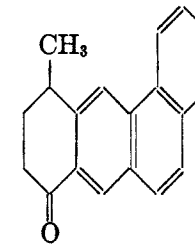
8-Methyl-1,2-benzanthracene (VI) was prepared starting from the readily available ketone, 3-acetylphenanthrene, excellent yields being obtained in all of the intermediate steps. Reduction of 3-acetylphenanthrene by aluminum isopropoxide gave methyl(3-phenanthryl) carbinol (VII) which was converted to the bromide. Sodio-malonic ester and the bromide ultimately gave β-(3-phenanthryl)butyric acid which was in turn converted to γ-(3-phenanthryl)valeric acid (VIII) by means of the Arndt-Eistert reaction (3). Cyclization of this acid through its acid chloride gave the cyclic ketone 5-keto-8-methyl-5,6,7,8-tetrahydro-1,2-benzan-



VII



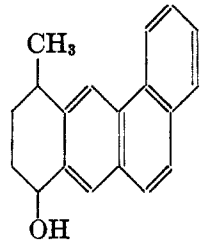
VIII



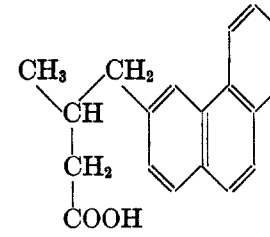
IX

thracene (IX). The latter was reduced by aluminum isopropoxide to the stereoisomeric mixture of alcohols (X) which was converted to 8-methyl-1,2-benzanthracene (VI) by means of palladium-charcoal.

Treatment of 5-keto-8-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene (IX) with methylmagnesium iodide gave an alcohol which was dehydrated and dehydrogenated by palladium-charcoal to 5,8-dimethyl-1,2-benzanthracene, previously described by Fieser and Johnson (4).



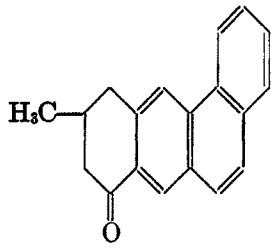
X



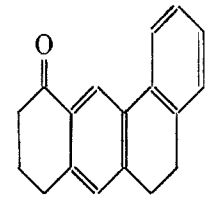
XI

We have also utilized the method of Fieser and Johnson (5) for the preparation of 8-methyl-1,2-benzanthracene from 8-keto-3,4,5,6,7,8-hexahydro-1,2-benzanthracene (XIII) with certain modifications which are described in the experimental section.

In our first synthesis of 7-methyl-1,2-benzanthracene (V), β-(3-phenanthroyl)butyric acid, available from 3-propionylphenanthrene (6), was reduced by the Clemmensen method to β-methyl-γ-(3-phenanthryl)butyric acid (XI) which was cyclized to 5-keto-7-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene (XII). 7-Methyl-1,2-benzanthracene was obtained from the tetrahydro hydrocarbon prepared by Clemmensen reduction of the cyclic ketone, and also from the alcohol obtained in quantitative yields by reduction of the cyclic ketone with aluminum isopropoxide. Of the two methods outlined, the dehydration and dehydrogenation of the alcohol represents the best conversion of the ketone to the hydrocarbon. The new hydrocarbon, 5,7-dimethyl-1,2-benzanthracene was obtained through the Grignard reaction as described above for 5,8-dimethyl-1,2-benzanthracene.

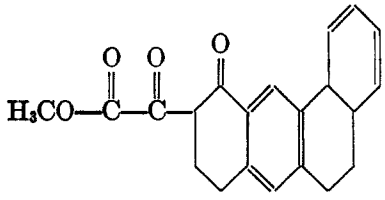


XII

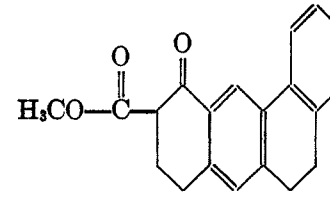


XIII

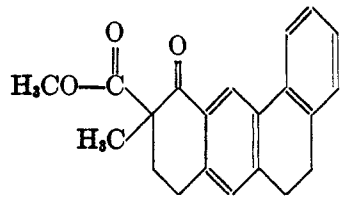
In the second synthesis of 7-methyl-1,2-benzanthracene, 8-keto-3,4,5,6,7,8-hexahydro-1,2-benzanthracene (XIII) was condensed with dimethyl oxalate (7) in the presence of sodium methoxide to give the glyoxalate (XIV) which was decarbonylated to the keto ester (XV). The sodio derivative of this keto ester, when treated with methyl iodide, gave the methylated keto ester (XVI), which was converted to the ketone (XVII) by hydrolysis. Reduction of XVII by aluminum isopropoxide, followed by dehydration and dehydrogenation of the resulting alcohol gave 7-methyl-1,2-benzanthracene.



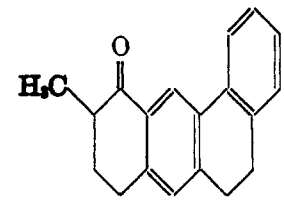
XIV



XV



XVI



XVII

5-Keto-5,6,7,8-tetrahydro-1,2-benzanthracene was carried through a similar series of reactions resulting in the preparation of 5-keto-6-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene, from which 6-methyl-1,2-benzanthracene and 5,6-dimethyl-1,2-benzanthracene were obtained.

EXPERIMENTAL

Methyl (3-phenanthryl) carbinol (VII). Eight grams of pure aluminum wire was dissolved in 250 cc. of anhydrous isopropyl alcohol (8) with the aid of a pinch of mercuric chloride and 1 cc. of carbon tetrachloride[2]. Then 24.5 g. of 3-acetylphenanthrene (9) was added and the isopropyl alcohol distilled off slowly until no test for acetone was obtained. The solution was cooled, added to ice-cold 5% sulfuric acid and extracted with benzene. After washing the benzene solution with dilute ammonium hydroxide, the solution was filtered and the benzene removed in a current of air. The resultant oil was triturated with ligroin and the crystalline product filtered off; yield 22.2 g. (90%); m.p. 76–79°. This product, almost colorless, was good enough for conversion to the bromide. Recrystallized from benzene-ligroin it melted constantly at 79–81° [reported (9) 83–83.5°].

Methyl (3-phenanthryl)bromomethane. To a cooled (−15°) mixture of 22.2 g. of methyl(3-phenanthryl) carbinol in 130 cc. of dry ether was added 6.6 cc. of phosphorus tribromide. After one-half hour at −15° and one hour at room temperature, the ether was removed in a current of dry air. The crude bromide was dissolved in benzene, the benzene solution decanted from the phosphorous acid, washed with ice-cold water, and finally with dilute sodium bicarbonate solution to remove traces of acid. Unless these traces of acid are removed, the bromide decomposes fairly rapidly on standing. The solvent was removed from the filtered solution by a current of air, and the residue triturated with ligroin; yield 25.0 g. (88%); m.p. 86–89°. This product was pure enough for the subsequent malonic ester reaction. Recrystallized from ether-ligroin, it formed colorless plates; m.p. 87–89°.

Anal. Calc'd for $C_{16}H_{13}Br$: Br, 28.0. Found: Br, 28.4.

β-(3-Phenanthryl)butyric acid. A solution of sodio-malonic ester was prepared from 3.1 g. of sodium, 65 cc. of absolute alcohol, and 38 cc. of diethyl malonate. The solution was cooled to 0° and a solution of 26 g. of methyl(3-phenanthrylbromomethane in 100 cc. of benzene was added slowly. The mixture, from which sodium bromide began to precipitate almost immediately, was kept in a refrigerator overnight, and finally refluxed for one hour. The alcohol and benzene were removed, the oily ester hydrolyzed by heating with 130 cc. of 45% potassium hydroxide solution, and a small amount of insoluble material was filtered off. The malonic acid

[2] Lund (15) found that carbon tetrachloride catalyzed the solution of magnesium in ethyl alcohol.

was precipitated by pouring the alkaline solution into an excess of hydrochloric acid, the acid was filtered off, dried, and decarboxylated in two batches at 175–180°. The decarboxylated acid was extracted with chloroform, the extracts combined, and the solution decolorized with Norit. β-(3-Phenanthryl)butyric acid was obtained by crystallization from ligroin-chloroform; yield 18.8 g. (85%); m.p. 104–106°. Hilleman (10), who prepared this same acid from 3-acetylphenanthrene by the Reformatsky reaction followed by reduction of the unsaturated acid, reported the melting point 105–107°.

γ-*(3-Phenanthryl)valeric acid* (VIII). Five grams of β-(3-phenanthryl)butyric acid was treated with 5 cc. of ether and 2.5 cc. of thionyl chloride, and the solution was refluxed for two hours. (The acid chloride can also be prepared from thionyl chloride and ether containing a few drops of pyridine, the reaction-mixture being allowed to stand at room temperature for two hours. This procedure is excellent for acids that react slowly with thionyl chloride but the acid chloride solution used in the subsequent reaction must be free from pyridine hydrochloride.) The ether and excess thionyl chloride were removed under reduced pressure on a bath of warm water, and the residue was freed from the last traces of ether and thionyl chloride by the successive addition and evaporation of three 5-cc. portions of benzene under reduced pressure. The acid chloride was dissolved in 50 cc. of dry ether and added slowly to an ice-cold solution of diazomethane (which had been dried over soda-lime and filtered before use) prepared from 15 g. of N-methyl-N-nitrosourea. After fifteen minutes the reaction-mixture was filtered and the ether removed under reduced pressure. The residual oily diazo ketone was dissolved in 50 cc. of absolute alcohol, and 0.6 g. of dry silver oxide was added. When the mixture was heated on the steam-bath a vigorous evolution of nitrogen occurred. The mixture was refluxed for half an hour, treated with an additional 0.6 g. of silver oxide and refluxed for another half hour. During the second half hour, very little nitrogen was evolved. The solution was filtered, the solvent removed, and the oily ester was hydrolyzed by heating with 10% sodium hydroxide solution. This solution containing insoluble inorganic material was filtered, the filtered solution acidified, and the oily acid extracted with benzene. After filtration of the benzene extract and removal of the solvent, the acid was distilled at 0.6 mm. Trituration of the distilled product with ligroin gave 4.2 g. (80%) of colorless acid; m.p. 74–77°. Attempts to purify the acid without distillation gave poor yields of impure acid. Recrystallized from ligroin-chloroform, γ-(3-phenanthryl)valeric acid formed colorless plates; m.p. 75–77°.

Anal. Calc'd for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5.
Found: C, 82.1; H, 6.9.

Runs of twice the size reported gave slightly lower yields. The use of methyl alcohol or *n*-propyl alcohol made very little difference in the yield of acid. The use of a six-fold excess of diazomethane to prepare the diazo ketone gave practically the same yield of acid. It was also ascertained that the presence of air was without effect on the yields obtained.

The acid can also be obtained conveniently through the corresponding amide but the yields are no better. The following procedure was found to be effective. The diazo ketone was prepared from one gram of β-(3-phenanthryl)butyric acid in the manner described above, dissolved in 20 cc. of methanol, treated with dry silver oxide from 2.5 cc. of 10% silver nitrate solution, and dry gaseous ammonia was passed in for one hour at room temperature. The reaction was quite vigorous and apparently was over in a short time. The mixture was filtered, the methanol removed, and the residue dissolved in benzene. The solution was passed through a tower of

alumina to free it from inorganic matter, and the amide was obtained by the addition of ligroin to the concentrated benzene solution; yield 0.75 g. (72%); m.p. 138–139.5°. γ-(3-Phenanthryl)valeramide crystallized from benzene-ligroin or acetone-ligroin as colorless needles; m.p. 138–139°. The use of aqueous ammonia gave only 50% yield of the desired amide. Hydrolysis of the amide with 10% sodium hydroxide solution gave the acid which was previously obtained from the ester.

Anal. Calc'd for $C_{19}H_{19}NO$: N, 5.1. Found: N, 4.7.

5-Keto-8-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene (IX). To 40 cc. of dry benzene and 7.8 g. of phosphorus pentachloride was added 7.8 g. of γ-(3-phenanthryl)valeric acid, and the mixture was allowed to remain at room temperature for two hours. All of the reactants dissolved within a short time. (The use of thionyl chloride and pyridine gave poorer yields of the final ketone.) The clear benzene solution was then cooled in ice-water and 7.8 cc. of stannic chloride was added. After fifteen minutes at room temperature, the bright red complex which precipitated was hydrolyzed with ice and hydrochloric acid. A few drops of ether hastened the hydrolysis. The benzene solution was washed successively with hydrochloric acid, water, and ammonium hydroxide. After removal of the benzene, the crude ketone crystallized from alcohol containing a small amount of benzene as small, shining, light tan prisms; yield 6.52 g. (88%); m.p. 129–131°. This material is sufficiently pure for the next reaction. A sample of the cyclic ketone was obtained colorless by passage of a benzene solution through a tower of alumina, removal of the solvent at room temperature, and recrystallization from alcohol-benzene; m.p. 130–131.5°.

Anal. Calc'd for $C_{19}H_{16}O$: C, 87.7; H, 6.2.
Found: C, 87.6; H, 6.5.

8-Methyl-1,2-benzanthracene (VI). (*a*). *From 5-keto-8-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene.* Five grams of the ketone was added to a solution of aluminum isopropoxide prepared from 1.7 g. of pure aluminum wire, 160 cc. of anhydrous isopropyl alcohol, a pinch of mercuric chloride, and 1 cc. of carbon tetrachloride. After 120 cc. of isopropyl alcohol had been distilled off slowly, no test for acetone was obtained in the distillate. The solution was cooled, poured into ice-cold 5% sulfuric acid, the oily alcohol was extracted with benzene, and the benzene solution washed with dilute ammonium hydroxide. After removal of the benzene, the alcohol was heated with 1.0 g. of palladium-charcoal (11) in an atmosphere of nitrogen, first at 230–250° to prevent splattering when dehydration occurred, and then at 300–310° to effect dehydrogenation. After forty minutes the hydrocarbon was extracted with benzene, and the crude hydrocarbon was distilled at 0.6 mm. From alcohol-acetone, 3.65 g. (79%) of yellow plates was obtained; m.p. 114–117° with remelting at 112–113°. The melting points obtained varied considerably. The hydrocarbon purified through the picrate (m.p. 158–159°), regenerated, and recrystallized twice from alcohol-acetone and finally from acetic acid was obtained as colorless rectangular plates; m.p. 117–117.5° with remelting at the same temperature. Fieser and Johnson (5) reported the melting point 118–118.5° (corr.) with remelting at 113–114° (corr.), and 159.5–160° (corr.) for the picrate. For oxidation to the quinone, the product obtained after distillation and recrystallization gave yields that were as good as those obtained from a highly purified product.

(*b*). *From 8-keto-3,4,5,6,7,8-hexahydro-1,2-benzanthracene* (XIII). This cyclic ketone was prepared in 90% yield by the cyclization of γ-2-(9,10-dihydrophenanthryl)butyric acid as the acid chloride, by stannic chloride. Fieser and Johnson (12) obtained the same yield using anhydrous hydrogen fluoride. To a suspension

of 10 g. of γ-2-(9,10-dihydrophenanthryl)butyric acid in 100 cc. of dry ether and two drops of pyridine was added 20 cc. of thionyl chloride. The mixture was allowed to stand at room temperature for half an hour and the ether and excess thionyl chloride were removed under reduced pressure. The acid chloride was dissolved in 100 cc. of dry benzene, and 15 cc. of stannic chloride was added to the ice-cold solution. After standing in the cold for an hour, the complex was hydrolyzed with ice and hydrochloric acid; the benzene layer was washed with ammonium hydroxide and then water, evaporated, and the residue crystallized from benzene-methanol; yield 8.37 g.; the product sintered at 91.5°, resolidified, and melted completely at 97–97.5°.

To an ice-cold solution of a Grignard reagent prepared from 2.6 cc. of methyl iodide in 35 cc. of ether was added 3.5 g. of the above ketone in 35 cc. of dry benzene. The mixture was allowed to stand in a refrigerator overnight and was then hydrolyzed with ice-cold ammonium chloride solution. Evaporation of the benzene-ether solution gave colorless needles of the alcohol; yield 3.44 g. (93%); m.p. 113–116°. After two recrystallizations from benzene-ligroin a sample of *8-methyl-8-hydroxy-3,4,5,6,7,8-hexahydro-1,2-benzanthracene* melted at 115.5–117°. It gave a rose color with sulfuric acid.

Anal. Calc'd for $C_{19}H_{20}O$: C, 86.4; H, 7.6.
Found: C, 86.0; H, 7.6.

A mixture of 3.44 g. of the alcohol and 0.4 g. of palladium-charcoal at 300–320° gave 2.63 g. (84%) of 8-methyl-1,2-benzanthracene, m.p. 111–117°. Without isolation of the alcohol, 11.4 g. of the ketone treated in the manner described gave 9.34 g. (84%) of 8-methyl-1,2-benzanthracene; m.p. 113.5–116.5°.

8-Methyl-1,2-benzanthraquinone (IV). The use of propionic acid instead of acetic acid, and sodium dichromate in place of potassium dichromate gave better yields in this oxidation (7). Two and one-tenth grams of 8-methyl-1,2-benzanthracene was dissolved in 10 cc. of boiling propionic acid, and to the slightly cooled solution was added 2.5 g. of pure sodium dichromate dihydrate. When the initially vigorous reaction had abated, the solution was refluxed for half an hour and allowed to cool. The quinone, (1.5 g.; 65%) which crystallized out was filtered off and washed with acetic acid, m.p. 185–189°. The quinone after recrystallization from acetic acid-alcohol formed yellow-brown needles; yield 1.32 g. (57%); m.p. 192–194°. Fieser and Johnson (5) reported golden-yellow needles having the melting point 196.5–197° (corr.). Upon standing in the light, the surface of this quinone becomes green.

Acetic acid as solvent gave erratic results. The best experiments gave only 40–50% yields of an impure product. In one experiment butyric acid as solvent gave a product from which no quinone was isolated.

8,9,10-Trimethyl-1,2-benzanthracene (II). To a solution of methylmagnesium iodide prepared from 6.1 g. of magnesium in 100 cc. of dry ether was added 100 cc. of dry benzene and then 4.2 g. of 8-methyl-1,2-benzanthraquinone; the mixture was shaken until the quinone was dissolved. After forty-eight hours at room temperature the golden-brown solution was decomposed with ice-cold ammonium chloride solution and the crude diol was obtained by evaporation of the benzene-ether solution at room temperature. Trituration of this gum, apparently a mixture of stereoisomers, with ligroin-acetone gave a total yield of 4.55 g. of diol; m.p. 130–142°. Occasionally a higher-melting diol was obtained, but the melting point of the diol dimethyl ether obtained was approximately the same regardless of its source. The diol retained solvent of crystallization tenaciously and the compound was analyzed as the diol dimethyl ether.

To a mixture of 2.35 g. of the diol, 5 cc. of methanol, and 2 cc. of benzene, was

added 0.05 cc. of sulfuric acid in 4 cc. of methanol. After one-half hour in the refrigerator, the diol dimethyl ether was filtered off, dissolved in benzene, and washed with dilute ammonium hydroxide solution. It was imperative to isolate the diol dimethyl ether after a short time, as it was destroyed on standing by the acid present. From benzene-methanol *8,9,10-trimethyl-9,10-dimethoxy-9,10-dihydro-1,2-benzanthracene* crystallized as colorless prisms; yield 1.4 g.; m.p. 205–210° in a bath preheated to 180°. Depending on the diol mixture methylated, the melting point varied from 200° to 213°. It gave a purplish-red color with sulfuric acid.

Anal. Calc'd for $C_{23}H_{24}O_2$: C, 83.1; H, 7.3.
Found: C, 83.0; H, 7.5.

For 2.26 g. of the diol dimethyl ether, 0.31 g. of sodium was weighed accurately and powdered. After shaking the mixture of sodium and the diol dimethyl ether in 25 cc. of benzene and 25 cc. of ether for twenty-four hours, an intensely dark brown solution with a blue fluorescence was obtained. The solution was decolorized with one drop of methanol, shaken with dilute hydrochloric acid, and the solvent removed at room temperature. From the residue, by crystallization from alcohol-acetone, was obtained 1.5 g. (82%) of yellow prisms m.p. 99.5–103°. After recrystallization from alcohol-acetone, purification through the picrate (necessary to remove a trace of diol dimethyl ether), and finally recrystallization of the regenerated hydrocarbon from alcohol-acetone, *8,9,10-trimethyl-1,2-benzanthracene* melted constantly at 102–103.5°.

Anal. Calc'd for $C_{21}H_{16}$: C, 93.3; H, 6.7.
Found: C, 93.0; H, 7.0.

A hot alcoholic solution of 8,9,10-trimethyl-1,2-benzanthracene and picric acid deposited chocolate-brown prisms of a *picrate* which was recrystallized from alcohol containing a little benzene; m.p. 116–117°.

Anal. Calc'd for $C_{21}H_{16} \cdot C_6H_3N_3O_7$: N, 8.4. Found: N, 8.2.

β-Methyl-γ-(3-phenanthryl)butyric acid (XI). The original directions of Bachmann and Struve (6) for the preparation of β-(3-phenanthroyl)butyric acid were modified somewhat, with increased yields. A solution of sodio-malonic ester was prepared from 1.9 g. of sodium and 19.1 g. of malonic ester in 96 cc. of benzene. Then 19.1 g. of 3-(α-bromopropionyl)phenanthrene was added and the suspension was refluxed for four hours. The mixture was filtered while hot, and the residue discarded. The substituted malonic ester, when freed from benzene, was treated with a solution of 12 g. of sodium hydroxide in 200 cc. of alcohol. A vigorous hydrolysis resulted, and the yellow disodium salt precipitated from solution. The disodium salt was filtered off, washed with alcohol, dissolved in water, and the substituted malonic acid precipitated by pouring the alkaline solution into an excess of hydrochloric acid. The product, which crystallized on scratching, was filtered, dried, and decarboxylated at 170–175° for fifteen minutes. By recrystallization from benzene, 9.95 g. (56%) of β-(3-phenanthroyl)butyric acid was obtained; m.p. 144–145°, with remelting at 155–156°. Sometimes the higher-melting form crystallized from solution.

A mixture of 20 g. of amalgamated zinc, 60 cc. of acetic acid, 60 cc. of hydrochloric acid, 20 cc. of toluene, and 10 g. of the keto acid was refluxed for twenty-four hours with the addition of 50 cc. of hydrochloric acid during that period. The toluene layer was separated, the toluene removed and the residue distilled at 0.6 mm. The viscous, light yellow oil was crystallized from ligroin containing a small amount of benzene, and formed short, thick, colorless needles; yield 8.0 g. (85%); m.p. 98–100°. A sample of β-methyl-γ-(3-phenanthryl)butyric acid melted at 99–101° after two recrystallizations from benzene-ligroin.

Anal. Calc'd for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5.
Found: C, 81.7; H, 6.6.

5-Keto-7-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene (XII). To 5.55 g. of the above reduced acid in 27 cc. of benzene was added 5.55 g. of phosphorus pentachloride and the mixture was allowed to remain at room temperature for two hours. The resulting light yellow solution was cooled to 0° and then 5.6 cc. of stannic chloride was added. The orange-red complex was hydrolyzed with ice and hydrochloric acid containing a little ether, and the residual ketone was filtered off after removal of the solvents. To remove uncyclized acid, the product was stirred with hot 10% sodium hydroxide solution, filtered, and washed well with hot water; yield 5.03 g. (97%) of practically pure ketone; m.p. 130–134°. From acetone-methanol or benzene-ligroin, 5-keto-7-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene crystallized as colorless prisms; m.p. 133.5–134°.

Anal. Calc'd for $C_{19}H_{16}O$: C, 87.7; H, 6.2.
Found: C, 87.3; H, 6.4.

Thionyl chloride in ether containing a few drops of pyridine can be used to prepare the acid chloride. Care must be taken to remove the last traces of ether and thionyl chloride prior to cyclization of the acid chloride by stannic chloride. In this manner an 86% yield of the pure ketone was obtained.

7-Methyl-5,6,7,8-tetrahydro-1,2-benzanthracene. A mixture of 1.0 g. of 5-keto-7-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene, 5 g. of amalgamated zinc, 7.5 cc. of acetic acid, 7.5 cc. of hydrochloric acid, and 3 cc. of toluene was refluxed for twenty-four hours. An additional 7.5 cc. of hydrochloric acid was added during this period. The toluene layer was separated and the residue obtained by evaporation of the toluene was sublimed at 0.4 mm. and then crystallized from benzene-alcohol; yield 0.64 g. (68%); m.p. 111–115°. After two recrystallizations from benzene-alcohol, the hydrocarbon formed colorless needles; m.p. 114–115.5°.

Anal. Calc'd for $C_{19}H_{18}$: C, 92.7; H, 7.3.
Found: C, 93.1; H, 7.3.

5-Hydroxy-7-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene. To an aluminum isopropoxide solution prepared from 1.4 g. of aluminum wire, 190 cc. of isopropyl alcohol, a pinch of mercuric chloride, and 1 cc. of carbon tetrachloride was added 6 g. of 5-keto-7-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene. After 120 cc. of isopropyl alcohol had been distilled off slowly, no test for acetone was obtained and the cooled solution was poured into ice-cold 5% sulfuric acid. The precipitated alcohol was filtered off, washed well with water and finally with dilute ammonium hydroxide to remove traces of acid. When partially dry, it was dissolved in acetone and filtered to remove small amounts of inorganic salts and mercury, and the alcohol was finally isolated by spontaneous evaporation of the solution at room temperature; yield 5.88 g. (98%); m.p. 132–139°. A sample of the alcohol after three recrystallizations from dilute acetone and one recrystallization from benzene-ligroin formed colorless needles; m.p. 145–146°.

Anal. Calc'd for $C_{19}H_{18}O_2$: C, 87.0; H, 6.9.
Found: C, 86.4; H, 7.2.

7-Methyl-1,2-benzanthracene (III). A mixture of 3.5 g. of the aforementioned alcohol (m.p. 132–139°) and 0.35 g. of palladium-charcoal was heated at 300–310° in an atmosphere of nitrogen for forty minutes. The hydrocarbon was extracted with benzene, filtered, and distilled at 0.8 mm. and finally crystallized from benzene; yield 2.39 g. (74%); m.p. 179–181° [reported (13) 182°].

7-Methyl-1,2-benzanthracene was also obtained by dehydrogenation of 7-methyl-

5,6,7,8-tetrahydro-1,2-benzanthracene with palladium-charcoal at 300–320° in an atmosphere of nitrogen for one hour, in 77% yield, corresponding to an overall yield of 52% from the ketone.

An excellent yield of 7-methyl-1,2-benzanthracene was obtained from 7-methyl-8-keto-3,4,5,6,7,8-hexahydro-1,2-benzanthracene (preparation described below). To a solution of 0.6 g. of pure aluminum wire in 125 cc. of anhydrous isopropyl alcohol prepared as described previously was added 3.1 g. of the cyclic ketone. When 100 cc. of isopropyl alcohol had been distilled off, reduction was complete and the cyclic alcohol was collected in the usual manner. By heating the product with 1.0 g. of palladium-charcoal at 300–310° for one hour in an atmosphere of nitrogen, 2.45 g. (89%) of 7-methyl-1,2-benzanthracene was obtained; m.p. 179.5–181°.

7,9,10-Trimethyl-1,2-benzanthracene (I). A solution of 2.45 g. of 7-methyl-1,2-benzanthracene in 49 cc. of boiling acetic acid was cooled slightly and 3.43 g. of sodium dichromate dihydrate was added. After refluxing for forty minutes, the crude quinone was isolated in quantitative yield by the addition of dilute sulfuric acid; m.p. 161–164°. After one recrystallization from acetic acid, 2.49 g. (90%); m.p. 164–166° [reported (13) 166°].

To a solution of methylmagnesium iodide from 3.5 g. of magnesium in 70 cc. of ether with the subsequent addition of 70 cc. of benzene, was added 2.84 g. of 7-methyl-1,2-benzanthraquinone. The mixture was shaken until all of the quinone dissolved; the initially green solution became brown on standing. After forty-eight hours at room temperature, the solution was hydrolyzed with ice-cold ammonium chloride solution and the benzene-ether layer extracted with warm sodium hydroxide-sodium hydrosulfite solution. Spontaneous evaporation of the solution and trituration of the gum obtained with ligroin-acetone gave 1.31 g. of colorless diol; m.p. 177–178.5° (not clear and with decomposition).

One gram of the diol was suspended in 5 cc. of methanol and 1 cc. of benzene and treated with 0.02 cc. of sulfuric acid in 2 cc. of methanol. After one-half hour at room temperature the diol dimethyl ether was filtered off, dissolved in benzene, and washed with dilute ammonium hydroxide. Concentration of the benzene solution and addition of methanol gave 0.79 g. of *7,9,10-trimethyl-9,10-dimethoxy-9,10-dihydro-1,2-benzanthracene* as small colorless prisms; m.p. 198–201°.

Anal. Calc'd for $C_{23}H_{24}O_2$: C, 83.1; H, 7.3.
Found: C, 82.8; H, 7.3.

One gram of the diol dimethyl ether was shaken with 0.139 g. of powdered sodium in 30 cc. of dry ether, 30 cc. of dry benzene and a dozen sharp particles of glass. After twenty-four hours it was noticed that particles of sodium were still present and that the solution was colored, which indicated that the hydrocarbon was competing effectively with the diol dimethyl ether in the reaction with sodium. After an additional six hours, when all of the sodium had disappeared, the dark blue, fluorescent solution was decolorized with one drop of methanol, washed with dilute hydrochloric acid, and evaporated. Crystallization of the residue gave 0.73 g. (89%) of *7,9,10-trimethyl-1,2-benzanthracene* as yellow needles; m.p. 99.5–100°. After purification through the picrate and recrystallization of the regenerated hydrocarbon from alcohol-acetone, it melted at 99.5–100.5°.

Anal. Calc'd for $C_{21}H_{18}$: C, 93.3; H, 6.7.
Found: C, 92.9; H, 6.7.

A hot solution of 7,9,10-trimethyl-1,2-benzanthracene and picric acid in alcohol deposited coal black prisms of a *picrate* which was recrystallized from alcohol-benzene; m.p. 139–140° in a Pyrex melting point tube.

Anal. Calc'd for $C_{21}H_{18}\cdot C_6H_3N_3O_7$: N, 8.4. Found: N, 8.4.

5,8-Dimethyl-1,2-benzanthracene. One-half gram of 5-keto-8-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene was treated with methylmagnesium iodide from 0.2 g. of magnesium and 5 cc. of ether with the subsequent addition of 5 cc. of benzene. After eighteen hours at room temperature, the mixture was hydrolyzed with ice-cold ammonium chloride solution and the oily alcohol collected. The alcohol was heated with 0.05 g. of palladium-charcoal for one-half hour at 310–320° in an atmosphere of nitrogen, the hydrocarbon isolated in the usual fashion, sublimed at 0.6 mm. and finally crystallized from alcohol; yield 0.4 g. (82%); m.p. 132–133.5°. After purification through the picrate (m.p. 173–173.5°) and treatment with alumina, the hydrocarbon crystallized from alcohol as colorless needles; m.p. 133.5–134.5°. Fieser and Johnson (4) reported melting points of 174.5–175° (corr.) for the picrate and 131.2–131° (corr.) with remelting at 134.4–137° (corr.) for the hydrocarbon.

5,7-Dimethyl-1,2-benzanthracene. One gram of 5-keto-7-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene was treated with methylmagnesium iodide as described above. The alcohol was heated with 0.1 g. of palladium-charcoal for twenty-five minutes at 300–310° in an atmosphere of nitrogen, and the product extracted with benzene. After removal of benzene, the hydrocarbon was crystallized from alcohol-acetone; yield 0.74 g. (74%); m.p. 122.5–124.5°, with remelting at 124–125°. 5,7-Dimethyl-1,2-benzanthracene, after regeneration from the pure picrate, crystallized from alcohol as thin tabular prisms; m.p. 124.5–125°. Recrystallized from alcohol once more, it melted at 123.5–124.5° but remelted at 124–125°.

Anal. Calc'd for $C_{20}H_{16}$: C, 93.7; H, 6.3.
Found: C, 93.5; H, 6.4.

A hot alcoholic solution of 5,7-dimethyl-1,2-benzanthracene and picric acid deposited bright red needles of a *picrate*; m.p. 186.5–187.5° in a Pyrex melting point tube.

Anal. Calc'd for $C_{20}H_{16}\cdot C_6H_3N_3O_7$: N, 8.7. Found: N, 8.5.

Methyl 8-keto-3,4,5,6,7,8-hexahydro-1,2-benzanthracene-7-glyoxalate (XIV). To a mixture of powdered sodium methoxide from 0.46 g. of sodium, 2.36 g. of dimethyl oxalate, and 2.48 g. of 8-keto-3,4,5,6,7,8-hexahydro-1,2-benzanthracene in an atmosphere of nitrogen, was added 50 cc. of dry benzene and the flask swirled until solution of the reactants was effected (7). In five minutes solution was complete, and an olive-green sodium salt precipitated from solution. After four hours at room temperature, cold water was added to extract the sodium salt of the glyoxalate, the benzene layer was extracted three times with 2% sodium hydroxide solution, and the extracts combined and acidified with dilute hydrochloric acid. The light yellow oil could be crystallized by scratching, and then filtered or, more conveniently, extracted with benzene. After removal of benzene at room temperature, the glyoxalate was crystallized by trituration with methanol; yield 3.05 g. (92%); m.p. 130–132°. From acetone-methanol it crystallized in yellow prisms, which after three recrystallizations softened at 128°, were melted by 133°, and remelted at 133–134°. It gave a very deep brown color with alcoholic ferric chloride.

Anal. Calc'd for $C_{21}H_{18}O_4$: C, 75.4; H, 5.4.
Found: C, 75.4; H, 5.6.

7-Carbomethoxy-8-keto-3,4,5,6,7,8-hexahydro-1,2-benzanthracene (XV). A mixture of 3.05 g. of the above glyoxalate and half its weight of powdered glass was heated at 175° for ten minutes. During this time carbon monoxide was evolved rapidly and the mixture darkened considerably. The keto ester was extracted with acetone, the solution was decolorized with Norit and the keto ester isolated by spon-

taneous evaporation of the acetone solution. Quantitative yields of the keto ester suitable for alkylation were obtained, the color varying from a light tan to a purplish brown. The melting point varied from 100–130° with different preparations. A sample after recrystallization from methanol melted at 110–125°. It gave a green color with alcoholic ferric chloride solution.

Anal. Calc'd for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9.
Found: C, 78.3; H, 6.1.

7-Methyl-7-carbomethoxy-8-keto-3,4,5,6,7,8-hexahydro-1,2-benzanthracene (XVI). A solution of sodium methoxide was prepared from 5.4 cc. of methanol and 0.43 g. of sodium. After the addition of 27 cc. of dry benzene, 2.7 g. of the above keto ester was added and the mixture heated on the water-bath. After fifteen minutes of refluxing, the keto ester dissolved to give a dark brown solution and then 3.5 cc. of methyl iodide was added and the refluxing continued. After two hours, 3.5 cc. more of methyl iodide was added and the solution refluxed for two more hours. After removal of the solvents, the product was extracted with benzene, the filtered solution passed through a tower of alumina, and the methylated keto ester obtained by trituration with methanol after removal of the benzene; yield 2.33 g. (84%) of colorless product; m.p. 100–109°. It gave no color with alcoholic ferric chloride solution and was pure enough for conversion to the ketone. After three recrystallizations from methanol-acetone a sample formed colorless needles; m.p. 109–111°.

Anal. Calc'd for $C_{21}H_{20}O_3$; C, 78.7; H, 6.3.
Found: C, 78.8; H, 6.6.

7-Methyl-8-keto-3,4,5,6,7,8-hexahydro-1,2-benzanthracene (XVII). Two grams of the above methylated keto ester was refluxed for four hours with 15 cc. of acetic acid and 4 cc. of hydrochloric acid. After removal of the acids, the pink semi-crystalline ketone was sublimed at 0.6 mm. and recrystallized from methanol; yield 1.51 g. (93%); m.p. 102–104°. A sample of the ketone, after three recrystallizations from methanol, formed hexagonal plates; m.p. 105.5–106°.

Anal. Calc'd for $C_{19}H_{18}O$; C, 87.0; H, 6.9.
Found: C, 86.5; H, 6.8.

Methyl 5-keto-5,6,7,8-tetrahydro-1,2-benzanthracene-6-glyoxalate. To a mixture of dry sodium methoxide from 0.8 g. of sodium, 4.1 g. of dimethyl oxalate, and 5 g. of 5-keto-5,6,7,8-tetrahydro-1,2-benzanthracene in an atmosphere of nitrogen was added 175 cc. of dry benzene, and the mixture was shaken and gently warmed to aid solution of the rather insoluble ketone. After ten minutes, dark yellow needles of the sodium salt of the glyoxalate precipitated from solution and the mixture was allowed to stand at room temperature for four hours. After isolation of the glyoxalate as previously described, 5.6 g. (83%) of yellow needles was obtained by crystallization from acetone; m.p. 161–162°. After two recrystallizations from acetone it melted at 162–163° with decomposition. It gave a dark brown color with alcoholic ferric chloride solution.

Anal. Calc'd for $C_{21}H_{16}O_4$: C, 75.9; H, 4.9.
Found: C, 75.4; H, 4.8.

5-Keto-6-carbomethoxy-5,6,7,8-tetrahydro-1,2-benzanthracene. A mixture of 4.8 g. of the above glyoxalate and half its weight of powdered glass was heated at 180–185° for twenty-five minutes. The keto ester was extracted with benzene, filtered, decolorized with Norit, and finally crystallized from benzene-methanol; 4.08 g. (93%); m.p. 158–159.5°. A sample after recrystallization from benzene-methanol formed colorless needles which melted at the same temperature. It gave a green color with alcoholic ferric chloride solution.

Anal. Calc'd for $C_{20}H_{16}O_3$: C, 78.9; H, 5.3.
Found: C, 78.9; H, 5.5.

5-Keto-6-methyl-6-carbomethoxy-5,6,7,8-tetrahydro-1,2-benzanthracene. Two and five-tenths grams of the above keto ester was added to a solution of 0.4 g. of sodium in 5 cc. of methanol and 25 cc. of benzene and the mixture heated on a steam-bath for half an hour. Occasionally the solid mass was pressed with a glass rod to prevent coating of the keto ester with the sodio derivative. Then 5 cc. of methyl iodide was added and the mixture was heated for two hours; a second addition of 5 cc. of methyl iodide was made and refluxing of the mixture was continued overnight. The solvents were removed and the methylated keto ester isolated as described above; yield 2.25 g. (86%); m.p. 112–114°. This material was suitable for hydrolysis to the ketone and gave no color with alcoholic ferric chloride solution. After two recrystallizations from methanol a sample formed colorless needles; m.p. 115–116°.

Anal. Calc'd for $C_{21}H_{18}O_3$: C, 79.2; H, 5.7.
Found: C, 79.1; H, 5.8.

5-Keto-6-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene. A mixture of 1.73 g. of the above keto ester, 15 cc. of acetic acid, and 15 cc. of hydrochloric acid was refluxed for four hours. The ketone was isolated as described above; yield 1.37 g. (95%); m.p. 137–138° [reported (14) 137–138.5°].

6-Methyl-1,2-benzanthracene. In the manner described above, 1.22 g. of 6-methyl-5-keto-5,6,7,8-tetrahydro-1,2-benzanthracene was reduced by aluminum isopropoxide, and the product was dehydrated and dehydrogenated by heating with palladium-charcoal; yield 1.02 g. (90%) of colorless hydrocarbon from benzene-alcohol; m.p. 144–145°. Recrystallization of the first crop and redehydrogenation of the mother liquors gave a total yield of 0.91 g. (81%) of pure hydrocarbon; m.p. 149–151.5° (picrate m.p. 157–158°). Cook reported the melting point 151° for the hydrocarbon and 152° for the picrate (13).

5,6-Dimethyl-1,2-benzanthracene. To a methylmagnesium iodide solution prepared from 0.23 g. of magnesium in 5 cc. of ether and 5 cc. of benzene was added 0.6 g. of 5-keto-6-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene. After thirty-six hours at room temperature the carbinol was isolated in the usual fashion and heated with 0.1 g. of palladium-charcoal at 300–310° for half an hour in an atmosphere of nitrogen. The hydrocarbon was extracted with benzene, sublimed, and finally crystallized from alcohol-acetone; yield 0.38 g. (63%); m.p. 187–188° (picrate m.p. 192–193°). Cook (14) obtained a smaller yield using selenium as a dehydrogenating agent; he reported the same melting points for the hydrocarbon and its picrate.

SUMMARY

7,9,10-Trimethyl-1,2-benzanthracene and 8,9,10-trimethyl-1,2-benzanthracene have been prepared for biological testing.

New methods have been developed for the synthesis of 7-methyl-1,2-benzanthracene and 8-methyl-1,2-benzanthracene and other 1,2-benzanthracene derivatives.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE SYNTHESIS OF 4-METHYLCHOLANTHRENE AND 5-METHYLCHOLANTHRENE[1]

W. E. BACHMANN AND J. M. CHEMERDA

Received September 19, 1940

The preparation of the isomeric methylcholanthrenes is of considerable interest and importance inasmuch as 3-methylcholanthrene is one of the most potent carcinogenic compounds known. When this investigation was initiated, 3-methylcholanthrene was the only one of the twelve possible methylcholanthrenes whose synthesis had been reported. Recently, however, Fieser and Bowen (1) have reported the preparation of two of the isomers through the Elbs reaction.

The successful synthesis of 5-keto-7-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene (III) and of the corresponding 8-methyl isomer (IV), which was described by us recently (2), enabled us to synthesize 4-methylcholanthrene[2] (I) and 5-methylcholanthrene (II) by the method employed by one of us to prepare the parent hydrocarbon cholanthrene from 5-keto-5,6,7,8-tetrahydro-1,2-benzanthracene (3).

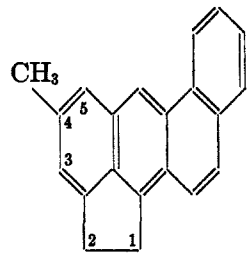
Thus, in the synthesis of 4-methylcholanthrene, the ketone III was reduced to the corresponding secondary alcohol with aluminum isopropoxide, and the alcohol was converted to the chloride by reaction with hydrogen chloride. From the chloride, the acid V was obtained through the malonic ester synthesis. Cyclization of V yielded 1-keto-4-methyltetrahydrocholanthrene (VI). Reduction by the Clemmensen method yielded the 4-methyltetrahydrocholanthrene which was dehydrogenated by palladium on charcoal to 4-methylcholanthrene (I). In a similar manner 5-methylcholanthrene (II) was prepared from IV.

The intermediates in the synthesis appeared to be mixtures and were used in the successive steps without purification or analysis, since it was difficult to effect a separation and to determine when the compounds were pure. These mixtures probably consisted of the stereoisomers which are possible in virtue of the two asymmetric carbon atoms in the reduced ring.

[1] Aided by a grant from the Anna Fuller Fund.

[2] The numbering system for the cholanthrene molecule is that employed in the index of *Chemical Abstracts*. According to Fieser's system, the 4-isomer is 22-methylcholanthrene, the 5-isomer is 23-methylcholanthrene.

When this ring was aromaticized in the final step, only a single compound was formed.



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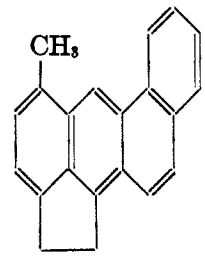

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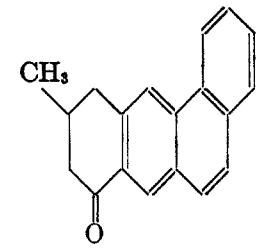
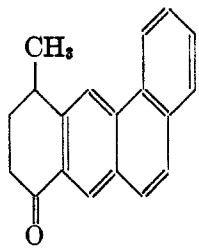


III



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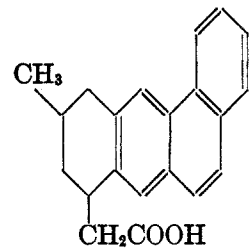
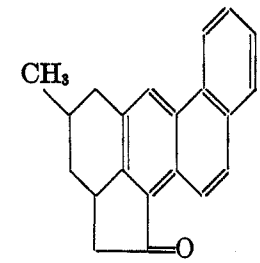


V



VI

EXPERIMENTAL

4-Methylcholanthrene (I). A rapid stream of dry hydrogen chloride was passed into a cooled solution of 3.84 g. of 5-hydroxy-7-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene (2) in 58 cc. of dry benzene containing 2.3 g. of calcium chloride. After fifteen minutes the mixture was allowed to stand at room temperature until it became clear. Evaporation of the filtered solution at room temperature yielded the chloride as a residue, which was sufficiently pure for the next step. A sample of the chloride after recrystallization from benzene-ligroin melted at 88–91°.

A solution of sodio-malonic ester was prepared from 0.62 g. of sodium, 11 cc. of absolute alcohol, and 6.7 cc. of malonic ester. After most of the alcohol had been removed under reduced pressure, the chloride obtained above was added, followed by 15 cc. of dry benzene. The mixture was refluxed on a water-bath for sixteen hours, the solvents were removed, and the substituted malonic ester was hydrolyzed by warming with 8.5 cc. of 45% potassium hydroxide solution. Water was added to dissolve the potassium salts which had precipitated, the solution was refluxed for one-half hour, and then filtered from unsaponifiable material. The substituted malonic acid was best precipitated by adding the alkaline solution to an excess of hydrochloric acid. The malonic acid was decarboxylated at 180° and the resulting 7-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene-5-acetic acid (V) was dissolved in 10% sodium hydroxide solution and reprecipitated with hydrochloric acid; yield, 3.0 g. (67% based on the alcohol); m.p. 145–150°.

A mixture of 1.07 g. of the acid and 1.07 g. of phosphorus pentachloride in 12 cc. of dry benzene was heated on a water-bath for one-half hour. The resultant

solution of the acid chloride was cooled in ice-water, treated with 2 cc. of stannic chloride and the mixture allowed to stand at room temperature for two hours. The olive-green complex was hydrolyzed with ice and hydrochloric acid, the solvent was removed, and the ketone (VI) was filtered off. The ketone was digested with 45% potassium hydroxide solution, filtered off, and washed well with hot water; yield, 0.94 g. (92%); m.p. 162–185°.

A mixture of 2.17 g. of the ketone, 34 g. of amalgamated zinc, 52 cc. of hydrochloric acid, 8.5 cc. of acetic acid, and 8.5 cc. of water was refluxed for forty-eight hours; an additional 52 cc. of hydrochloric acid was added during this period. The 4-methyl-2a,3,4,5-tetrahydrocholanthrene obtained by extraction with benzene crystallized when triturated with alcohol; yield, 1.8 g. (88%); m.p. 75–80°.

The crystalline product was heated with 0.4 g. of palladium on charcoal (4) in an atmosphere of nitrogen at 300–310° for twenty-five minutes. The *4-methylcholanthrene* (I) was separated from the catalyst by means of benzene and then recrystallized from acetone-propanol; yield, 1.54 g.; m.p. 148–150°. After a second recrystallization it formed pale yellow plates which melted at 153.5–154.5°. After sublimation at 0.6 mm., recrystallization from acetone-propanol, purification through the picrate, and two more recrystallizations, the hydrocarbon melted at 154–155° [reported, 154.5–155°, corr. (1)].

Anal. Calc'd for $C_{21}H_{16}$: C, 94.0; H, 6.0.
Found: C, 93.6; H, 5.9.

The *picrate* crystallized from benzene-alcohol in dark brown needles; m.p. 172–173° [reported, 173.6–174° corr. (1)].

Anal. Calc'd for $C_{21}H_{16}\cdot C_6H_3N_3O_7$: N, 8.4. Found: N, 8.4.

5-Methylcholanthrene (II). The 5-hydroxy-8-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene, prepared from 5.35 g. of the ketone IV by means of aluminum isopropoxide (2), was converted to the chloride with hydrogen chloride as described for the isomer. To remove traces of hydrogen chloride from the product, the oily chloride was redissolved in dry benzene and the solvent removed under reduced pressure. A solution of sodio-malonic ester was prepared from 0.86 g. of sodium, 15 cc. of absolute alcohol, and 10 cc. of malonic ester. After most of the alcohol had been removed under reduced pressure, the chloride, dissolved in 20 cc. of dry benzene, was added and the mixture was refluxed on a water-bath for seventeen hours. The solvents were removed and the residual ester was hydrolyzed with 45% potassium hydroxide solution in the manner described for the isomer. The substituted malonic acid, obtained as a gum, was decarboxylated at 200–210°. The resulting 8-methyl-5,6,7,8-tetrahydro-1,2-benzanthracene-5-acetic acid was dissolved in 10% sodium hydroxide solution and reprecipitated with hydrochloric acid. In this manner, 5.14 g. (82% based on the ketone) of the acid was obtained as a gum.

A solution of 1.33 g. of the acid was converted to the acid chloride and the latter cyclized as described. The benzene solution of the ketone was washed with water and ammonium hydroxide, the solvent was removed, and the residual 1-keto-5-methyl-2a,3,4,5-tetrahydrocholanthrene crystallized by trituration with alcohol; yield, 1.0 g. (80%); m.p. 129–135°.

A mixture of 2.67 g. of the ketone was reduced as described, and the oily 5-methyl-2a,3,4,5-tetrahydrocholanthrene was heated with 0.4 g. of palladium on charcoal in an atmosphere of nitrogen for twenty minutes at 300–315°. The *5-methylcholanthrene* (II), separated from the catalyst by means of benzene, crystallized from acetone-propanol in pale yellow plates; yield, 1.73 g. (70% based on the ketone); m.p. 162–163° with previous sintering. Further purification through the picrate

and recrystallization of the regenerated hydrocarbon from acetone gave a product which melted at 160–161.5° in an evacuated melting point tube and remelted at 164–165°. In an open tube the hydrocarbon darkened considerably and melted at a lower temperature.

Anal. Calc'd for $C_{21}H_{16}$: C, 94.0; H, 6.0.
Found: C, 94.1; H, 6.1.

The *picrate* crystallized from absolute alcohol in brown needles; m.p. 192–193° in a Pyrex melting point tube.

Anal. Calc'd for $C_{21}H_{16}\cdot C_6H_3N_3O_7$: N, 8.4. Found: N, 8.4.

SUMMARY

4-Methylcholanthrene and 5-methylcholanthrene have been prepared for biological testing.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

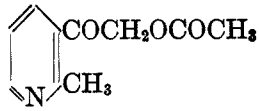
STUDIES IN THE PYRIDINE SERIES. II. SYNTHESIS OF 2-METHYL-3-(β-HYDROXYETHYL)PYRIDINE AND OF THE PYRIDINE ANALOG OF THIAMINE (VITAMIN B_1)

ANN H. TRACY AND ROBERT C. ELDERFIELD

Received August 16, 1940

As a result of the often striking similarity in both physical and chemical, as well as pharmacological properties of pairs of compounds, one of which contains a ring sulfur atom and the other an ethylenic linkage in the position occupied by the ring sulfur of the former, attention has recently been attracted to the possibility of modifying the properties of known substances by such a substitution. The term "isoster" has been suggested by Grimm to denote the relationship of such pairs of substances, and the idea has been extended largely by Erlenmeyer and his collaborators. A resumé of the literature has been given in an earlier paper (1). To this may be added a reference to the success attending the use of sulfathiazole, a substance which is isosteric with reference to sulfapyridine.

Recently the synthesis of 2-(β-hydroxyethyl)-3-methylpyridine and the condensation of this with 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide to yield a pyridine analog of thiamine (vitamin B_1), in which the relative positions of the methyl and hydroxyethyl are the reverse of those occupied in the true pyridine isoster of thiamine, was described by one of us (1). This study formed part of a general program dealing with the development of suitable synthetic methods leading to various hitherto comparatively inaccessible pyridine derivatives. Meanwhile the problem of the synthesis of the pyridine isoster of thiamine has attracted the attention of other workers. Schmelkes (2) and Baumgarten and Dornow (3) described the preparation of what was regarded as 2-methyl-3-(β-hydroxyethyl)pyridine (II) by different methods, the last step of which,



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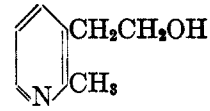

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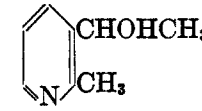


III

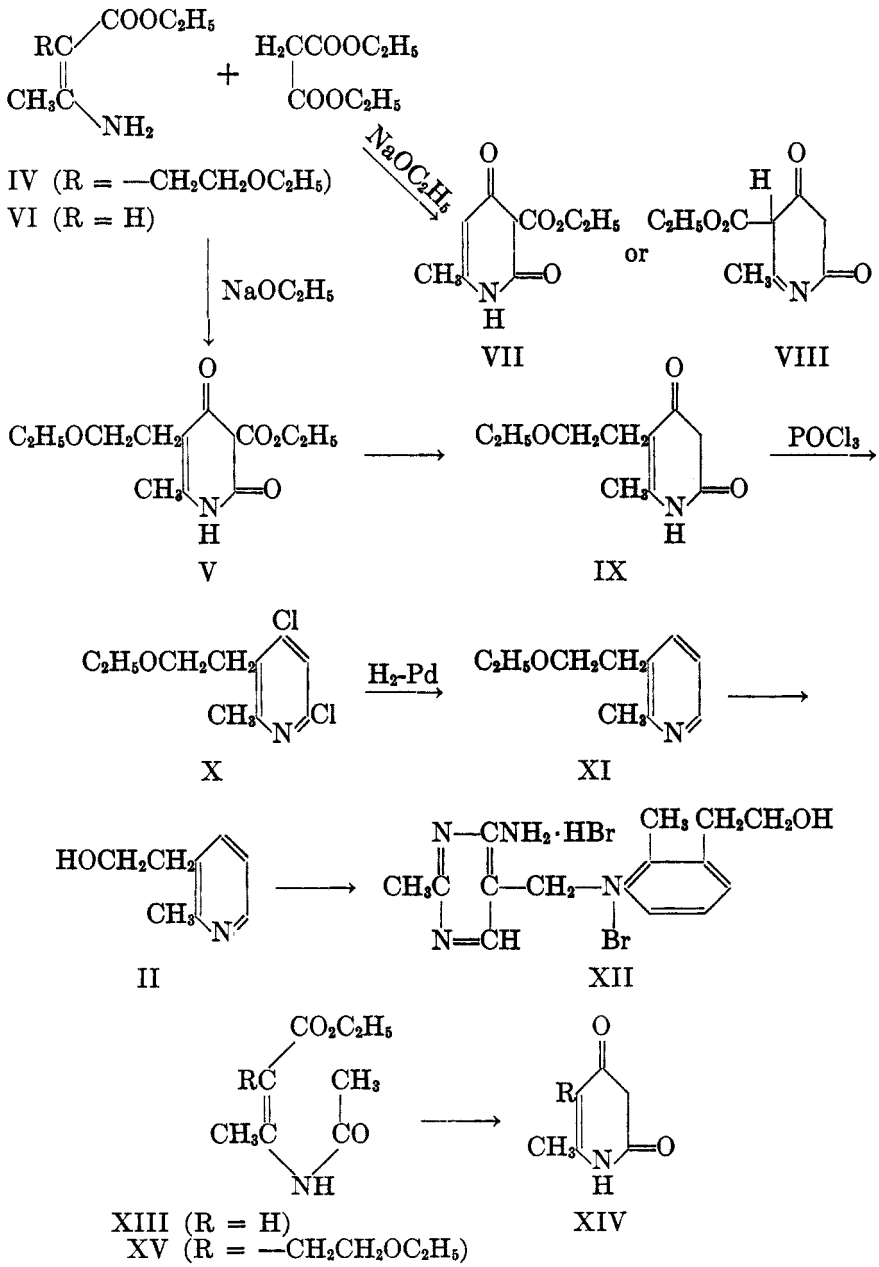
however, was the same in both cases, namely reduction of ω-acetoxy-3-(α-picolyl)methyl ketone (I) by the Clemmensen method to a substance

believed to be the pyridine in question. However, Dornow (4) in a later paper, in which he applied the observations of Birnbaum and Powell (5) on the reduction of ω-acetoxyacetophenone to his acetoxypyridine ketone, showed that the pyridine of both workers actually in hand was 2-methyl-3-(α-hydroxyethyl)pyridine (III). Inasmuch as the vitamin analog obtained by condensation of this pyridine with the pyrimidine of thiamine was reported by both workers to possess a certain anti-polyneuritic activity, and since the isosteric α-hydroxyethylthiazole derivative is inactive, the question of the true vitamin isoster assumes increased interest.

The present paper describes the synthesis of 2-methyl-3-(β-hydroxyethyl)pyridine by methods which leave no doubt as to its constitution, a preliminary note dealing with which has recently appeared (6). Ethyl α-(β-ethoxyethyl)-β-aminocrotonate (IV) was readily prepared by passing dry ammonia into a suspension of ammonium nitrate in ethyl α-(β-ethoxyethyl)acetoacetate, according to the general method of Conrad and Epstein (7). The aminocrotonic ester readily condensed with diethylmalonate in the presence of sodium ethoxide (8) to yield 2-methyl-3-(β-ethoxyethyl)-4,6-dihydroxy-5-carbethoxypyridine (V). In this connection it should be pointed out that Knoevenagel and Fries (8), who first described such a ring closure, with ethyl β-aminocrotonate (VI) and diethyl malonate, left open the question whether the reactants condensed to yield VII or VIII. In the present case the presence of the substituent β-ethoxyethyl group on the α-carbon atom of the aminocrotonic ester renders condensation to yield a pyridone of the type of VIII unlikely because of steric hindrance, an assumption later shown to be true. Ketonic decomposition of the diketo ester V yielded 2-methyl-3-(β-ethoxyethyl)-4,6-dihydroxypyridine (IX) which was then converted to the dichloropyridine (X) with phosphorus oxychloride. Removal of the chlorine atoms in X with palladium and hydrogen gave 2-methyl-3-(β-ethoxyethyl)-pyridine (XI), from which the desired 2-methyl-3-(β-hydroxyethyl)pyridine (II) was readily prepared by hydrolysis of the ether group. The structure of the last substance was demonstrated by the formation of a *p*-nitrobenzoyl derivative, by its non-identity with the substance of Schmelkes, and Baumgarten and Dornow, and by oxidation to quinolinic acid. The hydroxyethylpyridine condensed smoothly with 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide on warming in light petrolatum, to give the pyridine isoster of thiamine (XII).

In addition to the above successful synthesis of 2-methyl-3-(β-hydroxyethyl)pyridine, we have explored the possibility of utilizing β-acetaminocrotonic esters for the synthesis of 2,3-disubstituted pyridines. Ethyl β-acetaminocrotonate has been prepared by the direct acetylation of ethyl β-aminocrotonate (9) and by the condensation of ethyl acetoacetate with

acetamide in the presence of aluminum chloride (10), the latter method, however, having been rather incompletely described. The internal condensation of ethyl β-acetaminocrotonate (XIII) to 2-methyl-4,6-dihy-



droxypyridine (XIV) has been reported in the patent literature (11), and it was hoped to utilize this ring closure for the purpose in mind.

Ethyl β-acetaminocrotonate was readily prepared by direct condensation of acetoacetic ester with acetamide in the presence of aluminum chloride, but when the preparation of ethyl α-(β-ethoxyethyl)-β-acetaminocrotonate (XV) was attempted by a similar reaction, no definite product could be isolated from the reaction-mixture. Accordingly the latter acetamino derivative was prepared by acetylation of the corresponding amino derivative (IV) either with acetyl chloride or with acetic anhydride, the latter being preferable. When ring closure of either XIII or XV to the dihydroxypyridine was attempted, no well-defined products could be isolated, despite the fact that a variety of procedures were used.

Finally, another route to the desired compound was based on a modification of the general method of Finkelstein and Elderfield (1). Diethyl α-(β-ethoxyethyl)-α-acetylglutarate was prepared from ethyl α-(β-ethoxyethyl)acetoacetate and ethyl β-bromopropionate. It was hoped to proceed from this glutaric ester by ring closure through the amide of the γ-acetyl acid, obtained by ketonic decomposition of the β-keto ester, to 5-(β-ethoxyethyl)-6-methyldihydro-2-pyridone. However, the ketonic decomposition of the acetyl glutaric ester did not proceed smoothly, and this method of approach has been dropped.

The physiological action of the above isosteric vitamin will be described elsewhere, together with the action of certain other substances related to it. We wish to express our appreciation to Merck and Co., Inc., of Rahway, N. J., for the generous gift of the pyrimidine derivative used in this work.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Ethyl-α-(β-ethoxyethyl)acetoacetate. This was prepared from acetoacetic ester and ethyl-β-bromoethyl ether essentially according to Clarke and Gurin (12), except that dioxane was used as a solvent. Consistent yields of 56% were obtained. The product boiled at 113–117° at 10 mm. Clarke and Gurin report the boiling point 85–90° at 10 mm.; n_D^{25} 1.4281.

Anal. Calc'd for $C_{10}H_{18}O_4$: C, 59.4; H, 9.0.
Found: C, 59.7; H, 9.0.

Ethyl-α-(β-ethoxyethyl)-β-aminocrotonate (IV). A suspension of 21 g. of ammonium nitrate in 65.6 g. of the above acetoacetic ester was placed in a pressure bottle equipped with a rubber-gasketed spring top. The mixture was saturated with dry ammonia gas at 0°, during which the addition-compound of ammonia and ammonium nitrate separated as a heavy liquid. The bottle was sealed and slowly heated to 65° in water during 4 hours, and the temperature was then held at 65–70° for 3 hours longer. After cooling, the contents of the bottle were dissolved in ether, washed with water, dried with magnesium sulfate, and distilled at reduced pressure. The yield of aminocrotonic ester boiling at 96.5–98.5° at 0.4 mm. was 55.2 g. or 85%. The substance melts at 13–14° and slowly decomposes on standing at room temperature. It is reasonably stable when stored in the refrigerator.

Anal. Calc'd for $C_{10}H_{19}NO_3$: N, 7.0. Found: N, 7.0.

2-Methyl-3-(β-ethoxyethyl)-4,6-dihydroxy-5-carbethoxypyridine (V). Following the general method of Knoevenagel and Fries (8), 3.5 g. of sodium was dissolved in 60 cc. of absolute alcohol which had been distilled directly into a bomb tube.

Thirty and four-tenths grams of the above aminocrotonic ester and 24.2 g. of diethyl malonate were added, the tube was sealed and heated at 145–150° for 8 hours. At the end of the reaction the contents of the tube was a solid mass of matted needles of the sodium salt of the hydroxypyridine. These were filtered off and washed thoroughly with dry ether. The sodium salt was dissolved in water, and the solution was filtered through a wet filter paper to remove traces of malonic ester. The aqueous solution was carefully acidified with hydrochloric acid until it was just acid to Congo red, and the bulky precipitate of hydroxypyridine was filtered off and recrystallized from alcohol. The yield was 25 g. or 62%. The substance is soluble in dilute sodium hydroxide solution and also in dilute sodium carbonate and mineral acids; it is difficultly soluble in sodium bicarbonate. It gives an orange-red color with ferric chloride solution. It forms needles which melt at 174–176°.

Anal. Calc'd for $C_{13}H_{19}NO_5$: C, 58.0; H, 7.1.
Found: C, 58.4; H, 7.3.

The *dioxime* of the above pyridone was prepared by refluxing with excess hydroxylamine in alcoholic solution for several hours during which the solution turned blue. The dioxime crystallized from alcohol as fine, slender, colorless prisms, which melted at 240–242° with decomposition.

Anal. Calc'd for $C_{13}H_{21}N_3O_5$: C, 52.2; H, 7.0.
Found: C, 52.3; H, 6.7.

2-Methyl-3-(β-ethoxyethyl)-4,6-dihydroxypyridine (IX). A solution of 46 g. of 2-methyl-3-(β-ethoxyethyl)-4,6-dihydroxy-5-carbethoxypyridine in 250 cc. of 10% sodium hydroxide solution was refluxed for 3 hours. The hot, filtered solution was carefully acidified with hydrochloric acid until just acid to Congo red. Saturated sodium acetate solution was then added until the solution was neutral to Congo red but acid to litmus. An abundant evolution of carbon dioxide occurred during the acidification. After digesting on the steam-bath for 1 hour, the hydroxypyridine was collected with water. The yield was 30 g. or 87%. The material as thus obtained is sufficiently pure for further work. In order to secure an analytically pure sample, the substance was boiled for 5 hours with 10% hydrochloric acid in order to complete the decarboxylation. The cooled solution was carefully neutralized with sodium hydroxide. The dihydroxypyridine was recrystallized by addition of water to its alcoholic solution, followed by boiling off most of the alcohol. As thus obtained it formed fine, fluffy, colorless prisms which melted with decomposition at 290–293° in a copper block (13).

Anal. Calc'd for $C_{10}H_{15}NO_3$: C, 60.9; H, 7.7.
Found: C, 60.9; H, 7.8.

2-Methyl-3-(β-ethoxyethyl)-4,6-dichloropyridine (X). Thirty grams of the above dihydroxypyridine was refluxed with 150 cc. of phosphorus oxychloride for 6 hours. The excess of phosphorus oxychloride was removed under reduced pressure and the residual liquid, after addition of water, was made strongly alkaline with solid potassium hydroxide. The red, alkaline solution was steam distilled until no more chloropyridine came over, about 3 l. of distillate being collected. The steam distillate was extracted with ether, and after drying with magnesium sulfate, the dichloropyridine was distilled at reduced pressure, yielding 12.1 g. of colorless oil which boiled at 98–99° at 0.4 mm. The alkaline solution after the steam distillation was

carefully neutralized with hydrochloric acid and 13 g. of unreacted dihydroxypyridine was recovered. The yield of dichloropyridine was, therefore, 64% based on the dihydroxypyridine reacted.

Anal. Calc'd for $C_{10}H_{13}Cl_2NO$: C, 51.3; H, 5.6; Cl, 30.3.
Found: C, 50.7; H, 5.6; Cl, 32.5.

From the analytical figures, apparently partial cleavage of the ether group took place during this treatment. Subsequent operations, however, resulted in pure compounds.

2-Methyl-3-(β-ethoxyethyl)pyridine (XI). A solution of 15.2 g. of the above dichloropyridine and 6.35 g. of potassium acetate in methanol was shaken with 1 g. of palladium black (American Platinum Works) in an atmosphere of hydrogen at atmospheric pressure. After 4 hours, 3375 cc. of wet hydrogen at 25° and 733 mm. had been absorbed; calc'd for 2 moles of wet hydrogen: 3390 cc. The filtrate from the catalyst was concentrated to dryness under reduced pressure after the addition of 5 cc. of conc'd hydrochloric acid. The residue was dissolved in the minimum amount of water, the solution was saturated with potassium hydroxide, and then extracted with 8 portions of ether. After drying the ethereal solution, first with solid potassium hydroxide and then with sodium, the pyridine was distilled from sodium at reduced pressure. The yield of material boiling at 72–73° at 0.5 mm. was 9.1 g. or 84%.

The *picrate* crystallized as fine, lemon-yellow needles on addition of about 5 volumes of ether to its concentrated alcoholic solution, and melted at 63–64°.

Anal. Calc'd for $C_{16}H_{18}N_4O_8$: C, 48.7; H, 4.6.
Found: C, 49.0; H, 4.4.

The *chloroplatinate* crystallized as orange tablets from alcohol containing a trace of hydrochloric acid. It melted with decomposition at 165–168°.

Anal. Calc'd for $(C_{10}H_{15}NO\cdot HCl)_2\cdot PtCl_4$: C, 32.4; H, 4.4.; Pt, 26.4.
Found: C, 32.8; H, 4.6; Pt, 26.7.

The *chloraurate* formed yellow tablets from alcohol acidulated with hydrochloric acid and melted at 108–109°.

Anal. Calc'd for $C_{10}H_{15}NO\cdot HAuCl_4$: C, 23.8; H, 3.2; Au, 39.0.
Found: C, 23.8; H, 3.3; Au, 39.2.

2-Methyl-3-(β-chloroethyl)pyridine. A solution of 4.2 g. of the above ethoxyethylpyridine in 35 cc. of conc'd hydrochloric acid was heated in a sealed tube at 150° for 3 hours (12). The contents of the tube were decolorized with carbon (Norit) and then concentrated to dryness under reduced pressure several times with water. Portions of the crystalline residue were removed for the preparation of derivatives and the main amount was hydrolyzed further as indicated below.

The *picrate* crystallized as silky, lemon-yellow needles from alcohol and melted at 134–135°.

Anal. Calc'd for $C_{14}H_{13}ClN_4O_7$: C, 43.7; H, 3.4.
Found: C, 43.8; H, 3.6.

The *chloroplatinate* formed stout, orange needles or prisms from water acidulated with hydrochloric acid, and melted with decomposition at 189–190°.

Anal. Calc'd for $(C_8H_{10}ClN\cdot HCl)_2\cdot PtCl_4$: C, 26.6; H, 3.1; Pt, 27.1.
Found: C, 26.6; H, 3.1; Pt, 27.3.

The *chloraurate* was recrystallized by careful dilution of its cold alcoholic solution. It formed stout, lemon-yellow prisms and melted at 116–117°.

Anal. Calc'd for $C_8H_{10}ClN\cdot HAuCl_4$: C, 19.5; H, 2.2; Au, 39.8.
Found: C, 19.7; H, 2.5; Au, 39.9.

2-Methyl-3-(β-hydroxyethyl)pyridine (II). The above chloroethylpyridine hydrochloride was heated with 50 cc. of water in a sealed tube at 160° for 4 hours. The contents of the tube were decolorized with carbon (Norit) and concentrated to about 10 cc. under reduced pressure. The solution was then saturated with potassium hydroxide and exhaustively extracted with chloroform. The combined chloroform extracts were dried with magnesium sulfate and concentrated to about 5 cc. On addition of petroleum ether (Skellysolve B), the pyridine crystallized as the monohydrate after scratching and chilling. It was recrystallized from chloroform-petroleum ether and formed stout prisms which melted at 61–62°. The hydrate is unusually stable and distills unchanged at 120–125° at 0.5 mm. It is sparingly soluble in ether, although freely soluble in chloroform and methyl and ethyl alcohol.

Anal. Calc'd for $C_8H_{11}NO \cdot H_2O$: C, 61.9; H, 8.5.
Found: C, 62.2; H, 8.9.

The *picrate* formed fine needles from alcohol-ether and melted at 123–124°.

Anal. Calc'd for $C_{14}H_{14}N_4O_8$: C, 45.9; H, 3.9.
Found: C, 46.3; H, 4.1.

The *methiodide* was prepared by refluxing the pyridine hydrate with excess methyl iodide for 15 min. It formed hygroscopic prisms which melted at 103–104°.

Anal. Calc'd for $C_9H_{14}INO$: C, 38.8; H, 5.0.
Found: C, 39.1; H, 5.1.

The p-*nitrobenzoyl derivative* was prepared by boiling 1 equivalent of the pyridine hydrate with 2 equivalents of *p*-nitrobenzoyl chloride in pyridine for 2 min. and working up in the usual manner. It crystallized from alcohol as micaceous, flat needles, and melted at 114–115°.

Anal. Calc'd for $C_{15}H_{14}N_2O_4$: C, 62.9; H, 4.9.
Found: C, 62.5; H, 5.0.

The relative positions of the substituents in the pyridine was shown by oxidation to quinolinic acid with alkaline permanganate. The acid so obtained, after isolation as the copper salt, lost carbon dioxide at about 183° and then showed the characteristic melting point of nicotinic acid, 232°, which behavior is specific for quinolinic acid (14).

Anal. Calc'd for $C_7H_5NO_4$: C, 50.3; H, 3.0.
Found: C, 50.5; H, 2.9.

1-[(4-Amino-2-methyl)-5-pyrimidylmethyl]-2-methyl-3-(β-hydroxyethyl)pyridinium bromide hydrobromide (XII). A suspension of 0.5 g. of 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide and 0.305 g. of 2-methyl-3-(β-hydroxyethyl)pyridine hydrate in 20 cc. of light petrolatum (Merck) was heated at 100° for 1 hour. The pyrimidine and pyridine were gradually replaced by a gummy substance, which was continuously worked around with a glass rod. After cooling, the solid was centrifuged and thoroughly washed with petroleum ether (Skellysolve B). It was recrystallized from absolute alcohol, and formed hygroscopic fine needles which charred at 240–260°. For analysis the substance was dried at 100° and 20 mm., and still retained one molecule of water of crystallization.

Anal. Calc'd for $C_{14}H_{20}Br_2N_4O \cdot H_2O$: C, 38.4; H, 5.1.
Found: C, 38.5; 38.0; H, 4.7, 4.7.

Ethyl-β-acetaminocrotonate (XIII). The direct condensation of ethyl acetoacetate with acetamide has been described by Canzoneri and Spica (10), who, however, give but scanty experimental details. We have found the following procedure to lead to the best yields. A mixture of 19.5 g. of ethyl acetoacetate, 8.9 g. of acetamide, and 0.5 g. of anhydrous aluminum chloride was heated in a small

distilling flask in an oil-bath at 150–170° for 30 min., during which time 7.4 g. of distillate boiling up to 110° was collected. This consisted mostly of water and acetoacetic ester. The temperature of the bath was then raised and a fraction of 9.8 g. boiling up to 210° was collected. A third fraction of 5.6 g. of material boiling above 210° solidified in the receiver to a fine mass of crystals. The last fraction was dissolved in a little warm alcohol and the solution was diluted with 10 volumes of water. After thorough chilling the acetaminocrotonic ester was collected and dried at atmospheric pressure over calcium chloride. The fraction boiling from 110° to 210° deposited some crystalline material after refrigerating. This was filtered off and recrystallized from dilute alcohol. The total yield of material melting at 63–65° was 6.6 g. or 39%. Collie (9b) reports 63–65° as the melting point for the stable, or β-form, of ethyl β-acetaminocrotonate. Attempts to improve the yield by carrying out the reaction in sealed tubes, or by removing the water formed by use of the azeotropic mixture with *p*-cymene resulted in no definite product.

Ethyl-α-(β-ethoxyethyl)-β-acetaminocrotonate (XV). Because of the apparent splitting of the ether group in ethyl α-(β-ethoxyethyl)acetoacetate when aluminum chloride is used, this substance was prepared by direct acetylation of ethyl α-(β-ethoxyethyl)-β-aminocrotonate. A mixture of 10 g. of the aminocrotonic ester and 9.3 cc. of acetic anhydride was refluxed for 30 min., and the excess acetic anhydride and acetic acid were then removed at reduced pressure. The residue was distilled at reduced pressure and the fraction boiling at 118–120° at 0.5 mm. was collected. The yield was 9.7 g. or 80%; n_D^{25} 1.4857.

Anal. Calc'd for $C_{12}H_{21}NO_4$: C, 59.3; H, 8.7.
Found: C, 59.4; H, 8.6.

The same substance was also obtained in 68% yield by refluxing a mixture of 10 g. of the aminocrotonic ester, 18.6 cc. of acetic anhydride, and 10 cc. of dry pyridine for 30 min., and in poorer yield by acetylating with acetyl chloride in pyridine according to Benary (15).

All attempts to close the ring in either of the above acetaminocrotonic esters to a dihydroxypyridine by heating with sodium in toluene (11), or in dioxane, or by heating with sodium ethoxide in a sealed tube, resulted in the formation of unworkable tars.

Diethyl α-acetyl-α-(β-ethoxyethyl)glutarate. Four hundred grams of ethyl α-(β-ethoxyethyl)acetoacetate was slowly added to a suspension of 45.6 g. of finely cut sodium in 1900 cc. of absolute ether. When all the sodium had reacted, the mush of sodium salt was chilled to 0° and 20 g. of sodium iodide was added. Then 394 g. of ethyl β-bromopropionate was added with mechanical stirring, at such a rate that the temperature remained at 0°. The mixture was stirred for 48 hours at 0° and finally for 24 hours at room temperature. A liter of water was added, the ethereal layer was separated, and the aqueous layer was extracted several times with ether. After drying, the product was distilled at reduced pressure, giving 285 g. of the acetylglutaric ester which boiled at 133–136° at 1 mm.

Anal. Calc'd for $C_{15}H_{26}O_6$: C, 59.6; H, 8.7.
Found: C, 59.5; H, 8.7.

Ketonic decomposition of this β-keto ester was attempted using both dilute acid and dilute alkali, hot and cold. Likewise the method of Connor and Adkins (16) was used. In all cases a complex mixture of reaction-products was obtained from which no chemical individual could be isolated.

The microanalyses reported in this paper were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. 2-Methyl-3-(β-hydroxyethyl)pyridine has been synthesized and condensed with the pyrimidine component of thiamine to yield the pyridine analog, or isoster, of thiamine.

2. We have been unable to duplicate the reported internal condensation of β-acetaminocrotonic esters to dihydroxypyridine derivatives.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES IN THE PYRIDINE SERIES. III. SYNTHESIS OF 2,3-DIALKYLPYRIDINES FROM α-FORMYL KETONES

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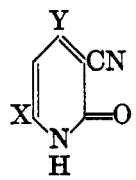
The use of α-hydroxymethylene, or α-formyl, ketones as possible sources of pyridine derivatives appears to have been incompletely explored, and such information as is available is of a rather conflicting nature. Sen-Gupta (1) condensed hydroxymethylenecyclohexanone with cyanoacetamide and obtained derivatives of *bz*-hexahydroquinoline. In this particular case the question whether the exact mechanism of the reaction proceeds through a Knoevenagel type reaction, or through a Michael addition of the cyanoacetamide to the ethylenic double bond of the hydroxymethylene ketone, is irrelevant since the same final product would be obtained in both cases. Sen-Gupta also reported the condensation of the hydroxymethylene derivative of diethyl ketone with cyanoacetamide as resulting in the formation of 3-cyano-5-methyl-6-ethyl-2-pyridone. No proof of structure of the latter was offered. Bardhan (2), in a study of the condensation of various β-dicarbonyl compounds with cyanoacetamide, noted that in an unsymmetrical substance of the type formula XC(OH):CHCOY two possible products might arise by such a condensation depending on whether the β-dicarbonyl derivative reacted in the ketonic or enolic form in the sense of the above type formula. I or II might thus result. It was found that with ethyl acetylpyruvate, the



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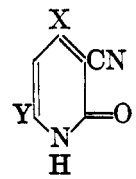


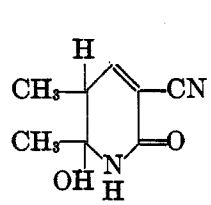
II

presence of the strongly electronegative carbethoxy group caused the condensation to yield exclusively the product corresponding to I, whereas in the similar condensation of propionylacetone with cyanoacetamide, two products were obtained. This question has been discussed more recently by Barat (3), who agreed with Sen-Gupta that the condensation of hydroxymethylene ketones with cyanoacetamide probably proceeds through a Michael addition. However, the structures assigned by Barat to his

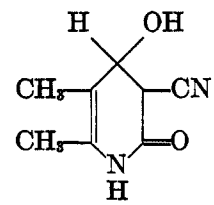
condensation-products appear to be lacking rigid proof. Furthermore the existing conflicting evidence concerning the structures of hydroxymethylene ketones derived from open-chain ketones of the type CH_3COCH_2R renders the structures of the pyridines prepared from them open to question in so far as the latter have been assigned.

In the condensation of ethyl formate with an unsymmetrical ketone of the above type, the possibility exists for the introduction of the formyl group on either side of the carbonyl group. However, in the condensation of methylethyl ketone with ethyl formate, at least, evidence is at hand, as a result of the investigations of Claisen and Meyerowitz (4) and of Diels and Ilberg (5), that the formyl group is introduced on the methylene rather than on the methyl group of the ketone. The resulting product thus is presumably 3-formylbutanone-2. On the other hand, Benary (6) has indicated that the condensation of ethyl formate with methylethyl ketone leads to a mixture of the two possible condensation-products. At the same time, he reports that the similar condensation of methyl-*n*-propyl ketone with ethyl formate leads exclusively to $HOCH:CHCOC_3H_7$, a finding which is difficult to reconcile with the data on the lower homolog. Therefore, if the product of the condensation of methylethyl ketone with ethyl formate is a mixture, then two pyridones, namely 3-cyano-5,6-dimethyl-2-pyridone and 3-cyano-6-ethyl-2-pyridone, should result from the condensation of the product with cyanoacetamide, and further, if condensation of the formyl ketone with cyanoacetamide takes place in the sense of a Knoevenagel reaction and of a Michael addition simultaneously, then 3-cyano-4,5-dimethyl-2-pyridone becomes a possible product. Barat (3) reports such a condensation, and assigns to the product the structure of 3-cyano-6-ethyl-2-pyridone, on the assumption that the formyl ketone is 1-formylbutanone-2. We now find Barat to be in error, and have shown that his substance is actually 3-cyano-5,6-dimethyl-2-pyridone.

When crude formyl methylethyl ketone is condensed with cyanoacetamide in the presence of piperidine, the sole product isolated is a hydroxy-3-cyano-5,6-dimethyldihydro-2-pyridone. Two structures for this substance are possible, III and IV. A structure of type III is favored by Sen-Gupta (1) in his work on hydroxymethylenecyclohexanone, while Barat (3) believes a structure similar to IV to be correct. We are inclined

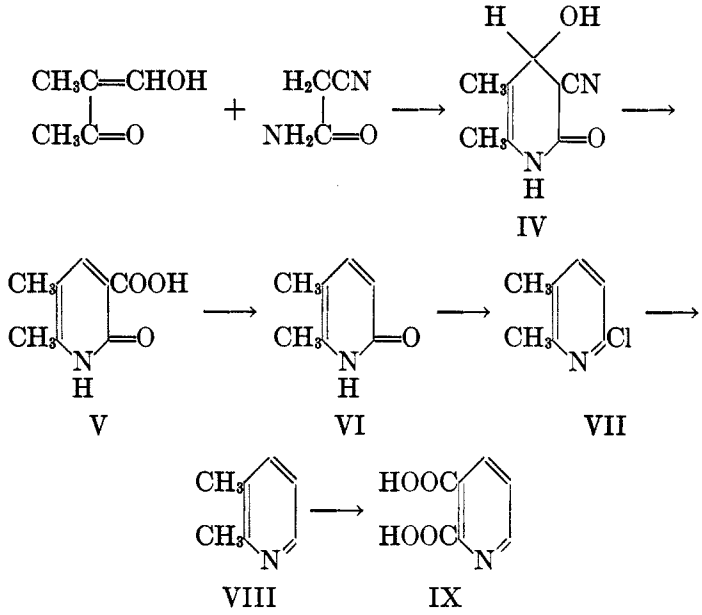


III



IV

to favor the second possibility, IV, since the substance readily yields an acetate with acetic anhydride. It is unlikely that the tertiary hydroxyl group of III would acetylate so easily. On hydrolysis of the nitrile group in IV with concentrated hydrochloric acid, 3-carboxy-5,6-dimethyl-2-pyridone (V) was obtained. The latter, on heating to its melting point gave 2-hydroxy-5,6-dimethylpyridine (VI). By the usual methods of treatment with phosphorus pentachloride, VI was converted to the corresponding chloropyridine (VII), which, on catalytic reduction with palladium, gave 2,3-dimethylpyridine (VIII) the structure of which was shown by comparison of the picrate with a known sample (7), and by



oxidation to quinolinic acid (IX). As a result of this series of reactions we conclude that, in so far as the formation of pyridine derivatives may be taken as evidence, the condensation of ethyl formate with methylethyl ketone yields 3-formylbutanone-2, and, further, that a derivative of 2,3-dimethylpyridine is the sole product of the reaction between the formyl ketone and cyanoacetamide, regardless of the mechanism by which the latter reaction may take place. Whether the same considerations hold for the higher homologs of methylethyl ketone awaits further investigation.

With this experience in mind we have attempted to apply the above general method to the preparation of 2-methyl-3-(β-hydroxyethyl)-pyridine preparatory to using this substance in the synthesis of the isoster of thiamine. Methyl-γ-ethoxypropyl ketone, prepared by the acetoacetic

ester synthesis, was condensed with ethyl formate in the presence of sodium. The resulting formyl ketone polymerized so easily that it was impossible to keep it in a state of purity. Therefore, it was immediately condensed in the crude state with cyanoacetamide, yielding a small amount of a substance to which the structure, 3-cyano-5-(β-ethoxyethyl)-6-methyl-2-pyridone, has been tentatively assigned. The major part of the formyl ketone polymerized before condensation had taken place. The cyanopyridone, on treatment with hydrobromic acid in a sealed tube, gave a poor yield of a substance which furnished analytical figures corresponding approximately to the expected 5-(β-bromoethyl)-6-methyl-2-pyridone. Further work along this line was abandoned in view of the poor yields.

EXPERIMENTAL

All melting points are corrected for stem exposure.

3-Cyano-5,6-dimethyl-4-hydroxydihydro-2-pyridone (IV). In view of the high vapor pressure of 3-formylbutanone-2, this substance was not isolated in the pure state. It was prepared according to the general procedure of Diels and Ilberg (5). Forty-six grams of finely sliced sodium was added to a vigorously stirred solution of 144 g. of carefully dried methylethyl ketone and 148 g. of pure ethyl formate in 2 l. of dry ether over a period of 4 hours, during which the mixture was chilled in an ice-salt freezing-bath. The mixture was then stirred for 14 hours at room temperature. It was chilled and the crystalline sodium salt was filtered off and washed thoroughly with dry ether. The sodium salt was dissolved in cold water, the solution was carefully acidified with dilute sulfuric acid, and then extracted with ether. After drying, the ether was removed by very careful distillation through a 20 cm. Vigreux column, and the residual solution was dissolved in 1 l. of commercial absolute alcohol. Eighty-four grams of cyanoacetamide was added and the solution was warmed until the cyanoacetamide completely dissolved. Fifty cubic centimeters of piperidine was added, the mixture was refluxed for 2 hours, and then refrigerated overnight. The crystalline deposit was collected and ground up with a little water to remove water-soluble unreacted cyanoacetamide. The alcoholic mother liquors were refluxed for a further 6 hours, after addition of 10 cc. of piperidine, and deposited a second crop of pyridone. The total yield of crude pyridone was 38 g. After recrystallization from acetic acid the pyridone formed stout, pale, yellow prisms which melted with decomposition at about 347° in a copper block (8). The substance was soluble in dilute sodium hydroxide solution and gave a faint red color with alcoholic ferric chloride solution.

Anal. Calc'd for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.1.
Found: C, 57.8; H, 6.4.

In an attempt to dehydrate the aldol formed as above, 13 g. of the aldol was refluxed with 100 cc. of acetic anhydride for 6 hours, during which the solid gradually went into solution. The cooled solution was diluted with 4 volumes of water and evaporated to about 100 cc. on the steam-bath. The crystalline precipitate was collected, after chilling, with water, and was recrystallized from acetic acid, from which it formed fine, silky needles melting with decomposition at 283–285°. The analytical data indicate that it is *3-cyano-4-acetoxy-5,6-dimethyldihydro-2-pyridone.*

Anal. Calc'd for $C_{10}H_{12}N_2O_3$: C, 57.7; H, 5.8; N, 13.5.
Found: C, 57.8; H, 5.9; N, 14.0.

3-Carboxy-5,6-dimethyl-2-pyridone (V). A suspension of 13 g. of 3-cyano-5,6-dimethyl-4-hydroxydihydro-2-pyridone in 150 cc. of conc'd hydrochloric acid was refluxed for 3 hours, during which the sparingly soluble material gradually went into solution. The mixture was diluted to about 300 cc. and, after chilling, the pyridone acid was collected and washed thoroughly with water. It was recrystallized from water, and formed fine, white needles which melted with decomposition at 310–312° in a copper block (8).

Anal. Calc'd for $C_8H_9NO_3$: C, 57.5; H, 5.4.
Found: C, 57.6; H, 5.6.

5,6-Dimethyl-2-hydroxypyridine (VI). Thirty-nine grams of the above pyridone acid was placed in a 1 l. round-bottom flask, the neck of which was loosely closed by a 200 cc. round-bottom flask through which cold water was circulated. The larger flask was then heated in a Wood's metal-bath. At a bath temperature of 325–335° vigorous evolution of carbon dioxide occurred and the decarboxylated pyridone sublimed copiously. After heating for 10 min. at this temperature, the contents of the flask were thoroughly extracted with chloroform. The filtered chloroform solution was concentrated to dryness and the residue was recrystallized from water with liberal use of decolorizing carbon (Norit). A second crop was obtained by evaporating the mother liquor to a small volume. The total yield was 25 g. The substance formed needles which melted at 208–209°.

Anal. Calc'd for C_7H_9NO: C, 68.3; H, 7.3.
Found: C, 68.3; H, 7.4.

2-Chloro-5,6-dimethylpyridine (VII). Thirty grams of 5,6-dimethyl-2-hydroxypyridine was placed in a 500 cc. distilling flask and moistened with 30 cc. of phosphorus oxychloride. The mixture was then heated to 100–120° and 45 g. of phosphorus pentachloride was added gradually during the course of 20 min. The bath temperature was then raised to 140° and held at that point for 45 min. After cooling, the phosphorus oxychloride was removed under reduced pressure, the residue was poured onto cracked ice, and the solution was made strongly alkaline with sodium hydroxide. The chloropyridine was steam distilled from this alkaline solution and extracted from the distillate with ether. On distillation it boiled at 100–101° at 18 mm. and melted at 10–11°. The yield was 24 g.

Anal. Calc'd for C_7H_8ClN: C, 59.3; H, 5.7.
Found: C, 59.5; H, 5.9.

The *picrate* formed yellow, glistening plates from alcohol and melted at 120.5–121°.

Anal. Calc'd for $C_{13}H_{11}ClN_4O_7$: C, 42.1; H, 3.0.
Found: C, 42.2; H, 3.1.

2,3-Dimethylpyridine (VIII). A solution of 24 g. of the above chloropyridine in 150 cc. of alcohol was shaken with 0.5 g. of palladium black (American Platinum Works) with hydrogen at 3 atm. pressure. Removal of the chlorine was complete in 3 hours. The filtrate from the catalyst was concentrated to dryness and the residue was made strongly alkaline with strong potassium hydroxide solution. The pyridine was extracted with ether, and, after drying with solid potassium hydroxide, was distilled from sodium, the fraction boiling at 161–164° amounting to 12.5 g. This agrees with the boiling point for 2,3-dimethylpyridine reported in the literature (7). The picrate melted at 187–188° and showed no depression when mixed with an authentic specimen (7).

Anal. Calc'd for $C_{13}H_{12}N_4O_7$: C, 46.4; H, 3.6.
Found: C, 46.5; H, 3.9.

In view of the sometimes misleading behavior of picrates in mixed melting point determinations, the identity of the above pyridine was confirmed by oxidation to quinolinic acid with alkaline permanganate solution. The acid so obtained evolved carbon dioxide at about 187° and the residue then showed the melting point of nicotinic acid, 233°, which behavior is specific for quinolinic acid (9).

Anal. Calc'd for $C_7H_5NO_4$: C, 50.3; H, 3.0.
Found: C, 50.3; H, 3.2.

γ-Ethoxypropylmethyl ketone. Ethyl α-(β-ethoxyethyl)acetoacetate (10) was hydrolyzed with 5% sodium hydroxide solution according to the general procedure of Johnson and Hager (11). The ketone was extracted from the acidified solution with ether. It boiled at 169–172°. The yield was 70%.

Anal. Calc'd for $C_7H_{14}O_2$: C, 64.6; H, 10.8.
Found: C, 64.3; H, 11.3.

1-Ethoxy-3-formylpentanone-4. A mixture of 100 g. of γ-ethoxypropylmethyl ketone and 57 g. of dry ethyl formate was added dropwise with stirring during the course of 4–5 hours to an ice-cold suspension of 17.7 g. of very finely cut sodium in 300 cc. of dry petroleum ether (Skellysolve B). The mixture was stirred at 0° for 22 hours. The bulky sodium salt of the formyl ketone was centrifuged, washed with petroleum ether, and dissolved in water. The aqueous solution was acidified with cold dilute sulfuric acid and extracted with ether as rapidly as possible. The ethereal extract was dried rapidly with magnesium sulfate, and the residue was distilled under reduced pressure, the fraction boiling at 70–85° at 11 mm. being collected. A dark brown tar remained in the flask. The yield was 24.7 g. The formyl ketone polymerizes and turns brown so rapidly that it was impossible to secure accurate analytical data. Likewise, attempts to prepare the usual carbonyl derivatives were unsuccessful because of the rapid polymerization of the ketone. The boiling point of the substance as accurately as could be determined was 85–87° at 14 mm. It was used directly and promptly for the subsequent condensation with cyanoacetamide.

3-Cyano-5-(β-ethoxyethyl)-6-methyl-2-pyridone. A solution of 14.7 g. of the above formyl ketone, 7.8 g. of cyanoacetamide, 3 cc. of piperidine, and 1.73 cc. of acetic acid in 100 cc. of alcohol was refluxed for 5–6 hours and then allowed to stand at room temperature for 3 days. The alcohol was removed at reduced pressure, and the residue was extracted with chloroform, which left 3.3 g. of unreacted insoluble cyanoacetamide. The combined chloroform extracts were washed with water, and the chloroform was removed, leaving a crystalline residue of 3.9 g. This was recrystallized from alcohol, and formed fine, fluffy needles which melted at 179–181°.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 64.0; H, 6.8.
Found: C, 64.1; H, 6.8.

The nitrile group in the above compound was hydrolyzed by heating with 48% hydrobromic acid in a sealed tube at 150–160° for 4 hours. The resulting product, which was obtained in poor yield, melted at 258°, with decomposition, after recrystallization from dilute alcohol. Analysis indicated that it was *5-(β-bromoethyl)-6-methyl-2-pyridone* contaminated with some undecarboxylated pyridone acid.

Anal. Calc'd for $C_8H_{10}BrNO$: C, 44.4; H, 4.7.
Found: C, 43.4; H, 4.6.

The substance was not investigated further because of the poor yields obtained.

The microanalyses reported in this paper were performed by Mr. Saul Gottlieb of these laboratories.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES IN THE PYRIDINE SERIES. IV. ETHYL PROPIONYLPYRUVATE: ITS CONDENSATION WITH PHENYLHYDRAZINE AND USE FOR THE SYNTHESIS OF 2-ETHYLISONICOTINIC ACID

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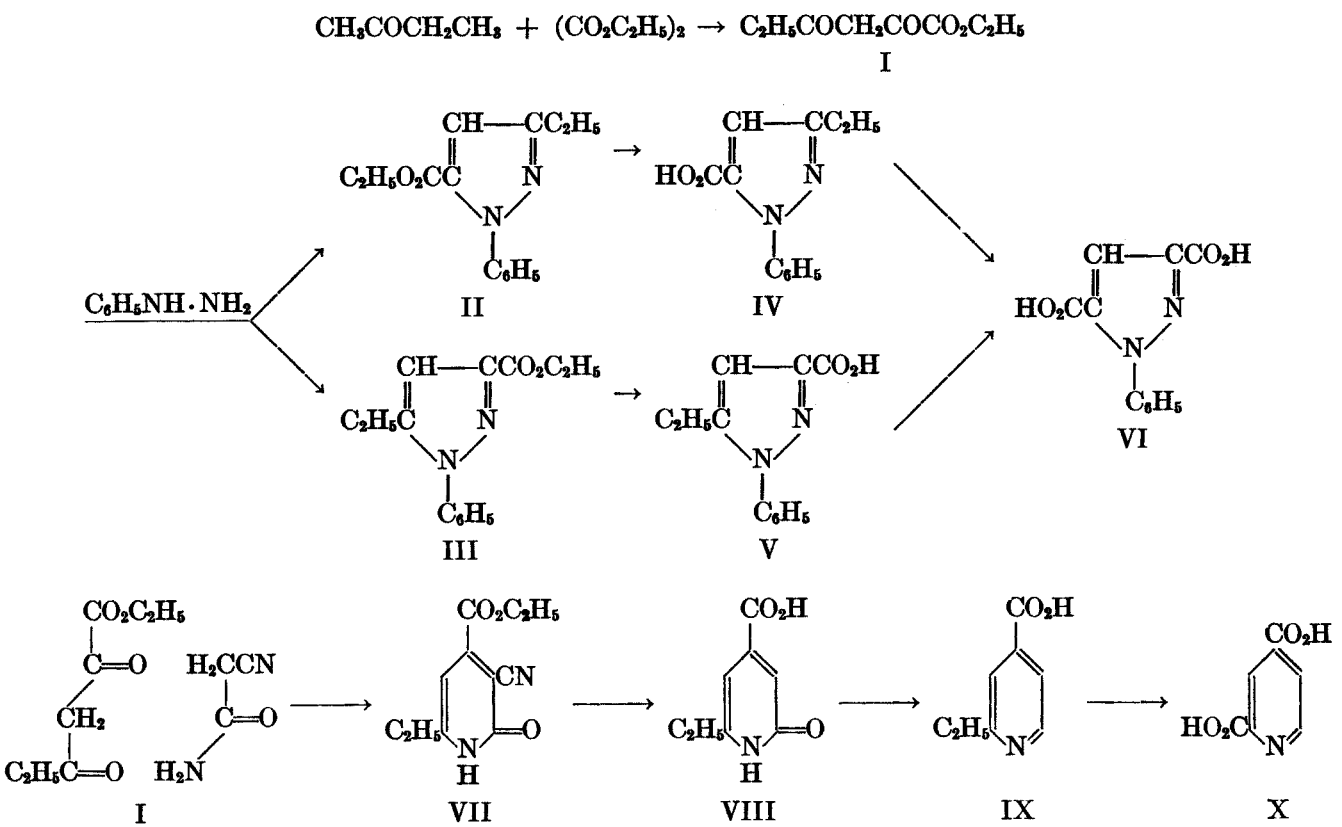
The condensation of ethyl acetylpyruvate with cyanoacetamide to yield 3-cyano-4-carbethoxy-6-methyl-2-pyridone has been reported by Bardhan (1). The possibility of using homologs of ethyl acetylpyruvate for the preparation of homologous pyridine derivatives does not seem to have been studied. Homologs of ethyl acetylpyruvate are commonly prepared by condensation of ethyl oxalate with an appropriate ketone in the presence of sodium ethoxide, according to the general method of Claisen, who prepared a variety of compounds of this nature. However, it is noteworthy that in the cases described by Claisen, *viz.*, those pyruvic esters formed by condensation of acetophenone (2), acetone (3), and mesityl oxide (4) with ethyl oxalate, as well as the ester described by Couturier (5) from pinacolone, condensation can reasonably be expected to occur on but one side of the carbonyl group of the ketone. Lapworth and Hann (6) condensed methyl-*n*-propyl ketone with ethyl oxalate and were unable to determine definitely whether the product possessed the structure $CH_3COCH(COCO_2C_2H_5)C_2H_5$ or $C_2H_5O_2CCOCH_2COC_3H_7$. Diels, Sielisch, and Müller (7) condensed two moles of ethyl oxalate with methylethyl ketone, but, beyond the fact that the ester condensed on both sides of the carbonyl group of the ketone, they did not show whether the first mole of ethyl oxalate condensed on the methyl or the methylene group of the ketone. As far as we have found, where two possible modes of condensation can occur, in no case has the nature of such condensation been demonstrated unequivocally.

Kötz and Lemien (8) described the alkylation of ethyl acetylpyruvate with sodium and methyl or ethyl iodide, the products of which reactions would presumably be identical with the compounds formed by condensation of ethyl oxalate on the methylene group of methylethyl and methylpropyl ketone, respectively. They also reported that the introduction of a second alkyl group into ethyl acetylpyruvate was impossible, and used the fact that the condensation-product of one mole of ethyl oxalate with

methylethyl ketone could be alkylated, as proof that this condensation takes place on the methyl group of the ketone. However, Favrel and Chrz (9) were unable to duplicate the alkylation experiments of Kötz and Lemien, so that the conclusions of the latter workers must be accepted with reservation.

In view of the fact that ethyl formate condenses on the methylene group of methylethyl ketone (10), it seemed not unlikely that ethyl oxalate might react in the same manner. The resulting substituted acetylpyruvic esters would then possess considerable advantages for synthetic purposes over the formyl esters, which are obtained generally in poor yield and are not easily manipulated, thus opening a comparatively simple route to 2,3-disubstituted pyridines. We have accordingly investigated the product of the condensation of one mole of ethyl oxalate with methylethyl ketone, with the object of definitely determining its structure and then of utilizing the substance as may be indicated.

As a result of investigations on the pyrazoles, largely by Claisen and by Knorr, all of the 1-phenylpyrazole carboxylic acids containing from one to three carboxyl groups have been characterized. These acids, therefore, furnish convenient reference substances for demonstrating the structure of the pyruvic ester in question. Ethyl oxalate condenses smoothly with methylethyl ketone (7) to give an apparently uniform product (I). No sign of a second condensation-product was observed. However, when the resulting ethyl propionylpyruvate was condensed with phenylhydrazine, two isomeric phenylpyrazole derivatives (II and III) were obtained. The nature of the isomerism was demonstrated by hydrolysis of the ester group and oxidation of the ethyl side chain to carboxyl, although we have been unable to make a definite decision which of the formulas II and III should be assigned to the respective phenylpyrazoles. On saponification of the ester groups in II and III, two isomeric acids (IV and V) were obtained. Oxidation of the ethyl side chain in IV and V with alkaline permanganate resulted in the formation of the same dibasic acid from both compounds, namely 1-phenylpyrazole-3,5-dicarboxylic acid (VI), which has been described by Claisen and Roosen (11). If the cause of the isomerism of the two pyrazole derivatives were due to the presence of a mixture of pyruvic esters corresponding to condensation of ethyl oxalate on both sides of the carbonyl group of methylethyl ketone, then the final product of the permanganate oxidation of one of the isomers would have been 1-phenylpyrazole-3,4,5-tricarboxylic acid, which has been described by Knorr and Laubmann (12). The structure of the initial condensation-product, I, therefore is that of ethyl propionylpyruvate, and the condensation of ethyl oxalate with methylethyl ketone takes a different course than does the condensation of ethyl formate with this ketone.


CH3COCH2CH3 + (CO2C2H5)2 → C2H5COCH2COCO2C2H5
I
C6H5NH·NH2
II
IV
III
V
VI
I
VII
VIII
IX
X

With this experience in mind, the condensation of ethyl propionylpyruvate with cyanoacetamide was investigated. The pyruvic ester condenses with cyanoacetamide in the presence of piperidine (1) to give a substance to which has been assigned the structure of 3-cyano-4-carbethoxy-6-ethyl-2-pyridone (VII) on the basis of Bardhan's experience with the similar condensation of ethyl acetylpyruvate (1). No trace of an isomeric pyridone was noted. Hydrolysis of the nitrile group in VII and loss of carbon dioxide gave 4-carboxy-6-ethyl-2-pyridone (VIII), which, on replacement of the hydroxyl group by hydrogen through the chloro derivative and catalytic reduction of the latter, gave 2-ethylisonicotinic acid (IX), in which the relative position of the substituents was shown by oxidation to lutidinic acid (X). Attempted decarboxylation of both VII and IX by a variety of methods was unsuccessful.

The preceding observations provide confirmation of the conclusions of Mumm and Böhme (13), who arrived at 3,6-dialkyl derivatives of isocinchomeronic acid by condensation of acetylpyruvic esters, prepared as above, with β-aminocrotonic ester. These workers, however, offered no structural proof of the constitution of their products, and hence produced no evidence concerning the structure of the product of the condensation of ethyl oxalate with methylethyl ketone.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Condensation of ethyl propionylpyruvate with phenylhydrazine (II and III). The reaction was carried out according to the general procedure of Claisen and Roosen (11). Thirty-eight grams of phenylhydrazine was slowly added to a solution of 60 g. of ethyl propionylpyruvate, prepared according to Diels, Sielisch, and Müller (7), in 150 cc. of glacial acetic acid, the mixture being cooled under the tap. After refluxing for 16 hours the solution was poured onto cracked ice and the mixture of pyrazole esters was extracted with ether. After washing the ethereal extracts free from phenylhydrazine with dilute acetic acid, the esters were fractionated at reduced pressure. The lower-boiling pyrazole ester, a light, yellow oil, was collected at 125–127° at 0.3 mm. and amounted to 23.7 g.; n_D^{25} 1.5488.

Anal. Calc'd for $C_{14}H_{16}N_2O_2$: C, 68.8; H, 6.6.
Found: C, 68.8; H, 6.4.

The isomeric ester was a much thicker, yellow oil and boiled at 152–154° at 0.3 mm. The yield was 37.6 g.; n_D^{25} 1.5554.

Anal. Found: C, 68.7; H, 6.6.

The isomeric phenylethylpyrazole acids (IV and V). The above esters were hydrolyzed by refluxing for 3 hours with a 5% solution of sodium hydroxide in 50% alcohol. The alcohol was then removed under reduced pressure and the aqueous solution was filtered and acidified to Congo red with hydrochloric acid. The acids were recrystallized several times from benzene.

The acid from the lower-boiling pyrazole ester formed prisms and melted at 135–136°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: C, 66.6; H, 5.6.
Found: C, 66.9; H, 5.5.

The acid from the higher-boiling pyrazole ester crystallized as needles and melted at 140–141°. A mixture of the two acids melted at 110–115°.

Anal. Found: C, 66.7; H, 5.7.

1-Phenylpyrazole-3,5-dicarboxylic acid (VI). The above acids were oxidized with alkaline potassium permanganate, according to Claisen and Roosen (11). The dicarboxylic acid from both sources melted with decomposition at 270–272°, after recrystallization from water. This agrees with the melting point of 1-phenylpyrazole-3,5-dicarboxylic acid reported by Claisen and Roosen.

Anal. Calc'd for $C_{11}H_8N_2O_4$: C, 56.9; H, 3.5.
Found: For the acid from one source: C, 56.9; H, 3.4.
For the acid from the other source: C, 57.0; H, 3.6.

The *dimethyl esters* prepared from the dibasic acids from the two sources with methyl alcoholic hydrogen chloride melted at 124–125° after recrystallization from methanol. They showed no depression in melting point when mixed in the proportions of 1:1, 1:2, and 1:3, and likewise showed no depression when mixed with an authentic sample of the dimethyl ester of the pyrazole acid prepared according to Claisen and Roosen (11).

Anal. Calc'd for $C_{13}H_{12}N_2O_4$: C, 60.0; H, 4.7.
Found: For the ester from one source: C, 60.0; H, 4.9.
For the ester from the other source: C, 59.7; H, 4.8.

3-Cyano-4-carbethoxy-6-ethyl-2-pyridone (VII). Fifteen cubic centimeters of piperidine was added to a solution of 80 g. of ethyl propionylpyruvate and 39 g. of cyanoacetamide in 750 cc. of alcohol at 60°. The solution became warmer, and after standing about 30 min. the pyridone started to separate. After refrigerating overnight, the crystalline deposit was collected and recrystallized from glacial acetic acid. The pyridone formed pale yellow needles; and melted with decomposition at 217–218°. An additional small amount was obtained after the original mother liquors had stood for several days. The yield was 60 g.

Anal. Calc'd for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5.
Found: C, 59.5; H, 5.4.

4-Carboxy-6-ethyl-2-pyridone (VIII). A suspension of 40 g. of the above cyanopyridone ester in 360 cc. of conc'd hydrochloric acid was refluxed for 4 hours, during which the material gradually went into solution. The solution was diluted to about a liter and, after refrigerating, the pyridone acid was collected with water. After recrystallization from water it formed fine white prisms which melted with charring at 308° in a copper block (14). The yield was 28 g.

Anal. Calc'd for $C_8H_9NO_3$: C, 57.5; H, 5.4.
Found: C, 57.5; H, 5.6.

The pyridone acid, on methylation with diazomethane, gave *2-methoxy-4-carbomethoxy-6-ethylpyridine* which was isolated as the *picrate*. The latter formed plates from methanol and melted at 133–135°.

Anal. Calc'd for $C_{16}H_{16}N_4O_{10}$: C, 45.3; H, 3.8.
Found: C, 45.8; H, 4.1.

Attempts to remove carbon dioxide from the pyridone acid by heating with soda-lime, by heating the sodium salt with calcium hydroxide, or by several variations of the copper method of decarboxylation were unsuccessful.

2-Chloro-4-carboxy-6-ethylpyridine. Fifteen grams of the above pyridone acid was moistened with 25 cc. of phosphorus oxychloride in a 250 cc. distilling flask. The mixture was heated to 100–110° and 47 g. of phosphorus pentachloride was added in small portions. The mass was then heated at 125–140° for 45 min. after which

the phosphorus oxychloride was removed at reduced pressure, and the residue was poured onto cracked ice. The chlorinated pyridine was extracted with ether, and the residue, after removal of the ether, was stirred for 3 hours with warm 5% sodium hydroxide solution to hydrolyze any acid chloride present. The clear, alkaline solution was concentrated to dryness under reduced pressure, leaving a red crystalline deposit. This was dissolved in a little water and the solution was carefully acidified to Congo red with hydrochloric acid. The chloropyridine slowly crystallized on scratching and chilling. It is best purified by sublimation at 0.3 mm. using a bath temperature of 130–150°, followed by crystallization from water. The substance forms white needles and melts at 136–137°. The yield was 8.2 g.

Anal. Calc'd for $C_8H_8ClNO_2$: C, 51.6; H, 4.4.
Found: C, 51.6; H, 4.7.

2-Ethylisonicotinic acid (IX). The above chloropyridine acid was reduced by shaking a solution of 7.1 g. in 75 cc. of acetic acid in an atmosphere of hydrogen at atmospheric pressure with 0.3 g. of palladium black (American Platinum Works). One mole of hydrogen was absorbed in 10 hrs., during which the hydrochloride of the acid crystallized. The catalyst was filtered off and washed thoroughly with fresh acetic acid, and the filtrate was concentrated to dryness at reduced pressure. The residue was dissolved in a little water and the filtered solution was buffered until neutral to Congo red by addition of sodium acetate. The acid precipitated and was recrystallized from water. It formed white needles which melted with decomposition at 233–235°. The yield was 4.3 g.

Anal. Calc'd for $C_8H_9NO_2$: C, 63.6; H, 6.0.
Found: C, 64.0; H, 6.2.

We were unsuccessful in attempts to decarboxylate this acid, using a variety of procedures.

On oxidation of the above acid with alkaline potassium permanganate, lutidinic acid was obtained. After crystallization from water, the latter formed glittering plates which were air-dried, and melted at 247–249°. Meyer and Tropsch (15) report lutidinic acid monohydrate as melting at 248–250°.

Anal. Calc'd for $C_7H_5NO_4 \cdot H_2O$: C, 45.5; H, 3.8.
Found: C, 45.5; H, 4.1.

The microanalyses reported in this paper were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. Ethyl propionylpyruvate has been proved to be the product of the condensation of one mole of ethyl oxalate with methylethyl ketone, and, presumably, similar condensation of other methyl ketones with ethyl oxalate takes a like course.

2. Condensation of ethyl propionylpyruvate with phenylhydrazine results in the formation of two isomeric phenylpyrazole acids.

3. A convenient synthesis of 2-substituted isonicotinic acids is available by condensing ethyl acylpyruvates with cyanoacetamide, followed by elimination of the nitrile and hydroxyl groups in the primary condensation-product.

NEW YORK, N. Y.

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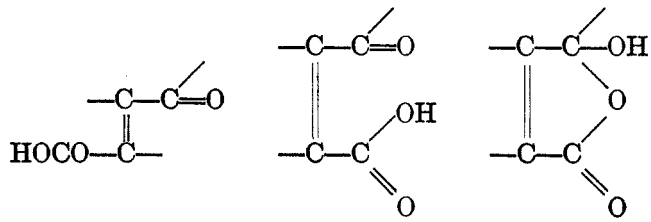
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

THE *CIS* AND *TRANS* 3-AROYL-2,3-DIMETHYLACRYLIC[1] ACIDS WITH PARTICULAR REFERENCE TO THE OPEN-CHAIN AND CYCLIC FORMS OF THE *CIS* DERIVATIVES

ROBERT E. LUTZ AND MONROE COUPER[2]

Received August 31, 1940

Substitution of groups on the ethylene linkage of the β-aroylacrylic acids affects in varying degree the interconversion of the *cis* and *trans* isomers (I and II), usually hindering the change in the direction *cis* to *trans* but often facilitating the change in the other direction from *trans* to *cis*, presumably through enhancing the tendency of the *cis* isomers to cyclize (*cf.* III).



I II III

Thus, *cis*-β-bromobenzoyl-α- and -β- methylacrylic acids evidently involve a mobile ring-chain shift (1) with both open-chain and cyclic derivatives easily obtainable; but aroylacrylic acids with alkyl or aryl substituents at both the α- and the β-positions (2) appear to exist and react chiefly in the cyclic forms (III).

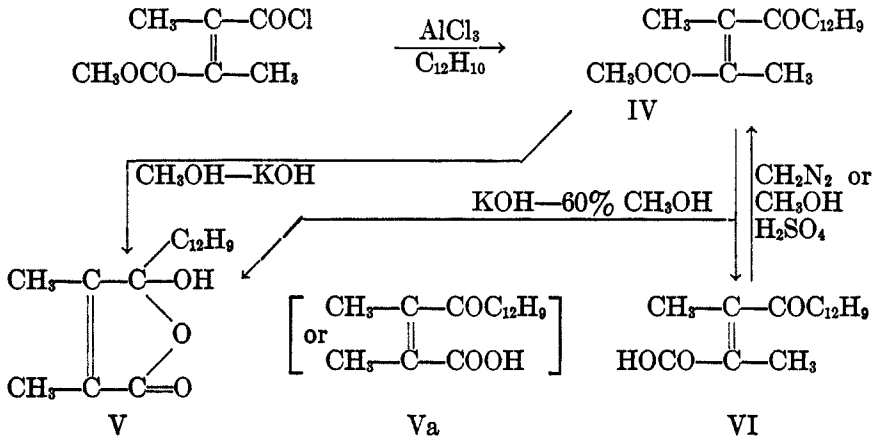
In view of the work done so far in this field, it seemed desirable to extend and complete the study of the β-aroyl-α,β-dimethylacrylic acids and their derivatives, particularly because the two methyl groups are certain to have a very pronounced effect on the tendency to cyclize, as is the case with dimethylmaleic acid.

The trans *acids and their methyl esters.* The phenyl and mesityl derivatives have already been made (2b). We have now prepared the *p*-xenyl

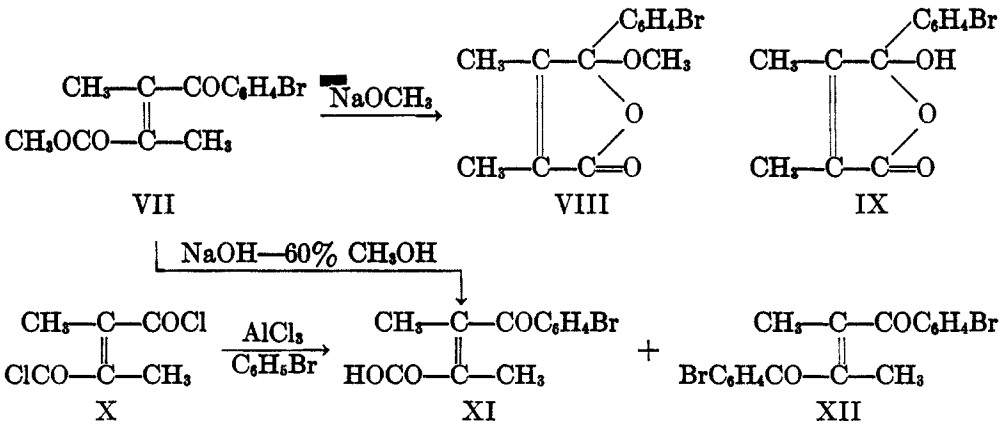
[1] Named in terms of acrylic rather than tiglic acid in order to minimize the use of special names in this field and to simplify the naming of compounds with various substituents on the ethylene linkage.

[2] Holder of a Philip Francis duPont Research Fellowship, 1937–1938; at present Instructor in Chemistry, University of Virginia.

(biphenyl) derivatives and have chosen them for particular study because of their advantageous melting points and crystallizability. The *trans* ester (IV) was prepared from dimethylfumaric monomethyl ester acid chloride by the Friedel-Crafts reaction (2b, 3). The free acid (VI) was obtained easily from the ester by hydrolysis with alkali in 60% methanol. Under these conditions only a very small amount of the *cis* acid was formed through stereochemical inversion. When hydrolysis was carried out in pure methanol as solvent, however, inversion to the *cis* configuration (V or Va) was the chief result. Since *trans*-β-xenoyldimethylacrylic acid once formed is stable towards alkali under the various conditions used, the stereochemical rearrangements must involve the ester directly or some intermediate phase during hydrolysis.



Esterification of the *trans* acid by diazomethane or methanol and sulfuric acid produced exclusively the *trans* ester (IV).

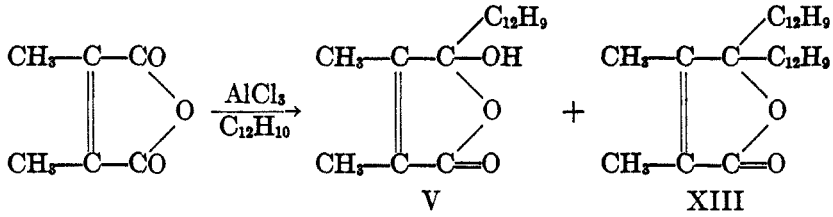


Trans-3-(*p*-bromobenzoyl)-2,3-dimethylacrylic acid (XI) also was prepared, and in two ways, through the ester (VII) obtained by the Friedel-Crafts reaction on dimethylfumaric monomethyl ester acid chloride, and also through the Friedel-Crafts reaction directly on dimethylfumaryl chloride (X). In the latter reaction a low yield of the aroylacrylic acid (XI) was obtained along with the unsaturated diketone (XII).

Alkaline hydrolysis of *trans*-bromobenzoyldimethylacrylic ester (VII) in 60% methanol gave exclusively in this case the *trans* acid (XI). However, when sodium methoxide in methanol was used instead as the reagent there was isolated a 10% yield of the cyclic *cis* ester (VIII) (better termed the *cis* "pseudo" ester). Thus, here also it is clear that rearrangement as well as cyclization involves the *trans* ester directly and precedes hydrolysis.

The preparation of the cis *acids.* The *cis* 3-aroyl-2,3-dimethylacrylic acids are best prepared directly by the Friedel-Crafts reaction on dimethylmaleic anhydride. Only the phenyl derivative has been reported and attempts to make the mesityl derivative led instead to the *trans* isomer (2b). We have now made the bromophenyl and xenyl compounds, V and IX.

In the reaction utilizing biphenyl,[3] the diaryl lactone (XIII) was invariably obtained as a by-product and special care had to be exercised in order to minimize its formation. The most favorable procedure was to add biphenyl to the reaction-mixture in carbon disulfide as solvent with the amount of biphenyl held to a practical minimum; the yield of β-xenoyldimethylacrylic acid (V) averaged 50% and the dixenyl lactone 15%. However, when the order of adding materials was reversed and dimethylmaleic anhydride was added to the reaction-mixture containing biphenyl in excess, the chief crystalline product was the dixenyl lactone (yield 25%) together with a 3% yield of the acid (V).



It is curious that in the parallel Friedel-Crafts reactions using benzene and bromobenzene, the formation of a diaryl lactone was not observed; if this reaction occurred at all, it did not interfere with the isolation of the β-aroyldimethylacrylic acid.

[3] This reaction was first carried out in this laboratory by Dr. H. M. Fitch (now at the Jackson Laboratory of duPont de Nemours & Company, Inc.).

This *cis*-β-xenoyldimethylacrylic acid and also the phenyl and bromophenyl analogs probably have cyclic structures corresponding to V because they are insoluble in sodium bicarbonate solution and dissolve very slowly in aqueous sodium carbonate, in contrast with the *trans* compounds corresponding to VI and XI, which dissolve readily. In the aroyldimethylacrylic acid series this difference between the *cis* and *trans* isomers in the rate of solution in weak alkali is unmistakable and to be contrasted with the much smaller and less significant difference between the rates of solution of the *cis* and *trans* β-bromobenzoyl-α- and β- monomethylacrylic acids (1d).

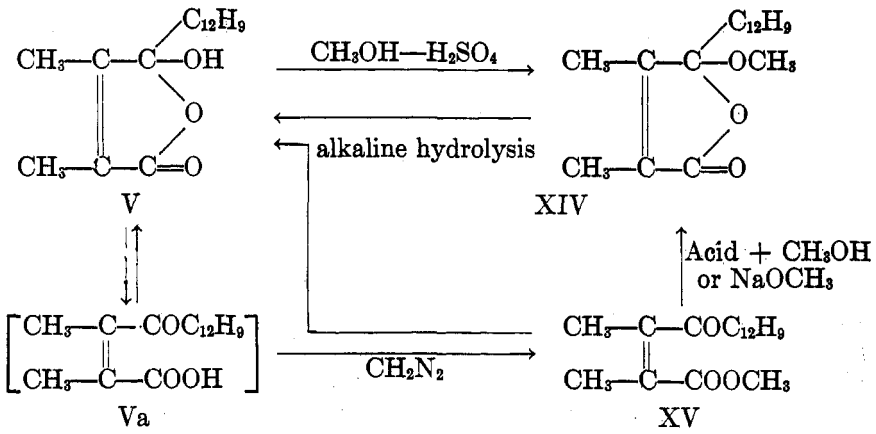
The formation of the dixenyl lactone (XIII) in the Friedel-Crafts reaction between dimethylmaleic anhydride and diphenyl is suggestive. A similar type of reaction has already been observed in Friedel-Crafts reactions with dibromomaleic anhydride (1e) and with *o*-benzoylbenzoic acid (4). Probably the reactions proceed through conversion of the acids into the cyclic acid chlorides (*cf.* XVI) under the conditions involved, a hypothesis which is plausible in view of the ease of formation of the cyclic acid halides of this type to be described below.

In connection with the foregoing discussion, an explanation in terms of steric hindrance might be suggested for the production of the *trans* rather than the *cis*-β-(trimethylbenzoyl)dimethylacrylic acid in the Friedel-Crafts reaction between dimethylmaleic anhydride and mesitylene (2b). Rearrangement here from *cis* to *trans* may be a consequence of two factors, steric hindrance by the mesityl group at the carbonyl to which it becomes attached, preventing formation of stabilizing intermediate complex ring compounds, and the unbalanced and inherently unstable *cis* configuration.

The isomeric cis *esters.* The esterification of acids which can exhibit ring-chain tautomerism may proceed in two ways. The action of diazomethane on the free acid, or of methyl iodide on the silver salt, has been found always to give the open-chain esters (5, 1), whereas acid catalysts and alcohol in the aroylacrylic acid series usually, but not always, produce cyclic (or "pseudo") esters.

With the xenyl *cis* acid (V or Va), diazomethane produces one ester easily and in good yield, whereas the action of boiling methanol with a trace of sulfuric acid gives the isomeric ester. These esters, therefore, must be, respectively, the open-chain and cyclic isomers, and are to be formulated as XV and XIV. Alkaline hydrolysis of both esters regenerates the *cis* acid (V).

In view of the esterification with diazomethane, it might be assumed that a mobile tautomerism exists between the two forms of the acid, V and Va, with the cyclic form (V) dominant. But this assumption is not necessarily correct, because a mechanism involving the cyclic form directly is conceivable, and will be considered in the subsequent paper.



Open-chain and pseudo methyl esters of *cis*-β-(*p*-bromobenzoyl)dimethylacrylic acid also have been made and hydrolyzed back to the same *cis* acid.

The previously reported methyl ester of *cis*-β-benzoyldimethylacrylic acid, prepared by the action of methanolic hydrogen chloride and formerly written as an open-chain compound (2b), is obviously cyclic in view of the mode of preparation, and corresponds therefore to XIV. The true open-chain methyl ester corresponding to XV has now been made by the action of diazomethane on the *cis* acid. The two isomeric esters are easily hydrolyzed back to the same *cis* acid.

Relative stability of open-chain and pseudo esters. As expected, the pseudo esters in the β-aroylacrylic acid series are the stable forms, and the open-chain isomers are labile and easily cyclized by the action of methanolic hydrogen chloride. The open-chain methyl ester in the xenyl series (XV) is converted into the cyclic isomer (XIV) also by the action of sodium methoxide under controlled conditions. This rearrangement is much more rapid than the rate of inversion of the *trans* ester to the *cis* acid during hydrolysis, as is shown by the fact that under given and comparable conditions the open-chain *cis* ester can be rearranged completely into the pseudo ester, whereas the *trans* ester is unchanged by the same treatment.

There seems at present to be no general rule as to which of the two types of esters is the stable and which the labile one. Among the ortho aldehydo and keto esters the cyclic forms seem generally to be the labile ones, although the opposite is true for the esters of *m*-opianic acid (6) and for derivatives of opianic acid itself with bromine or the nitro group in the position ortho to the aldehyde group (7). In the aliphatic types, mucobromic acid (8) and the many *cis* α- and β- mono- and di- substituted aroylacrylic esters, the open-chain isomers are the labile forms. However, the esters of the aroylacrylic acids with no ethylenic substituents

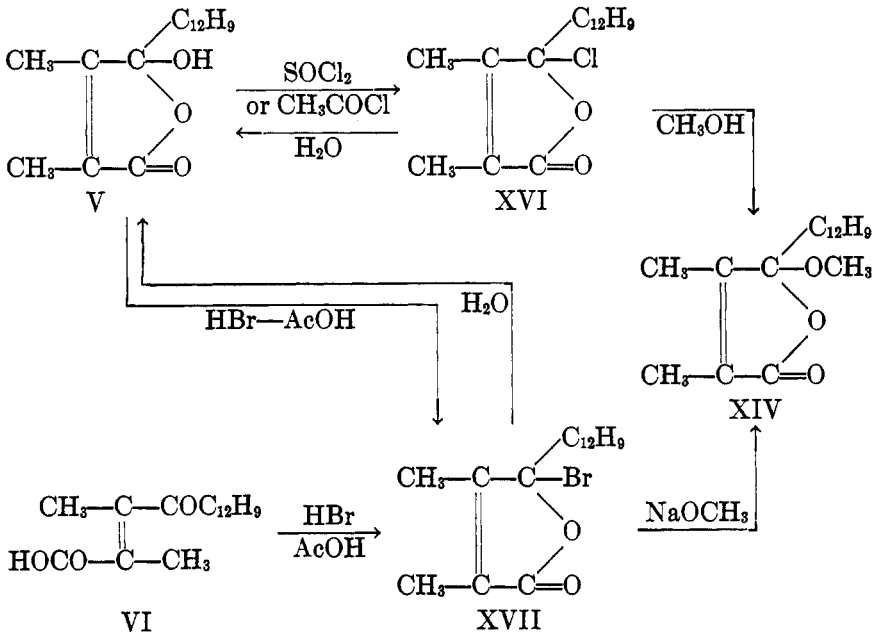
[now under investigation in this laboratory (9)] have as yet been obtained only in the open-chain forms.

In connection with this discussion, attention should be called to the anomaly of the rearrangement of the opianic esters in opposite directions from cyclic to open-chain under the influence of acid and alcohol, and from open-chain to cyclic under the influence of saturated alcoholic alkali (10). This presents a problem which merits further investigation.

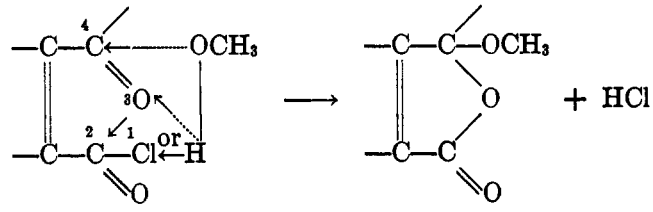
Inversion from trans *to* cis *during hydrolysis of the ester.* In an earlier paper it was noted that hydrolysis of *trans*-β-benzoyldimethylacrylic ester with alkali in a water-alcohol medium gave the expected *trans* acid, but gave the *cis* acid when absolute alcohol was used as the solvent (2c). In view of this and the above described rearrangements of the xenyl and bromophenyl analogs before or during hydrolysis, the inversion of configuration of the esters from *trans* to *cis* through the influence of alkali or alkoxide must be regarded as a general phenomenon in the β-aroyldimethylacrylic acid series. Possibly the rearrangement involves slow equilibration of the *cis* and *trans* esters, with the thermodynamically more stable *trans* form dominant, but with rapid cyclization of the open-chain *cis* ester (which has been shown above to take place in separate test) removing this form and thereby forcing the reaction further and to completion, fixing the product in the stable cyclic form, XIV. Thus, cyclization may be regarded as the real driving force in the reaction (*cf.* 2b, 3).

The cis *acid halides.* Both the acid chloride and the acid bromide of *cis*-β-xenoyldimethylacrylic acid are easily obtained; the acid chloride was made by treatment of the acid with thionyl or acetyl chloride; the acid bromide was obtained through the action of hydrogen bromide in acetic acid. These compounds are very easily hydrolyzed by water, and differ in this respect from the chlorides of *cis*-β-benzoyldibromoacrylic and -β-(*p*-bromobenzoyl)-β-methylacrylic acids, which require long contact with water for hydrolysis, and which can be crystallized unchanged from methanol. They are undoubtedly cyclic and have the γ-halogenolactone or halogenofuranone structures, XVI and XVII, in view of the characteristic mode of formation by means of acetyl chloride or hydrogen bromide, and in view of the significant inversion of the *trans* acid (VI) to the *cis* acid bromide (XVII) by hydrogen bromide in concentrated acetic acid where the formation of a cyclic product may reasonably be postulated as the driving force in the transformation.

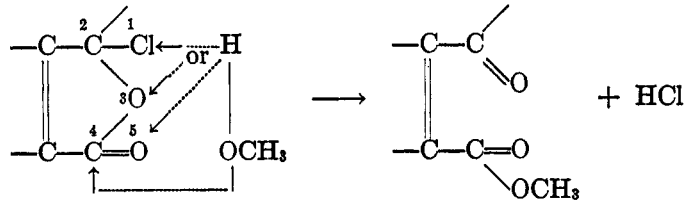
The interaction of the chloride (XVI) directly with methanol to give the cyclic ester (XIV) under conditions which are without effect on the open-chain ester, and the conversion of the bromide (XVII) by means of sodium methoxide directly into the pseudo methyl ester (XIV) might be adduced as supporting evidence for the cyclic formulation of the acid



halides. However, it should be pointed out that these reactions might conceivably have involved the open-chain forms by reaction directly at the spatially proximate but not directly inter-linked *cis* groups, for example, by reaction at positions 1 and 4 or at the γ-carbonyl followed by loss of hydrogen chloride, as follows:

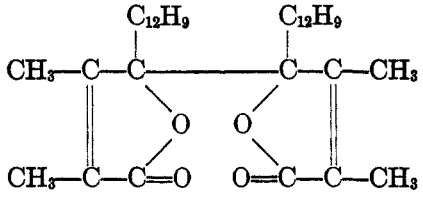


Conversely a cyclic acid chloride might conceivably give an open-chain ester by reaction at positions 1 and 4 or at positions 4, 5 or 4, 3 followed by loss of hydrogen chloride, thus:

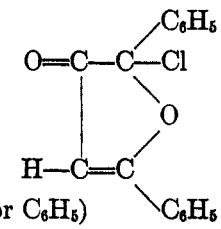


Reactions which may possibly be of the latter type have been reported in the literature. For example, alcoholysis of ortho-benzildicarboxylic acid chloride by means of sodium alkoxide gives the *open-chain* diester (11),[4] the reaction being expressed however as alcoholysis of the lactone ring (at points 3 and 4 in the above formula) followed by loss of hydrogen chloride. These considerations call to mind the allylic reactions where distinction must be made between rearrangements during reaction and 1,4-reactions of the system as a whole, and where the structure of the product is not necessarily indicative of the structure of the starting material.

Dimolecular coupling (or reduction) of the halides (XVI or XVII) by means of copper bronze produces XVIII.



XVIII



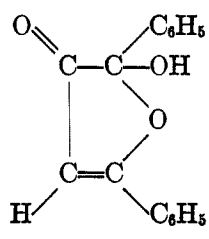
XIX

Attention should be called to the obvious analogy between these cyclic acid halides, which are really also 5-halogeno-2-furanones,[5] and the well-known 2-halogeno-3-furanones[5] such as XIX (12). In the latter type (XIX) the halogen is alpha to the carbonyl group, whereas in the former (XVI and XVII) the halogens are gamma to the carbonyl but in conjugation with it nevertheless through the intervening vinyl group. Also, there is a striking analogy between the *cis* aroylacrylic acids and the 1,2,4-triketone enols such as XXII in respect to ring-chain tautomerism. In the cyclic forms the *cis* aroylacrylic acids (III) are actually 5-hydroxy-2-furanones and thereby analogous to the typical 2-hydroxy-3-furanone, XX; the analogy in reactivities is well illustrated by the conversion of both types into halides by means of phosphorus pentachloride or hydrogen bromide, by the etherification with acid and alcohol, and the reaction in the sense of the open-chain forms with diazomethane. In both types of

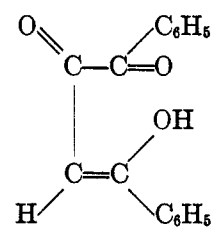
[4] In view of the theoretical importance of this reaction, we are at present repeating and extending the work on this series of compounds.

[5] The term furanone is obviously a misnomer. More properly it should be dihydrofuranone and numbered to indicate the positions involved. However, since a true furanone is impossible and since the abbreviated term has been used extensively (12), it will be retained here, but the expanded and proper term dihydrofuranone will be used when it is necessary to indicate the carbons involved.

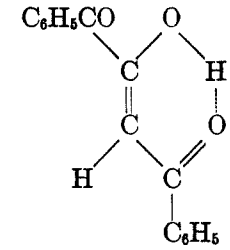
hydroxyfuranones complete substitution in the molecule (at positions 3, 4, and 5 in V and 2, 4, and 5 in XX) favors and stabilizes the cyclic form.



XX
2-Hydroxy-3-furanone



XXI



XXII
Chelated enol

EXPERIMENTAL

Trans-*2,3-dimethyl-3*-p-*xenoylacrylic acid* (VI). The acid was never obtained pure from the hydrolysis of the *trans* ester because invariably some *cis* acid was formed also by inversion. Alkaline hydrolysis in dilute methanol minimizes but does not entirely prevent this.

A solution of 5 g. of the *trans* ester (IV) in 50 cc. of 60% methanol containing 2.0 g. of potassium hydroxide was refluxed for one hour and filtered. Upon acidification with 5 cc. of conc'd acetic acid, 4.6 g. of acids was obtained melting at 138–143°. Crystallization from 25 cc. of a 1:1 mixture of ligroin and ethyl acetate gave 3.0 g. of nearly pure *trans* acid melting at 145–148°. A practical method of separation of the *cis* and *trans* acids was based on the insolubility of the former in sodium bicarbonate solution (filtered off or extracted by ether); the *trans* acid dissolved readily in bicarbonate and was precipitated by acidification. After repeated crystallization from benzene and removal of the persistent solvent of crystallization by heating at 100° for 12 hours at 2 mm., the pure acid was found to melt at 152–153°.

Anal. Calc'd for $C_{18}H_{16}O_3$: C, 77.1; H, 5.8.
Found: C, 77.5; H, 5.8.

A test for the presence of *cis* acid is as follows: A sample (0.2 g.) is mixed with 1 cc. of a saturated sodium bicarbonate solution, followed by addition of 1 cc. of water and warming to 40°. The sodium salt separates as a voluminous crystalline mass, which dissolves on diluting with 5 cc. of water and heating to 60°. If the solution is clear, there is present less than 5 to 7% of *cis* acid; amounts greater than this appear as a solid residue.

Esterfication with methanol and sulfuric acid (refluxed for one hour) or with ethereal diazomethane gave excellent yields.

Trans-*2,3-dimethyl-3*-p-*xenoylacrylic methyl ester* (IV). The mixture obtained by interaction of 15.0 g. of dimethylfumaric acid monomethyl ester and 19.8 g. of phosphorus pentachloride was added dropwise over a period of 30 minutes to a well-stirred mixture of 45 g. of aluminum chloride, 15.3 g. of biphenyl, and 150 cc. of carbon disulfide. The mass was refluxed for 1.5 hours and hydrolyzed in ice and 100 cc. of conc'd hydrochloric acid (stirring for one hour). The mixture was filtered (with difficulty) to remove amorphous material, and the carbon disulfide layer was separated and evaporated. The crude product was crystallized from 90 cc. of methanol, giving 20.6 g. (74%) which after repeated crystallization from this solvent melted at 83.5–84°.

Anal. Calc'd for $C_{19}H_{18}O_3$: C, 77.5; H, 6.2.
Found: C, 77.6; H, 5.9.

Alkaline hydrolysis was always accompanied by partial inversion to the *cis* isomer. *Acid hydrolysis* by refluxing for 30 minutes in a 1:3 mixture of conc'd hydrochloric and acetic acids gave a small yield of the *cis* acid; when 30% hydrogen bromide in conc'd acetic acid was used (standing for a few minutes at room temperature), crystallization set in (presumably the acid bromide), and on hydrolysis with water, the *cis* acid was obtained in 90% yield.

When 0.2 g. of the *trans* ester was allowed to stand for 30 min. at room temperature with 0.1 cc. of methanol containing 0.005 g. of dissolved sodium, only unchanged material was recovered.

Cis-*2,3-dimethyl-3*-p-*xenoylacrylic acid*[3] (V). A solution of 32.3 g. of biphenyl in 50 cc. of carbon disulfide was added dropwise over a period of 45 minutes to a mechanically stirred mixture of 25 g. of dimethylmaleic anhydride, 53 g. of powdered anhydrous aluminum chloride, and 150 cc. of carbon disulfide. The mixture was then refluxed with stirring for 1.5 hours. The resulting viscous purple mass solidified on cooling to a hard tar and this was broken up and hydrolyzed by stirring for several hours with ice and water containing 100 cc. of conc'd hydrochloric acid. The crude product separated out, and was filtered from the mixture of solvents and fractionally crystallized from ethanol and then from benzene to separate the *cis* acid from the dixenyl lactone. The yield of nearly pure *cis* acid was 50% and the yields of the dixenyl lactone averaged from 10–15%. The *cis* acid was purified by repeated crystallizations from benzene, and melted at 162°.

Anal. Calc'd for $C_{18}H_{16}O_3$: C, 77.1; H, 5.8.
Found: C, 77.1; H, 5.8.

A method of separation of the *cis* acid from the dixenyl lactone based on solubility in cold sodium carbonate solution was not practical on a large scale, because of the low solubility of the sodium salt.

The *cis* acid was completely insoluble in boiling saturated sodium bicarbonate solution, was partly soluble in cold sodium carbonate solution, but dissolved when the solution was heated, the sodium salt separating on standing.

Oxidation of the *cis* acid (as the sodium salt) with aqueous potassium permanganate used up six oxygen equivalents, and gave *p*-phenylbenzoic acid, which was identified by melting point and conversion to the methyl ester.

Cis-*2,3-dimethyl-3*-p-*xenoylacrylic methyl ester* (XV) was made from the *cis* acid with diazomethane in the usual way (yield quantitative). After several crystallizations from methanol it melted at 101°.

Anal. Calc'd for $C_{19}H_{18}O_3$; C, 77.5; H, 6.2.
Found: C, 77.4; H, 6.3.

Hydrolysis by conc'd hydrochloric and acetic acids (as above) gave similar results.

Rearrangement to the cyclic form was effected by the action of methanolic sulfuric acid (refluxing for 30 minutes); yield 76%. This rearrangement was effected in good yield also by the action of methanolic sodium methoxide (30 minutes at room temperature).

3,4-Dimethyl-5-methoxy-5-p-*xenylfuranone-2* (2,3-dimethyl-3-xenoylacrylic *pseudo* methyl ester XIV). A solution of 10 g. of the *cis* acid in 60 cc. of methanol and 3 cc. of conc'd sulfuric acid was refluxed for 4 hours, and on cooling 8.7 g. (83%) of nearly pure ester crystallized. Upon recrystallization from methanol, it melted at 121.5°. It gave a sharp mixture melting point depression with the open-chain isomer.

Anal. Calc'd for $C_{19}H_{18}O_3$; C, 77.5; H, 6.2.
Found: C, 77.3; H, 6.1.

Hydrolysis by means of a 1:2 conc'd hydrochloric-acetic acid mixture (refluxed for 30 minutes) gave the *cis* acid in good yield.

3,4-Dimethyl-5,5-di-p-*xenylfuranone-2* (2,3-dimethyl-4,4-dixenylcrotolactone XIII). The preparation was similar to that described above, but double the amounts of diphenyl and of aluminum chloride were used; the dimethylmaleic anhydride was added slowly to the mixture, which was heated for three hours. The yield of *cis* acid was 3% and of the dixenyl lactone 25%. Purified by crystallization from benzene, the lactone melted at 215–218° with decomposition.

Anal. Calc'd for $C_{30}H_{24}O_2$: C, 86.5; H, 5.8.
Found: C, 86.4; H, 5.9.

5-Chloro-3,4-dimethyl-5-p-*xenylfuranone-2* (*Cis*-2,3-dimethyl-3-xenoylacrylic *pseudo* acid chloride XVI). Five grams of the acid was dissolved in 25 cc. of purified thionyl chloride, and after 12 hours at room temperature, the solvent was evaporated under diminished pressure. The residue was crystallized from ethyl acetate; yield 75%; melting point 115–123° with decomposition. Hydrolysis in contact with the atmosphere occurred so rapidly that a sharply melting sample was not obtained. Crystallization was carried out in isopropyl ether with a small amount of added thionyl chloride to minimize hydrolysis, and the melting point was raised to 122–125.5° with decomposition. It was stored in a vacuum desiccator over Ascarite. Analysis indicated unmistakably the presence of one atom of chlorine, but the value was low, indicating partial hydrolysis.

Similar results were obtained when phosphorus pentachloride or acetyl chloride was used in place of thionyl chloride.

Hydrolysis to the acid was complete after a sample was allowed to stand for several hours in the air.

Alcoholysis with methanol (standing for 30 minutes) gave the pseudo ester in good yield. Similar results were obtained in another experiment using methanol and conc'd acetic acid containing enough hydrogen chloride to correspond to that generated during alcoholysis. Both the open-chain *cis* ester and the *cis* acid were then subjected to the same conditions and were recovered unchanged.

5-Bromo-3,4-dimethyl-5-p-*xenylfuranone-2* (*Cis*-2,3-dimethyl-3-xenoylacrylic *pseudo* acid bromide XVII). The *cis* or the *trans* acid reacted at room temperature with 30% hydrogen bromide in conc'd acetic acid, the mixture setting to a mass of crystals within 8 minutes. It was filtered, and the crystals were dried quickly; the melting point, determined immediately, was 141–144° with decomposition. After the product stood in the air for a short time, the melting point dropped to 111–119°, and after several days hydrolysis to the acid was complete and the sample showed the higher melting point 153–157°. The bromo compound could be crystallized from conc'd acetic acid. Analyses showed one atom of halogen to be present, but were low, indicating considerable hydrolysis in the best sample obtained. Alcoholysis with methanol containing the calculated amount of sodium methoxide gave the pseudo ester.

5,5'-Bis-(3,4-dimethyl-5-p-*xenylfuranone-2*) (XVIII). A solution of 1.4 g. of the pseudo acid chloride (XVI) in 7 cc. of dry benzene was treated with 0.7 g. of copper bronze (refluxing for one hour). Upon filtering and leaching the copper bronze with chloroform, and concentrating the solutions, a solid was obtained and crystallized from large quantities of ethyl acetate; yield 54%; melting point 231–234° with decomposition.

Anal. Calc'd for $C_{16}H_{20}O_4$: C, 82.1; H, 5.7.
Found: C, 82.2; H, 6.0.

Trans-*3*-(p-*bromobenzoyl*)-*2,3-dimethylacrylic acid* (XI). A solution of 2 g. of the ester in 10 cc. of 60% methanol containing 0.57 g. (1.5 equivalents) of potassium hydroxide was refluxed for one hour and diluted with water, the non-acidic material being extracted with ether. Acidification with 4 cc. of 6 *N* sulfuric acid gave 1.8 g. (93%) of crude *trans* acid which was purified by repeated crystallization from benzene and from carbon tetrachloride, and by vacuum sublimation; m.p. 128.5–129.5°.

Anal. Calc'd for $C_{12}H_{11}BrO_3$: Br, 28.2. Found: Br, 27.7.

The acid dissolved slowly in cold aqueous sodium bicarbonate.

Esterification was effected by heating for 1.5 hours with methanol and sulfuric acid (yield 50%). Diazomethane in ether gave the same product.

Trans-*3*-(p-*bromobenzoyl*)-*2,3-dimethylacrylic methyl ester* (VII). Five grams of the monomethyl ester of dimethylfumaric acid (3) was allowed to react with 6.6 g. (one equivalent) of phosphorus pentachloride and the resulting mixture was added dropwise to a mechanically stirred suspension of 15 g. of anhydrous aluminum chloride in 50 cc. of dry carbon disulfide and 3.5 cc. of bromobenzene. After 30 minutes the orange colored mixture was refluxed for two hours and hydrolyzed in ice and hydrochloric acid. The carbon disulfide layer was partly evaporated under reduced pressure and the resulting precipitate filtered off; yield 6.4 g. (68%). It was recrystallized from methanol; m.p. 70–70.5°.

Anal. Calc'd for $C_{13}H_{13}BrO_3$: C, 52.5; H, 4.4.
Found: C, 52.4; H, 4.4.

Inversion was brought about by allowing 0.5 g. of the ester to stand in 5 cc. of methanol containing 1.3 equivalents of sodium methoxide for 11 days at room temperature. On dilution with water, 0.15 g. of crystalline solid ester was obtained, and recrystallization from methanol gave 0.05 g. of pure *cis* pseudo ester (VIII) which was identified. The bulk of the product was an acidic oil which could not be induced to crystallize.

Cis-*3*-(p-*bromobenzoyl*)-*2,3-dimethylacrylic acid* (IX). A mixture of 9.4 cc. of bromobenzene and 10 cc. of dry carbon disulfide was added dropwise over a period of 45 minutes to a mechanically stirred mixture of 10 g. of dimethylmaleic anhydride and 43 g. of powdered anhydrous aluminum bromide in 70 cc. of carbon disulfide. The mixture was then refluxed with continued stirring for one hour. The mass become dark red and there was a copious evolution of hydrogen bromide. The mixture was then hydrolyzed in ice to which had been added 80 cc. of conc'd hydrochloric acid. Filtering at this point gave 3.7 g. of unreacted dimethylmaleic anhydride. The carbon disulfide layer was washed with water and steam-distilled, and the oily residue was seeded and finally induced to crystallize. It proved to be very soluble, and tended to come out from solvents as an oil. It was crystallized with difficulty from water-ethanol and ethyl acetate-ligroin mixtures, but the melting point was unsharp (116–119°); yield 9 g. (40%). The acid was then purified by successive evaporations in the vacuum oven onto a cold-finger condenser; m.p. 120–121°.

Anal. Calc'd for $C_{12}H_{11}BrO_3$: C, 50.9; H, 3.9.
Found: C, 51.0; H, 3.9.

When aluminum chloride was used in the above experiment, only unchanged material was obtained. When the reaction was forced, using nitrobenzene, no reaction occurred at temperatures up to 100°, and above that only resinous products were obtained. Aluminum chloride with bromobenzene as solvent at 50–60° and at 80–90° for 10 minutes gave crude yields of 18% and 27%, respectively.

The acid is insoluble in cold sodium bicarbonate, but dissolves when heated.

Cis-*3*-(p-*bromobenzoyl*)-*2,3-dimethylacrylic methyl ester*, $BrC_6H_4COC(CH_3)=C(CH_3)COOCH_3$, was prepared from the acid with diazomethane in the usual way (yield 91%). The reaction proceeded rapidly at room temperature. Upon repeated crystallization from methanol, it melted at 87°.

Anal. Calc'd for $C_{13}H_{13}BrO_3$: C, 52.5; H, 4.4.
Found: C, 52.3; H, 4.6.

Hydrolysis and *rearrangement* were effected by allowing a solution of 0.95 g. of the ester in methanol containing 0.2 g. of potassium hydroxide to stand for 16 hours at room temperature. Dilution with water gave 0.1 g. (10%) of the pseudo ester. On acidification, 0.68 g. (71%) of the *cis* acid precipitated.

5-Bromophenyl-3,4-dimethyl-5-methoxyfuranone-2 (*Cis*-2,3-dimethyl-3-xenoylacrylic *pseudo* methyl ester VIII) was prepared from the acid by the action of methanolic sulfuric acid (refluxing for 2 hours, yield 51%). Upon repeated crystallization from ethanol, it melted at 91.5°. It gave a sharp mixture melting point depression with the open-chain ester.

Anal. Calc'd for $C_{13}H_{13}BrO_3$: C, 52.5; H, 4.4.
Found: C, 52.8; H, 4.6.

Hydrolysis was effected with methanolic potassium hydroxide (refluxing for 30 minutes).

Cis- *and* trans-*3-benzoyl-2,3-dimethylacrylic acids*. The *cis* acid is insoluble in cold saturated sodium bicarbonate solution but dissolves when heated, while the *trans* acid dissolves immediately with effervescence under similar conditions.

Cis-*3-benzoyl-2,3-dimethylacrylic methyl ester*, $C_6H_5COC(CH_3)=C(CH_3)COOCH_3$, was prepared by the action of ethereal diazomethane on the acid, the reaction proceeding rapidly (yield 79%). After repeated crystallization from 75% ethanol, it melted at 60°. A mixture melting point with the pseudo ester prepared by the acid catalytic methylation (2b) showed a sharp depression.

Anal. Calc'd for $C_{13}H_{14}O_3$: C, 71.5; H, 6.5.
Found: C, 71.1; H, 6.4.

Hydrolysis in methanolic potassium hydroxide (19 hours at room temperature) gave the *cis* acid in good yield.

Rearrangement to the cyclic form was brought about in good yield by the action of refluxing methanolic sulfuric acid.

Attempts to prepare a cis-*2,3-dimethyl-3-(trimethylbenzoyl)acrylic acid* were made by carrying out the Friedel-Crafts reaction between dimethylmaleic anhydride and mesitylene under mild conditions in the hope of avoiding inversion of configuration during the reaction. These were unsuccessful, and included reactions carried out in nitrobenzene at 0°.

Trans-*2,3-dimethyl-3-(2,4,6-trimethylbenzoyl)acrylic methyl ester* (2b) was made also by the action of diazomethane on the acid.

SUMMARY

The *cis* and *trans* 3-xenoyl- and 3-(*p*-bromobenzoyl)-2,3-dimethylacrylic acids and their methyl esters, including the pseudo *cis* esters, have been synthesized. The *trans* compounds were made through the Friedel-Crafts reaction on dimethylfumaric monomethyl ester monochloride, and the *cis* compounds similarly from dimethylmaleic anhydride.

The formation of the 4,4-dixenyl crotolactone was observed in the Friedel-Crafts reaction between diphenyl and dimethylmaleic anhydride.

The isomerism of the *cis* dimethylxenoylacrylic esters was studied. The cyclic isomer proved to be the stable form.

The general tendency of the *trans* aroyldimethylacrylic esters to undergo rearrangement into the *cis* cyclic isomers under the influence of alkali was demonstrated.

The acid halides of *cis*-dimethylxenoylacrylic acid are shown to be cyclic. Their reactions are discussed. Coupling by means of copper bronze produced a dimolecular product.

The close analogy between the aroyldimethylacrylic acids and the triketone enols and 2-hydroxy-3-furanones and between their derivatives has been considered.

CHARLOTTESVILLE, VA.

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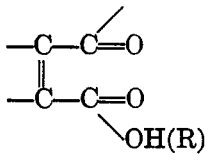
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

THE REDUCTION OF *CIS* AND *TRANS* 2,3-DIMETHYL-3-*p*-XENOYLACRYLIC[1] ACIDS AND THEIR ESTERS

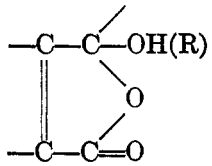
ROBERT E. LUTZ AND MONROE COUPER[2]

Received August 31, 1940

In the open-chain forms of the *cis* unsaturated 1,4-ketonic acids and their esters (I) and also in the corresponding *trans* compounds, there is present the conjugated unsaturated 1,4-dicarbonyl system, O=C—C=C—C=O, reduction of which undoubtedly involves primary addition of hydrogen or its equivalent at the terminal oxygen atoms. In the cyclic forms of the *cis* acids and their esters (II) there is present the analogous system, O=C—C=C—C—O, in which a C—O link is in place of one of the carbonyl groups; this system also may function in some degree as a unit, as it does in the reduction of the cyclic *cis*-3-bromobenzoyl-3-methylacrylic ester (1). The 2,3-dimethyl-3-xenoylacrylic derivatives have been studied further in this connection because they show a particularly marked tendency to function in the cyclic forms.

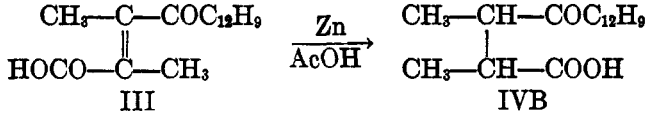


I



II

Reduction of the open-chain compounds. The reduction of *trans*-2,3-dimethyl-3-xenoylacrylic acid (III) with zinc and acetic acid proceeds directly to the less stable of the two stereoisomeric saturated 1,4-ketonic acids (IVB). Reduction by zinc and aqueous sodium carbonate produces a mixture of the two stereoisomers, IVA and IVB (these two acids will be described below in a separate section). The methyl ester of the *trans* acid (V) and also the *cis* open-chain ester (VII) are likewise reduced by

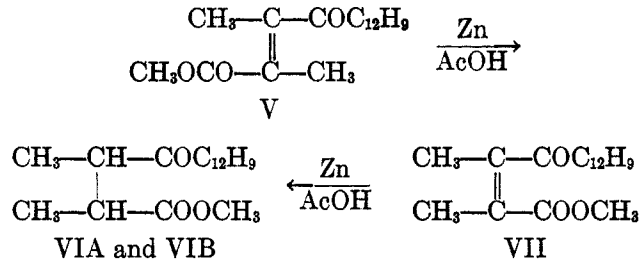


III IVB

[1] Named in terms of acrylic rather than tiglic acid in order to minimize the use of special names in this field and to simplify the naming of compounds with various substituents on the ethylene linkage.

[2] Holder of a Philip Francis duPont Research Fellowship, 1937–1938; at present Instructor in Chemistry, University of Virginia.

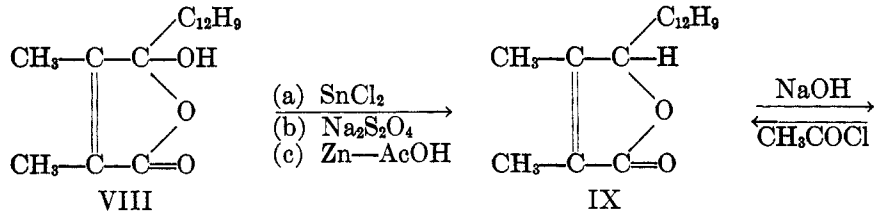
zinc and acetic acid but to mixtures of the two stereoisomeric 2,3-dimethyl-3-xenoylpropionic esters.

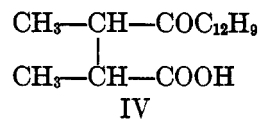


It is evident from the ease of reduction of these compounds and from the formation of the same products from both *cis* and *trans* esters, that the conjugated system is involved through 1,6-reduction. The formation chiefly of the unstable acid (IVB) in the zinc-acetic acid reduction of the unsaturated *trans* acid (III) was surprising, and it would be of interest to know what the open-chain form of the *cis* acid would give under the same conditions. This point, it now appears, cannot be determined, since the *cis* acid seems to function largely if not exclusively in the cyclic form.

Reduction of the cyclic ester. The cyclic or pseudo ester of *cis*-2,3-dimethyl-3-xenoylacrylic acid (VIII) is not acted upon by zinc and boiling conc'd acetic acid. This was disappointing, but perhaps not surprising in view of the absence of the complete unsaturated 1,4-dicarbonyl system; however, it is to be contrasted with the facile reduction of the analogous cyclic *cis*-3-bromobenzoyl-3-methylacrylic pseudo ester (1) by the same reagent.

Reductions of the cis *acid* (VIII) with stannous chloride, sodium hydrosulfite, or zinc and acetic acid, give the α,β-unsaturated lactone (IX) described below in a separate section. The saturated 1,4-ketonic acid (IV) is not formed to any significant extent in these reductions, although it can be made from the unsaturated lactone (IX) by hydrolysis with sodium hydroxide. The course of these reductions is to be contrasted with that of the open-chain *cis* ester, which takes place in a normal fashion to give directly the ester of the saturated ketonic acid.



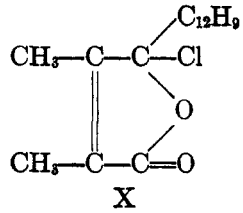


IV

In connection with the mechanism of these reductions of the *cis* acid, several points should be considered. The stereoisomeric saturated acids (IVA and IVB) once formed are stable under the various reducing conditions and can be converted into the unsaturated lactone (IX or XIV) only upon dehydration, using acetyl chloride or acetic anhydride and sulfuric acid; neither of the saturated acids, therefore, can have been involved as an intermediate in the reductions. The unsaturated lactone (IX) therefore must have been formed either through direct reduction of the acid in its lactonol[3] form (VIII) or through cyclization of an intermediate enolate produced by 1,6-reduction of either form, VIII or I. The *trans* acid (III), necessarily open-chain, is reduced normally and presumably 1,6 to give intermediate enolates which ketonize to the saturated ketonic acid (IV); in this case, no evidence of cyclization was observed. The entirely different course of reduction of the *cis* acid, then, indicates that 1,6-reduction of the open-chain form is not involved, although one might assume the formation of a stereoisomeric intermediate enolate which would cyclize rather than ketonize during the reaction, just as one highly hindered γ-diketone monoenolate stereoisomer is known to furanize consistently rather than to ketonize (2). Reduction of the *cis* acid, then, probably involves exclusively the direct (or possibly 1,4) reductive elimination of hydroxyl from the lactonol form, VIII.

The reduction of the *cis* acid (VIII) by stannous chloride in hydrochloric and acetic acids may be regarded as a special case, and very probably involves conversion into the pseudo acid chloride (X) (a type of reaction which occurs easily in this series), followed by direct reductive elimination of the halogen to give as the chief product the stable α,β-unsaturated lactone (IX). The unstable enol lactone (XIV) could not have been involved here to any considerable extent, because under these conditions it is converted only partly into the stable α,β-unsaturated lactone (IX) and undergoes hydrolysis instead largely to the saturated ketonic acid (IV), as was shown in separate experiment. The mechanism suggested would explain why the reduction goes with such extraordinary ease as compared with the relatively slow reduction when the more powerful reducing combination, zinc and acetic acid, is used. Analogous reductions of mucobromyl bromide (3) and the pseudo acid bromide of β-phenyl-β-benzoylacrylic acid (4) may be cited.

[3] The term lactol is commonly used for this type of compound but we have expanded this to lactonol to express better the relationships involved.



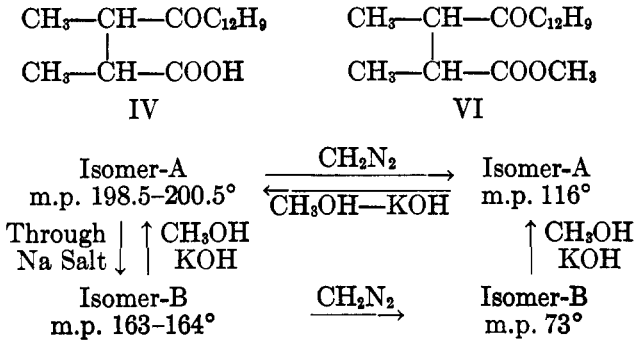
X

Reduction of the *cis* acid (or rather perhaps its sodium salt) with zinc and aqueous sodium carbonate, gives directly the saturated 1,4-ketonic acid (IV). The α,β-unsaturated lactone (IX) under these conditions is stable, and therefore could not have been an intermediate. It would therefore appear that the sodium salt is involved, and functions in the open-chain form or possibly a resonance hybrid between the open-chain and cyclic forms. However, in view of the relatively few reactions of the acid which might reasonably be attributed to the open-chain form, namely, this reduction with zinc and sodium carbonate, and methylation with diazomethane, it seems worth while to suggest the possibility that the acid and even the sodium salt may function exclusively in the cyclic form, but may react at times through a conjugated system in such a way as to produce open-chain products [*cf.* the discussion of alcoholysis of the *cis* acid halides in the preceding paper (5)]. Analogy for this is to be seen in the reduction of the *cis*-3-bromobenzoyl-3-methylacrylic pseudo ester to the open-chain enol ether of the saturated 1,4-ketonic acid (1). Such a possibility has been suggested in the methylation of 4-benzoyloxy-2,5-diphenyl-2-hydroxyfuranone[4]-3 with diazomethane (6) and may be applied also to the methylation of the silver salt. In fact, methylation by methyl iodide of the colorless silver salt of *ortho*-benzilcarboxylic acid, which is believed to be in the lactonol form, produces directly the open-chain ester (7).

The stereoisomeric 3-p-xenoyl-2,3-dimethylpropionic acids (IV). The product obtained on hydrolysis of the unsaturated lactone (IX) was a mixture of two stereoisomeric saturated ketonic acids with the higher-melting form-A predominating. The isomer-B was not easily isolated from this mixture and was separated best as the methyl ester after diazomethane esterification of the residual mixtures from fractional crystallizations. A way was found to prepare in good yield the low-melting isomeric acid (IVB) and from it the methyl ester (VIB). The action of alkali on

[4] The term furanone is obviously a misnomer. More properly it should be dihydrofuranone and numbered to indicate the positions involved. However, since a true furanone is impossible and since the abbreviated term has been used extensively (9), it will be retained here, but the expanded and proper term dihydrofuranone will be used when it is necessary to indicate the carbons involved.

either acid-A or -B produced an equilibrium-mixture of the two acids with the less soluble form-A predominating. However, the sodium salt of the isomer-B proved to be difficultly soluble in 10% sodium hydroxide in contrast with the isomer-A sodium salt which is very soluble, and it crystallized from solution in good yield under properly controlled conditions. The free acid-B could then be liberated by treatment with acids, and was purified, characterized, and converted with diazomethane into the low-melting ester (VIB). Alkaline hydrolysis of both of the esters (VIA and VIB) produced chiefly the acid (IVA).

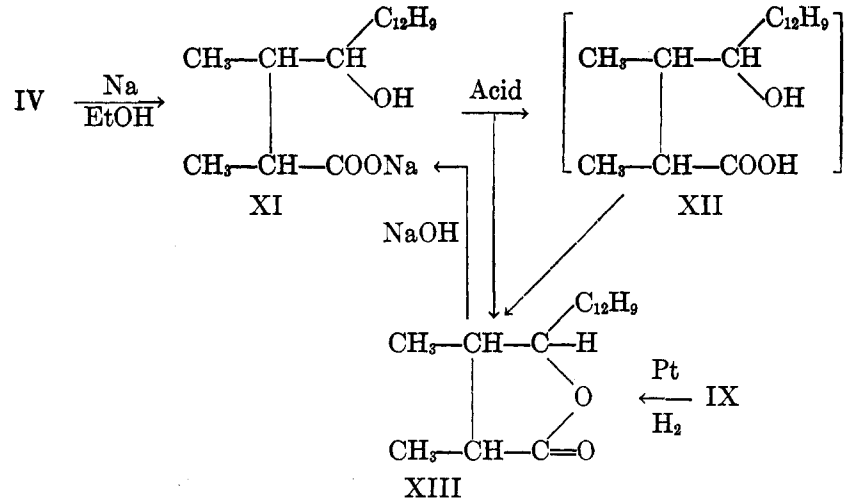


The less soluble and higher-melting isomeric acid-A and its ester are the more stable isomers as shown by the predominance of the acid-A at equilibrium in alkaline solution, and by the conversion of the ester-B into the ester-A by means of alcoholic alkali, a reaction which precedes the eventual hydrolysis.

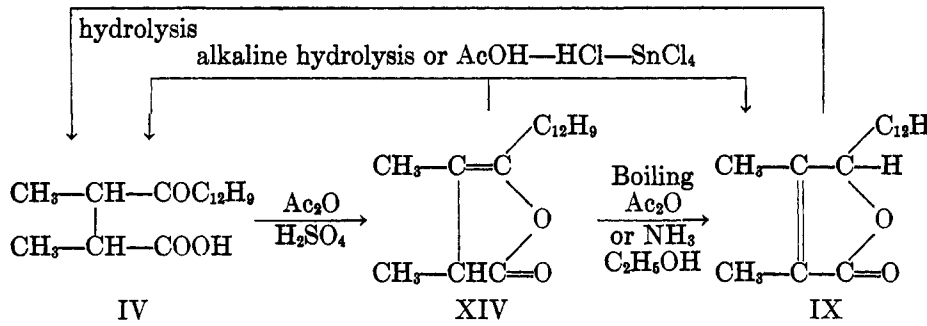
Both the 3-xenoyl-2,3-dimethylpropionic acids-A and B are converted by acetic anhydride and sulfuric acid into the same unsaturated lactone (IX) in which the possibility of stereoisomerism has disappeared.

*Reduction of 2,3-dimethyl-3-*p*-xenoylpropionic acid-A* (IV). The combination sodium and alcohol attacked the carbonyl group of this acid; on acidification of the product, the hydroxy acid lactonized, and was obtained as a mixture, presumably of stereoisomers, from which one compound (XIII) was isolated by painstaking fractional crystallization. Catalytic hydrogenation of the unsaturated lactone (IX) also gave this same butyrolactone (XIII). In one isolated experiment the free hydroxy acid (XII) was obtained on acidification of the sodium salt (XI), but this was not duplicated in several attempts. The sample of hydroxy acid (XII) lost water on melting, giving the lactone (XIII).

The isomeric unsaturated lactones. The unsaturated lactone obtained in reduction of the *cis* acid undoubtedly has the structure (IX) with the double bond α,β to the carbonyl group. Interest in the mechanism of



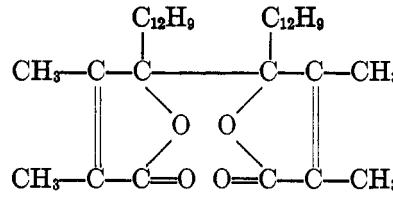
reduction here led us to a further study of the lactone and to the isolation of an unstable isomer. Similar stable and unstable unsaturated butyrolactones have already been reported by Thiele (4), who showed that γ-ketonic acids tend to enolize under the influence of acetic anhydride and sulfuric acid to give first a true enol lactone, which is unstable and is readily rearranged under the influence of acids or bases, with migration of the double bond into conjugation with the carbonyl group. In the case in hand the results are exactly parallel. The saturated γ-ketonic acid (IVA or IVB) when treated at room temperature with acetic anhydride containing a trace of sulfuric acid gives the unstable enol lactone (XIV), and this in turn is readily rearranged into the stable isomer (IX) when treated in alcohol with a little ammonium hydroxide, or when subjected to the action of boiling acetic anhydride.



Alkaline hydrolysis of the unstable enol lactone (XIV) gives the saturated acid (IV) along with some of the stable lactone (IX), which is some-

what less easily hydrolyzed under these conditions, but which in the end also can be converted into the acid. Acid hydrolysis, using a mixture of conc'd acetic and hydrochloric acids (containing stannic and stannous chlorides in order to simulate more exactly the conditions employed in reduction of the *cis* acid), also brought about rearrangement to the stable unsaturated lactone (IX) in 40% yield, this product being shown in separate experiments to be stable under these and even more drastic conditions. Along with the stable unsaturated lactone, there was obtained also a 57% yield of the saturated acid (IV), a product of hydrolysis independent of the rearrangement.

Both unsaturated lactones (XIV and IX) react with Tollen's reagent to give a deposit of silver and a crystalline dimolecular oxidation-product which is identical with the product of coupling two molecules of the *cis* pseudo acid chloride (X) by means of copper bronze. The structure XV is therefore assigned to the dimolecular compound and is analogous to that of the dimolecular compounds obtained from the 3-hydroxyfurans by air oxidation or by the action of copper bronze on the 2-bromo-3-furanones (9).

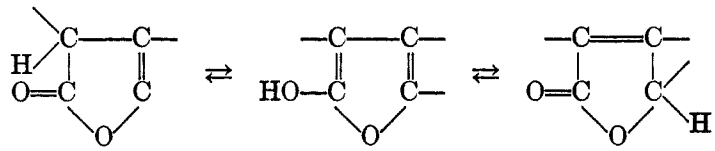


XV

It is worthy of note that the enol lactone (XIV) is oxidized to the dimolecular product (XV) by sulfuric acid in acetic anhydride, and in this respect is unlike the more stable α,β-unsaturated lactone (IX). Apparently, this oxidation, which proceeds even in the presence of zinc dust, is due to sulfuric acid since the reaction takes place equally well when air is excluded but not when phosphoric acid is substituted for sulfuric. Small amounts of the dimolecular product also are obtained in the reduction of the *cis* unsaturated acid (VIII) with zinc, acetic anhydride, and conc'd sulfuric acid; possibly dimolecular reduction is involved here; however, this is not certain, because the dimolecular product is formed also upon application of these conditions directly to the unstable enol lactone (XIV) which might conceivably have been formed as an intermediate in amounts sufficient to account for the result.

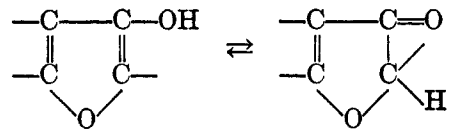
Both unsaturated lactones (IX and XIV) on treatment with alkali give the yellow color which is characteristic of the type, as noted by Thiele

(8), and which was attributed by him to the enolic or α-hydroxyfuran form (XVII).



XVI XVII XVIII

There is obviously a close analogy between this group of compounds and the β-hydroxyfurans (XIX) and β-furanones (XX). The β-hydroxy-



XIX XX

furans are obtained best as acylates or halogenomagnesium derivatives; they are unstable in the free state, ketonize rapidly, and are easily oxidized to peroxides or to α,α-dimolecular compounds (9). In the ketonic form as β-furanones they are straightforward analogs of the unstable enol lactones of the type XIV, and are also, though to a lesser degree, analogs of the stable unsaturated lactones of type (IX). Evidently the relative stability of the unsaturated lactones of the latter type is connected with the conjugation of the α,β-unsaturated carbonyl system which is present. The β-hydroxyfuran (XIX) has the adjacent α-position as the reactive one, and in the hypothetical α-hydroxyfuran (XVII) the opposite α-position is the active position, as would be expected.

Incidentally, attention should be called to the close analogy between the dimolecular oxidation in both the α- and β-oxyfuran series and the first steps in the dimolecular oxidation of indoxyl to indigo.

EXPERIMENTAL

*3,4-Dimethyl-5-*p*-xenyl-2,5-dihydrofuranone-2* (2,3-dimethyl-4-xenylbutenoic acid γ-lactone) (IX). A mixture of 10 g. of *cis*-dimethylxenoylacrylic acid, 15 cc. of conc'd hydrochloric acid, 45 cc. of conc'd acetic acid, and 20 g. of stannous chloride was refluxed for 30 minutes. The hot solution was filtered directly into several volumes of water. After coagulation, the product was crystallized from ethanol, giving 8 g. (85%), and on repeated crystallization from methanol, it melted at 133.5°.

Anal. Calc'd for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1.

Found: C, 81.6, 82.2; H, 6.3, 6.3.

A similar result was obtained using conditions similar to those above but involving long standing at room temperature, with production largely of the same product

(IX) together with unchanged material and a very small amount of the higher-melting form of the saturated acid (IVA).

Ammoniacal silver nitrate solution reacted with IX to give an immediate deposition of silver (an intermediate and fleeting yellow coloration was noted).

Ozonolysis did not give significant results. No evidence of bromination was observed in chloroform (on standing). Sulfuric acid in acetic anhydride was without action. The compound is stable toward the prolonged action of stannous chloride-hydrochloric-acetic acid mixtures, and toward refluxing methanolic sulfuric acid.

*5,5'-Bis-(3,4-dimethyl-5-*p*-xenylfuranone-2)* (XV). In a typical experiment, 2.5 g. of silver nitrate in 12 cc. of water and 12 cc. of conc'd ammonium hydroxide was mixed with 25 cc. of 10% sodium hydroxide, and poured into 50 cc. of ethanol containing 1 g. of either the above unsaturated lactone (IX) or the labile enol lactone (XIV). Rapid precipitation of silver and the dimolecular oxidation-product occurred. After standing for 2 hours, the precipitate was filtered off and the product leached from the silver residue with chloroform. In an alternative scheme, the silver was removed by washing the residue with dilute nitric acid (yield 0.91 g. or 91%).

*2,3-Dimethyl-3-*p*-xenoylpropionic acid-A* (IVA). A mixture of 6.6 g. of the α,β-unsaturated lactone (IX), 2.1 g. of potassium hydroxide, and 40 cc. of methanol was shaken occasionally over a period of a few hours until the solution became clear. After standing, a total of 20 hours, the solution was diluted with water (it showed no turbidity) and was acidified with 5 cc. of conc'd acetic acid. The precipitate after coagulation was digested with 70 cc. of hot methanol and on cooling a 62% yield of nearly pure acid was obtained (in other runs, the yields ranged from 60–75%). From the residues the lower-melting isomer-B could be isolated as the methyl ester after treatment with diazomethane. Hydrolysis at refluxing temperatures (30 minutes) was more rapid but the yields were lowered to 50%.

The acid-A was purified by repeated crystallization from methanol and from other solvents, conc'd acetic acid, acetone, ethanol, chloroform, and benzene-ethyl acetate mixtures. It was obtained as colorless needles melting at 198.5–200.5°.

Anal. Calc'd for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4.
Found: C, 76.3; H, 6.5.

The acid-A was converted in good yield into the α,β-unsaturated lactone on treatment for one hour at refluxing temperature with acetyl chloride. It is stable toward the various reducing combinations; namely, stannous chloride-conc'd acetic and hydrochloric acid mixtures at room temperature (it was dehydrated to the α,β-unsaturated lactone by this reagent at refluxing temperature), sodium hydrosulfite in boiling sodium carbonate solution, and zinc dust and boiling conc'd acetic acid (heating for 1 hour).

The methyl ester (VIA) was prepared from the acid in the usual way with ethereal diazomethane (yield 91%), or by the action of methanol and sulfuric acid (refluxing for one hour). On crystallization from methanol, it melted at 116°.

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8.
Found: C, 77.0; H, 6.6.

Hydrolysis in methanolic potassium hydroxide (12 hours at room temperature) gave a crude acid mixture from which a yield of 61% of the isomer-A was isolated.

*2,3-Dimethyl-3-*p*-xenoylpropionic acid-B* (IVB). A solution of 0.5 g. of the isomer-A in 5 cc. of 10% sodium hydroxide was prepared by warming the mixture to 50–60°. After 20 hours at room temperature, crystals began to deposit. After 3 days, 0.35 g. (65%) of the sodium salt of the isomer-B had separated. It was recrystallized from water, and melted at 118–120° (it evidently held solvent of crystallization).

Upon dissolving in hot conc'd acetic acid and diluting with water and cooling, 1.8 g. of the free acid-B was obtained. Crystallization from benzene brought the melting point to 164–165°. It gave a sharp mixture melting point depression with the isomer-A.

Anal. Calc'd for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4.
Found: C, 76.4; H, 6.6.

In connection with reduction studies, it was shown that this acid (IVB) was stable toward aqueous sodium carbonate and sodium hydrosulfite (refluxing for 1.5 hours).

The methyl ester (VIB) was obtained from the acid in the usual way with diazomethane or with acid and methanol, and it was isolated also upon methylation of the low-melting residues obtained from hydrolysis of the α,β-unsaturated lactone (IX) (separated from the high-melting isomeric ester by fractional crystallization from 75% ethanol). The melting point was 73°.

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8.
Found: C, 77.0; H, 6.5.

Hydrolysis. The action of methanolic potassium hydroxide (15 minutes at room temperature) on this ester gave the higher-melting ester (VIA) which crystallized directly from the solution. These crystals were filtered off and identified. Upon standing for 4 hours, the filtrate was acidified and a sample of the high-melting acid (isomer-A) was obtained.

*3,4-Dimethyl-5-*p*-xenyl-2,3-dihydrofuranone-2* (XIV) (2,3-dimethyl-3-xenoylpropionic acid enol lactone). One drop of conc'd sulfuric acid was added to a suspension of 2.2 g. of either acid IVA or IVB in 10 cc. of acetic anhydride, and after shaking for 5 minutes, the solution became clear and bright yellow. Upon successive additions of a few drops of water, cautiously, and on standing, a crystalline precipitate appeared (1.8 g. or 87%). This product required careful handling since excessive heating in solvents caused rearrangement. It was crystallized best from methanol by saturating at room temperature and then cooling to −25°. The colorless product, dried in a vacuum desiccator, melted at 93.5–95°.

Anal. Calc'd for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1.
Found: C, 81.9; H, 6.5.

This compound showed an immediate reaction with Tollen's reagent and gave the dimolecular oxidation-product XV. It reacted with bromine in carbon tetrachloride to give a non-crystalline product. Rearrangement to the stable isomer (IX) was brought about by the action of refluxing acetic anhydride (15 minutes), by adding a few drops of conc'd ammonium hydroxide to a hot alcohol solution (a fleeting yellow coloration was noted); and it was also brought about by the typical reducing combination, 70% alcohol and sodium hydrosulfite (refluxing for 2 hours).

Oxidation resulted when a solution of 0.1 g. of the enol lactone (XIV) in 2.5 cc. of acetic anhydride was treated with 3 drops of sulfuric acid, the dimolecular product XV precipitating upon standing for 10 minutes. After standing for a total of one hour, 0.03 g. was obtained (m.p. 230–232°). A second crop brought the yield to 50%. Small amounts of this product were often obtained during the preparation of the enol lactone (XIV). Exclusion of air through use of an atmosphere of nitrogen did not change the result, nor did the presence of zinc dust. When 85% phosphoric acid was used in place of sulfuric acid, and air bubbled through the solution, no dimolecular product was found.

Alkali hydrolysis with methanolic potassium hydroxide involved a yellow coloration which disappeared within 6 hours. After standing for a total of 12 hours, the saturated acid IVA was isolated in 64% yield.

Acid hydrolysis took place under certain of the reducing conditions employed in this research, and, therefore, this labile enol lactone XIV could not have been the chief intermediate product in the reactions concerned. Since in the reduction the unstable enol lactone, if formed, would have been produced slowly and in the presence of ever-increasing amounts of stannic chloride, the following test was carried out. Two grams of the enol lactone (XIV) and 2.67 g. of stannic chloride ($SnCl_4 \cdot 5 H_2O$) were weighed in separate containers and added in ten portions each to a stirred mixture of 4 g. of conc'd hydrochloric acid, 42.5 cc. of conc'd acetic acid, and 4 g. of stannous chloride ($SnCl_2 \cdot 2 H_2O$). After 15 hours at room temperature, the reaction-mixture was diluted with water and the precipitate leached with sodium carbonate, which removed 1.21 g. (57%) of impure dimethylxenoylpropionic acid-A (recovered by acidification of the extract and identified). There remained 0.8 g. (40%) of material insoluble in sodium carbonate, which was identified as the stable α,β-unsaturated lactone (IX). Each of these products was shown to be stable under these reaction conditions.

Reduction of cis-*2,3-dimethyl-3*-p-*xenoylacrylic acid* (VIII). The reductions with stannous chloride are described under the preparation of the α,β-unsaturated lactone (IX).

Reduction with sodium hydrosulfite was without effect on the *cis* acid in 70% methanol (refluxing for 2 hours), but when small or large amounts of sodium carbonate were added to the mixture, reduction proceeded; in a typical case, after refluxing the mixture for one hour, the α,β-unsaturated lactone (IX) was obtained in 86% yield.

Zinc dust and conc'd acetic acid reduction in the usual way (refluxing for 2 hours) gave a poor yield of the same α,β-unsaturated lactone (IX), and reductions with shorter heating time gave considerable amounts of unchanged material.

The action of 1 g. of zinc dust on a mixture of 0.5 g. of the *cis* acid and 5 cc. of saturated aqueous sodium carbonate (stirring for 0.5 hours at 80–90°) gave 0.38 g. of the saturated acid IVA (contaminated evidently by some of the stereoisomer). None of the α,β-unsaturated lactone (IX) was detected, and this compound (IX) was subsequently subjected to identical conditions and was recovered unchanged.

Reduction of 0.5 g. in 10 cc. of acetic anhydride containing 2 drops of conc'd sulfuric acid (one hour at room temperature) gave largely unchanged material together with 0.05 g. of the dimolecular compound (XV) which was obtained as a residue when the product was dissolved in methanol. Without the zinc dust, no reaction occurred.

Reduction of the cis *ester* (*open-chain*) (VII) with zinc dust and conc'd acetic acid (refluxing for 2 hours) gave a mixture of the saturated esters VIA and VIB. The pseudo ester was partly unchanged when treated under the same conditions, but some non-crystalline by-products were produced.

Reduction of trans-*2,3-dimethyl-3-xenoylacrylic acid* (III) with zinc dust and conc'd acetic acid (room temperature for one hour) gave a product (92%) which consisted largely of the saturated acid-B. It was purified and identified. No definite reduction-products were obtained when sodium hydrosulfite was used under various conditions. The combination zinc dust and aqueous sodium carbonate (boiling for 0.5 hours) produced an 85% yield of a mixture of the saturated acids IVA and IVB from which the higher-melting isomer was isolated and identified specifically.

Reduction of the methyl ester (V) did not take place under the same conditions, but when the reaction-mixture was refluxed for one hour, a mixture (87%) of the two saturated esters was obtained. The action of stannous chloride, conc'd acetic

and hydrochloric acids (refluxing for 30 minutes) produced the stable α,β-unsaturated lactone (IX).

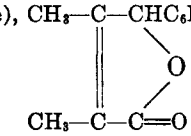
2,3-Dimethyl-4-p-xenylbutyrolactone (XIII). Catalytic reduction of the stable α,β-unsaturated lactone (IX) in ethanol proceeded slowly. The absorption of hydrogen continued beyond five molecules without any break, indicating an attack upon the aromatic nucleus. Even after absorption of two molecules of hydrogen some unchanged material remained. The best method for obtaining small but optimum yields of the dihydro compound was to stop the reaction after absorption of 1.5 to 2 molecules of hydrogen; absolute ethanol was used as solvent with the platinum oxide catalyst. Slow, quiet crystallization gave the dihydro compound, which was purified by crystallizing from methanol; melting point 151°.

Anal. Calc'd for $C_{18}H_{16}O_2$: C, 81.2; H, 6.8.
Found: C, 81.5; H, 7.1.

A small amount of this same product was isolated in a similar catalytic reduction of the labile enol lactone (XIV) but in this case, surprisingly, the chief product was the stable α,β-unsaturated lactone (IX) formed by rearrangement. It was demonstrated that the solvent alone did not bring about this rearrangement and the phenomenon may possibly be attributed to traces of alkali in the catalyst.

Sodium and alcohol reduction of the higher-melting dimethylxenoylpropionic acid (IVA) required drastic conditions, and a large excess of sodium was used. The product, on fractional crystallization from ethyl acetate and from methanol, gave a 5% yield of the dihydro compound (XIII).

Hydrolysis in one experiment (not repeated) on a very small scale with 10% sodium hydroxide to which was added a few drops of ethanol, gave a new acid which melted at 90–108° and which could be dissolved in alkali and reprecipitated by acid. Upon crystallization from benzene it melted at 110–113.5° with effervescence, resolidified at once, remelted at 142–149°, and was then identified as the lactone (XIII). The acid changed to the lactone spontaneously on standing for several days at room temperature.

3,4-Dimethyl-5-phenyl-3,4-furanone-2 (2,3-dimethyl-4-phenyl-2,3-butenoic acid γ-lactone),  The yield of *cis*-3-benzoyl-2,3-dimethylacrylic acid (10) was greatly improved by crystallization of the product from a 9:1 mixture of ligroin and ethyl acetate. A suspension of 4.6 g. of this acid in 25 cc. of water was treated with saturated sodium carbonate solution until it dissolved; 25 cc. of a saturated solution of sodium hydrosulfite was then added and the mixture refluxed for 10 minutes. The amber colored oil which appeared (3.7 g. or 87%) was distilled under reduced pressure; b.p. 141° at 21 mm. pressure; n_D^{25} 1.5442; dispersion ($n_F - n_C$) 0.0162.

Anal. Calc'd for $C_{12}H_{12}O_2$: C, 76.6; H. 6.4.
Found: C, 76.2; H, 6.4.

Similar results were obtained using stannous chloride in a conc'd acetic and hydrochloric acid mixture (refluxing for 30 minutes).

The product with Tollen's reagent gave an immediate yellow coloration followed by formation of the characteristic black precipitate.

3-Benzoyl-2,3-dimethylpropionic acid, $C_6H_5COCH(CH_3)CH(CH_3)COOH$, was prepared by hydrolysis of the above described furanone by allowing a solution of 40 g.

in 125 cc. of methanol and 15 g. of potassium hydroxide to stand at room temperature for 10 days. The product was crystallized from ethyl acetate; yield 31.9 g. (73%). When a larger excess of alkali was used or the reaction carried out at a higher temperature, the yield was greatly diminished, and propiophenone was isolated from the residual oils as the semicarbazone (identified). Careful search failed to reveal a stereoisomeric acid. This acid has been mentioned already in the literature (11) (m.p. 140–145°) but no analysis was given. Our product was crystallized twice from ethyl acetate and eight times from 75% ethanol and melted at 150–152°.

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8.
Found: C, 69.5, 69.5; H, 6.9, 6.9.

The methyl ester, $C_6H_5COCH(CH_3)CH(CH_3)COOCH_3$, was made in good yield by the action of diazomethane on the acid in the usual way. The reaction was immediate and vigorous. The product distilled at 137–139° at 2–3 mm. pressure; n_D^{25} 1.511; dispersion ($n_F - n_C$) 0.0144.

Anal. Calc'd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3.
Found: C, 70.7; H, 6.9.

The ester was prepared also by the action of refluxing methanol and sulfuric acid. Hydrolysis with alcoholic potassium hydroxide (standing 17 hours at room temperature) of samples prepared by either method gave the parent acid. Attempts to make a crystalline semicarbazone failed.

SUMMARY

Reduction of *trans*-2,3-dimethyl-3-*p*-xenoylacrylic acid and methyl ester and of the open-chain *cis* ester gives the saturated compounds, presumably through 1,6-reactions. The *cis* pseudo ester is not easily reduced.

The *cis* acid in reduction appears to function as the α,β-unsaturated lactonol or 5-hydroxyfuranone. Stannous chloride reduction probably involves the 5-chlorofuranone as an intermediate. The product of these reductions is the α,β-unsaturated lactone. Reduction in alkaline medium gives the saturated acid and appears to involve the open-chain form.

The stereoisomeric 2,3-dimethyl-3-xenoylpropionic acids and their esters have been prepared. Further reduction by sodium and alcohol gives the corresponding γ-lactone which is obtainable also by catalytic reduction of the α,β-unsaturated lactone.

The dimethylxenoylpropionic acids are dehydrated to an unstable enol lactone which readily undergoes rearrangement into the more stable α,β-unsaturated lactone (by shift of the double bond). Hydrolysis of these unsaturated lactones regenerates the saturated ketonic acids and oxidation gives an 5,5′-dimolecular product.

The analogy between the unsaturated lactones (as α-furanones) and the β-hydroxyfurans and β-furanones is discussed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

SPIROCYCLOHEXANE-1,1′-INDANE, ITS SYNTHESIS AND PROPERTIES[1]

MEYER LEVITZ, DAVID PERLMAN[2], AND MARSTON TAYLOR BOGERT

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In their study of the cyclodehydration of 1-*beta*-phenylethylcyclohexanol-1 (I) with sulfuric acid, Perlman, Davidson, and Bogert (1) postulated the intermediate formation of the olefin 1-*beta*-phenylethylcyclohexene-1 (II). Cyclization at the *gamma* carbon should yield spirocyclohexane-1,1′-indane (IV), while cyclization at the cyclohexene ring carbon 2 should yield *as*-octahydrophenanthrene (III). They proved the formation of *as*-octahydrophenanthrene by obtaining phenanthrene when the products of cyclodehydration were subjected to selenium dehydrogenation. The presence of the spirane in the lower-boiling fractions of the cyclodehydration products was shown by oxidation with permanganate to *alpha,alpha*-pentamethylenehomophthalic acid (VI). *as*-Octahydrophenanthrene itself can exist in *cis* and *trans* forms. By fractional distillation of the hydrocarbon mixture obtained by the cyclodehydration of 1-*beta*-phenylethylcyclohexanol-1 with phosphorus pentoxide, van de Kamp and Mosettig (2) believed that they obtained the *cis* and *trans* isomerides in two main fractions, 20% being *trans*-octahydrophenanthrene, 70% *cis*-octahydrophenanthrene and "a relatively small mixed fraction." No mention was made of the spirane. Cook, Hewett, and Robinson (3) questioned the validity of this work. By a series of fractional distillations of the product obtained by this method and also by the cyclization of 1-*beta*-phenylethylcyclohexene-1 (made by the action of potassium hydrogen sulfate on 1-*beta*-phenylethylcyclohexanol-1) with aluminum chloride, they obtained fractions having refractive indices similar to those reported by van de Kamp and Mosettig for the *cis* and *trans* isomerides. Analysis of each fraction by oxidation to ketones followed by oximation and fractional crystallization showed that none of the fractions was homogeneous. It seemed likely that the refractive indices reported by van de Kamp and Mosettig were for mixtures of *cis*- and *trans*-octahydrophenanthrene and spirane in various proportions. No work, however, was done on checking the solid derivatives prepared by van de Kamp and Mosettig.

[1] Presented before the Organic Division of the American Chemical Society, at its Cincinnati Meeting, April 8–12, 1940.

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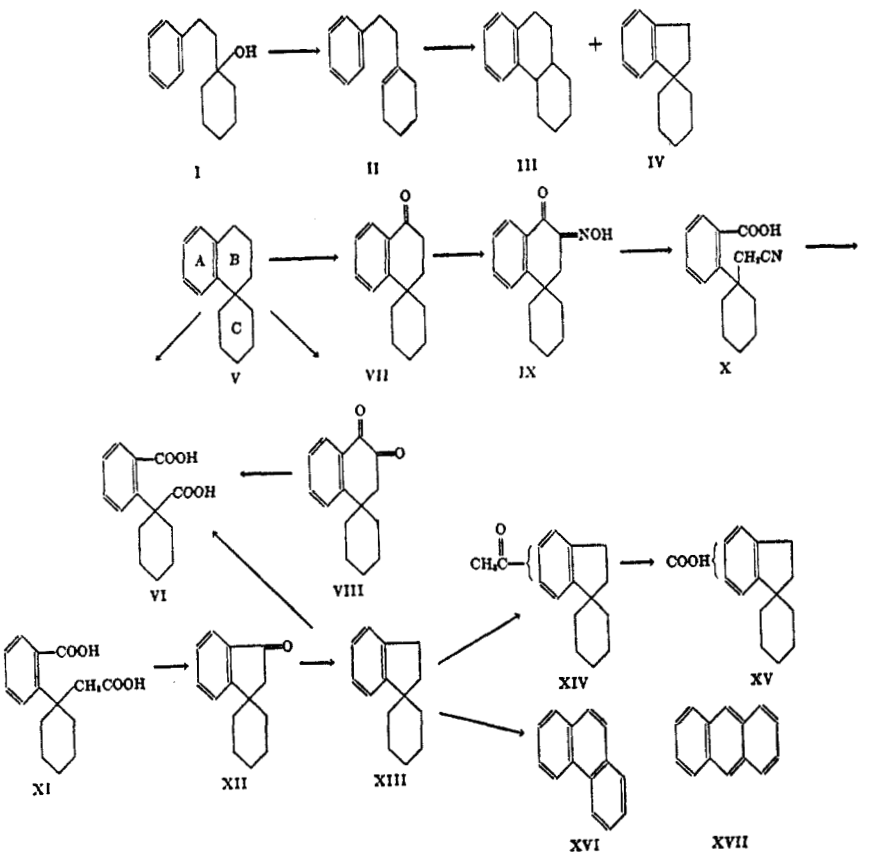
The physical constants for *trans*-octahydrophenanthrene reported by the latter workers have subsequently been used as references by investigators who have been interested in obtaining compounds free from steric isomers. Marvel and co-workers (4) reported the synthesis of trans-Δ^{11}-dodecahydrophenanthrene by the cyclization of di-Δ^1-cyclohexenylacetylene followed by a Clemmensen reduction. The dodecahydrophenanthrene was considered to be *trans* because when it was subjected to selenium dehydrogenation (5) a compound was produced with physical constants similar to those of the *trans*-octahydrophenanthrene of van de Kamp and Mosettig. No solid derivatives were prepared for comparison with corresponding derivatives made by the latter.

Linstead and Walpole (6, 7) hydrogenated and oxidized the *trans*-9-ketododecahydrophenanthrene of Marvel to prepare a *trans*-perhydrodiphenic acid. This acid and isomeric perhydrodiphenic acids from other sources were used by them for a study of the Blanc rule (8). Although, according to this rule, a dibasic acid with two carboxyl groups occupying the 1,6 positions in the chain should yield a ketone on treatment with acetic anhydride and subsequent distillation, notable exceptions occur in the steroid group. Thilobilianic acid, for example, yields only an anhydride on such treatment (9). Linstead and Walpole found, that of the four isomeric perhydrodiphenic acids which they examined, only the one derived from the *trans*-9-ketododecahydrophenanthrene of Marvel failed to give a ketone, an anhydride being produced. They suggest that with this perhydrodiphenic acid and with similar acids derived from sterols, failure to give a ketone is due to a *trans* configuration. The explanation, however, rests ultimately on the validity of the work of van de Kamp and Mosettig on *trans*-octahydrophenanthrene. It seemed important, therefore, to re-investigate the products of the cyclodehydration of 1-*beta*-phenylethylcyclohexanol-1, particularly the lower-boiling fractions from which van de Kamp and Mosettig believed they isolated the *trans* isomeride. Since it was shown by Perlman, Davidson, and Bogert (1) that the lower-boiling fractions also contained spirocyclohexane-1,1′-indane, a synthesis was undertaken to obtain the pure spirane.

Spirocyclohexane-1,1′-tetralin (V), prepared according to the method of Perlman, Davidson, and Bogert (10), was oxidized with chromic acid in glacial acetic acid at room temperature to the corresponding ketone (VII). The method was similar to the one used by Schroeter (11) in oxidizing tetralin to *alpha*-tetralone. A small amount of the diketone (VIII) was obtained at the same time. Oxidation of the diketone with hydrogen peroxide to *alpha,alpha*-pentamethylenehomophthalic acid and the formation of a quinoxaline derivative with *ortho*-phenylenediamine

point to the structure assigned to it. By the action of butyl nitrite and hydrochloric acid on an alcoholic solution of the monoketone an isonitroso derivative (IX) was produced. A Beckmann rearrangement of the second order (12) opened ring B, producing 1-*ortho*-carboxyphenylcyclohexylacetonitrile (X), which on hydrolysis gave the dibasic acid, 1-*ortho*-carboxyphenylcyclohexylacetic acid (XI). Ring closure to spirocyclo-



hexane-1,1′-indanone-3′ (XII) was effected by the Blanc method (8). A Clemmensen reduction (13) gave the desired hydrocarbon, spirocyclohexane-1,1′-indane (XIII). That no change had taken place in any part of the molecule but ring B during the synthesis was proved by chromic acid oxidation of this spirane to *alpha,alpha*-pentamethylenehomophthalic acid. The original spirane, spirocyclohexane-1,1′-tetralin, gives the identical acid on oxidation (10).

An acetyl derivative (XIV) and its semicarbazone were prepared from spirocyclohexane-1,1′-indane. The acetyl group was oxidized with sodium hypochlorite, spirocyclohexane-1,1′-indanecarboxylic acid (XV) being produced.

The oxime of spirocyclohexane-1,1′-indanone-3′ melted at 137–138°. Cook *et al.* (3, 14), by cold chromic acid oxidation of a glacial acetic acid solution of the mixture of hydrocarbons resulting from the cyclization of 1-*beta*-phenylethylcyclohexanol-1, obtained a mixture of ketones which were converted to oximes. By fractional crystallization they isolated three oximes which melted respectively at 187.5°, 175–177°, and 124°. The first of these they believed to be the oxime of spirocyclohexane-1,1′-indanone-3′, and the other two, those of *trans*- and *cis*-ketoöctahydrophenanthrene respectively. The wide divergence in melting points (137–138° and 187.5°) for what was supposedly the same compound, led us to re-investigate the aforementioned hydrocarbon mixture by a procedure essentially identical with that of Cook *et al.* Three oximes were isolated which melted at 187–188°, 136.5–137°, and 123–124° respectively. Each oxime was nitrated and hydrolyzed to a nitro ketone. Comparison with compounds previously reported follows:

(a) The oxime m.p. 187–188° which yielded a nitro ketone m.p. 222° (decomp.) is evidently the same as the oxime m.p. 187.5° reported by Cook *et al.*

(b) The oxime m.p. 136.5–137° is identical with the oxime m.p. 137–138° of the synthesized spirocyclohexane-1,1′-indanone-3′ (XII). Each oxime gave identical nitro oximes m.p. 187–188°, and identical nitro ketones m.p. 192–192.5°.

(c) The oxime m.p. 123–124° which yielded a nitro ketone m.p. 149–150° is evidently the same as the oxime m.p. 124° reported by Cook *et al.* The nitro ketone prepared by them melted at 150–150.5°.

No oxime corresponding to the one of m.p. 175–177° could be isolated. The isolation of the oxime of spirocyclohexane-1,1′-indanone-3′ from the hydrocarbon mixture, and its identity with the synthesized oxime, is the first proof based on synthesis, that a spirane is one of the products of the cyclodehydration of 1-*beta*-phenylethylcyclohexanol-1. This confirms the findings of Perlman *et al.* (1) based on oxidation methods.

A comparison of the physical properties of spirocyclohexane-1,1′-indane and its derivatives with the compounds thought to be *cis*- and *trans*-octahydrophenanthrene by van de Kamp and Mosettig is made in Table I. The constants reported by Cook, Hewett, and Robinson (3) for the *cis* and *trans* isomerides, and the constants reported by Marvel and co-workers for their dodecahydrophenanthrene (4) and the *trans*- octahydrophenan-

threne (5) thought to be obtained by selenium dehydrogenation of this dodecahydrophenanthrene are also given.

It seems likely that the substance which van de Kamp and Mosettig separated from the cyclization products of 1-*beta*-phenylethylcyclohexanol-1 was not *trans*-octahydrophenanthrene but mainly spirocyclohexane-1,1′-indane. The differences in densities, refractive indices and melting points of derivatives can be accounted for by the presence of

TABLE I

	BOILING POINT, °C.	REFRACTIVE INDEX		DENSITY		—COCH₃, M.P., °C.	SEMICARBAZONE, M.P., °C.	—COOH, M.P., °C.
		Temp., °C.	n_D	Temp., °C.	d_4			
Spirocyclohexane-1,1-indane	99–100/2 mm.	15	1.5483	25	0.9912	97–97.5	231–231.5	239–240
	132–133/10 mm.	25	1.5440					
trans-Octahydrophenanthrene, van de K. and M. (2)	135.5–135.7/ 10.5–10.8 mm.	15	1.5460	25	0.9828	94–94.5	230–231.5	226–228
trans-Octahydrophenanthrene, Cook *et al.* (3)		20.7	1.5528	20	1.0060			
trans-Octahydrophenanthrene, Marvel *et al.* (5)	94–95/1.5 mm.	15	1.5452	25	0.9840			
Dodecahydrophenanthrene, Marvel *et al.* (4)	81–82/1.5 mm.	20	1.5102	20	0.9674			
cis-Octahydrophenanthrene, van de K. and M. (2)	142.6–142.8/9.2 mm.	10.6	1.5592	25	1.0053	oily	211–213	230–232
cis-Octahydrophenanthrene, Cook *et al.* (3)	88–90/0.1–0.15 mm.	12.2	1.5586	13	1.0164			
		20.7	1.5549	20	1.0110			

isomeric compounds in the fractionation sample of van de Kamp and Mosettig. This is in harmony with the work of Perlman *et al.* (1) and Cook *et al.* (3), who found that mixtures of *cis*- and *trans*- octahydrophenanthrene and spirocyclohexane-1,1′-indane could not be separated into pure components by fractional distillation.

A study was undertaken to see whether spirocyclohexane-1,1′-indane would rearrange with concurrent aromatization to phenanthrene when subjected to conditions employed in dehydrogenating compounds thought

to be hydrogenated phenanthrenes. There is often the possibility that the latter compounds are not hydrogenated phenanthrenes but isomeric spiranes. After Cook *et al.* (3) had cited evidence to show that the fractions of van de Kamp and Mosettig were mixtures, Marvel, Mozingo, and Kirkpatrick (15) reconsidered the structure of the *trans*-dodecahydrophenanthrene previously reported (5), with the possibility in mind that the compound might be the isomeric spirane. Confirmation of the hydrophenanthrene structure was lacking, since selenium fusion at 300–335° for 23 hours had given no phenanthrene (5). Since they now obtained 2.3 g. of phenanthrene by passing 4.2 g. of the compound repeatedly over platinum on charcoal at 300–320°, they cited this fact as definitely establishing the compound as a phenanthrene derivative. Linstead and Walpole (6) boiled the compound for 24 hours with palladium-charcoal and found that the product failed to yield a picrate although its physical properties were considerably changed (b.p. 95–98/1.5 mm., n_D^{16} 1.5452, d_4^{25} 0.9872). When they passed 1.25 g. of the original compound over palladium-charcoal at 330° during 8 hours, and then swept the tube with hydrogen, only a small quantity of liquid, from which phenanthrene picrate was obtained, collected in the receiver. Sweeping the tube at 340–350° yielded 0.5 g. of a sublimate m.p. 94–95° identified as phenanthrene. They cited these experiments as evidence of the correctness of Marvel's view that the hydrocarbon was a hydrophenanthrene.

Several cases have been reported where spirane compounds have rearranged during dehydrogenation operations. Clemo and Ormston (16) obtained 0.06 g. of naphthalene when 1.2 g. of cyclohexanespirocyclopentane was heated with selenium at 280–320° for 43 hours. Sen-Gupta (17) reported that spirocyclopentane-2,2′-tetralin gave phenanthrene and a small amount of anthracene (yields not given) when subjected to selenium at 300–350° for 40 hours. The same author (18) reported that under similar conditions 7-methylspirocyclopentane-2,2′-tetralin gave 3-methylphenanthrene and "probably *beta*-methylanthracene" (yields not given). Cook and Hewett (19), by similar selenium fusion, found that 3 g. of 7,8-dihydrophenalyl-7-spirocyclopentane gave 0.6 g. of 2-methylpyrene (20) and 5 g. of 7,8-dihydrophenalyl-7-spirocyclohexane gave pyrene (0.15 g. of picrate); while spirocyclopentane-1′,1′-cyclopentanonaphthalene-1,2 gave chrysofluorene.

Several cases have been reported where spiranes did not undergo rearrangement under dehydrogenation conditions. Cook and co-workers (21) reported that 4,5-benzhydrindene-1-spirocyclohexane was not affected by selenium or platinum black at 300–320°. Perlman *et al.* (10) found that

spirocyclohexane-1,1′-tetralin (V) and spirocyclopentane-1,1′-tetralin gave no aromatic products when heated with selenium at 290–350°.

It was found that heating spirocyclohexane-1,1′-indane with either selenium at 300–340° for 44 hours or sulfur at 300° for 40 hours gave no aromatic products. Heating with palladium-charcoal at an internal temperature of 330–340° for 15 hours gave a small amount of phenanthrene. Vapor-phase dehydrogenation at 370–375° gave considerable phenanthrene while at 400–420° the main product was anthracene.

ACKNOWLEDGMENTS. We are deeply indebted to Dr. Eric C. Kunz, Executive Manager of Givaudan-Delawanna, Inc., for a generous supply of the phenylpropyl alcohol required for this investigation.

We are also under obligation to Mr. Saul Gottlieb, of these laboratories, who carried out the analytical work reported.

EXPERIMENTAL

Thermometers used for distillations and melting points were calibrated against a set of total immersion thermometers calibrated by the Bureau of Standards. Melting points were taken in an open beaker with mechanical stirring while the temperature was raised at the rate of 2 to 3 degrees per minute. All melting points determined were corrected. Densities were measured with a 3 ml. pyknometer and were precise to ±0.0002. Refractive indices were taken with an Abbé refractometer kept at 25° ± .01° by circulating water from a thermostat controlled by a thermoregulator (22) by means of a gear pump. The readings were precise to ±0.0002.

Spirocyclohexane-1,1′-tetralin (V) was prepared according to the method of Perlman, Davidson, and Bogert (10). Phenylpropyl bromide, from phenylpropyl alcohol and phosphorus tribromide, was put through Grignard's reaction with cyclohexanone. The resulting 1-*gamma*-phenylpropylcyclohexanol-1 was cyclodehydrated by means of 85% sulfuric acid to the hydrocarbon: yield, 41.5% (on the basis of the phenylpropyl alcohol used); b.p., 135°/4 mm.; m.p. 40–41°. Previously reported (10): yield, 41.8%; b.p. 154°/10 mm.; m.p. 40–41°.

Spirocyclohexane-1,1′-tetralone-4′ (VII). Two hundred and fifty milliliters of chromic acid solution (50 g. of chromic acid dissolved in 30 ml. of water and diluted with sufficient glacial acetic acid to make 250 ml.) was added dropwise with stirring to 50 g. of spirocyclohexane-1,1′-tetralin dissolved in 300 ml. of glacial acetic acid. The solution was cooled to keep the temperature between 20° and 25° during the process. After the solution had stood for a week at room temperature most of the acetic acid was removed under a vacuum. Water was added and the mixture was extracted twice with 200-ml. portions of petroleum ether. The petroleum ether solution was colored pink due to the presence of a small amount of diketone. The latter was removed by vigorous mechanical agitation with a saturated aqueous sodium bisulfite solution until the pink color disappeared. A white solid bisulfite compound of the diketone formed. The petroleum ether layer was separated, washed with water, sodium carbonate solution, and water. After drying over magnesium sulfate, the solvent was removed by distillation and the ketone was

distilled under reduced pressure. Recrystallization from petroleum ether gave white, flat plates; yield, 38 g. or 71%, b.p. 147–150°/1 mm.; m.p. 63.5–64°.

Anal. Calc'd for $C_{15}H_{18}O$: C, 84.1; H, 8.5.
Found: C, 84.3; H, 8.6.

Semicarbazone. Prepared by refluxing the ketone with semicarbazide hydrochloride and sodium acetate in ethyl alcohol for two hours. Recrystallization from hot ethyl alcohol produced white needles, m.p. 236.5–237°.

Anal. Calc'd for $C_{16}H_{21}N_3O$: C, 70.8; H, 7.8; N, 15.5.
Found: C, 70.7; H, 7.8; N, 15.6.

Oxime. Prepared by refluxing the ketone with hydroxylamine hydrochloride and sodium acetate in ethyl alcohol for four hours. Recrystallization from hot ethyl alcohol produced white needles, m.p. 178–178.5°.

Anal. Calc'd for $C_{15}H_{19}NO$: C, 78.6; H, 8.4; N, 6.1.
Found: C, 78.7; H, 8.6; N, 6.3.

3,4-Diketospirocyclohexane-1,1'-tetralin (VIII). The white solid bisulfite compound formed by the treatment of the above petroleum ether solution with sodium bisulfite was decomposed with hydrochloric acid and extracted with ether. The orange ether solution was washed with water, sodium carbonate solution, and water. After drying over magnesium sulfate, the ether was evaporated and the orange crystals formed were recrystallized from hot ethyl alcohol, giving orange plates, m.p. 131.5–132.5°; yield, 2.5 g. or 4.4%.

Anal. Calc'd for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1.
Found: C, 79.0; H, 7.1.

The diketone was oxidized in hot ethyl alcohol solution according to the method of Holleman (23), by adding 30% hydrogen peroxide and a few drops of 10% sodium hydroxide from time to time. After heating for one hour on the steam-bath, the solution was diluted with water, treated with boneblack, and acidified. The acid produced was *alpha,alpha*-pentamethylenehomophthalic acid as shown by its melting point (154–155°), which was not depressed when the acid was mixed with an authentic sample.

Quinoxaline derivative. Prepared by refluxing the diketone with *o*-phenylenediamine in ethyl alcohol. Recrystallized from hot ethyl alcohol, it formed long white needles; m.p., 142.5–143.5°.

Anal. Calc'd for $C_{21}H_{20}N_2$: C, 84.0; H, 6.7; N, 9.3.
Found: C, 83.8; H, 6.7; N, 9.5.

Isonitrosospirocyclohexane-1,1'-tetralone-4' (IX). Prepared according to the method of Claisen and Manasse for making isonitroso compounds (24). Better yields with cleaner products were obtained when ether was used as diluent. Three and three-tenths milliliters of concentrated hydrochloric acid was added to a solution of 30 g. of the ketone in 40 ml. of ethyl alcohol and 20 ml. ether. The solution was stirred and 23 ml. of butyl nitrite added at such a rate that the temperature was kept just below the boiling point of the ether. The stirring was continued for two hours and the mixture allowed to stand at room temperature for two days, then filtered and washed with ether; yield, 24 g., or 71%. Recrystallization from hot ethyl alcohol gave very pale yellow needles, m.p. 203.5–204.5° with decomposition.

Anal. Calc'd for $C_{15}H_{17}NO_2$: C, 74.0; H, 7.0; N, 5.8.
Found: C, 74.2; H, 7.2; N, 5.5.

1-ortho-*Carboxyphenylcyclohexylacetonitrile* (X). A small amount of *p*-toluenesulfonyl chloride was added to 20 g. of the isonitroso compound suspended in 150 ml.

of 10% sodium hydroxide. The mixture was heated on a steam-bath and the remainder of 28 g. of *p*-toluenesulfonyl chloride was added in small portions. Heating was continued for one-half hour until complete solution took place. The clear red solution was treated with boneblack. On acidification, a gummy precipitate formed, which changed to a crystalline mass when allowed to stand overnight. When recrystallized by dissolving in hot benzene and adding "Skellysolve D," white needles formed on cooling; yield, 18 g., or 90%; m.p. 147.5–148.5°.

Anal. Calc'd for $C_{15}H_{17}NO_2$: C, 74.0; H, 7.0; N, 5.8.
Found: C, 74.0; H, 6.9; N, 5.6.

1-ortho-*Carboxyphenylcyclohexylacetic acid* (XI). Twenty-five grams of the nitrile acid and 250 ml. of 10% aqueous sodium hydroxide were refluxed on a sand-bath for twelve hours. The solution was decolorized and acidified. Unreacted nitrile acid was removed by extracting with hot benzene, the dibasic acid being relatively insoluble. Recrystallization from hot methyl alcohol-water gave white plates; yield, 22.5 g., or 84%; m.p. 206–207°.

Anal. Calc'd for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9.
Found: C, 68.9; H, 7.1.

Spirocyclohexane-1,1′-indanone-3′ (XII). Since the mixture of dibasic acid and acetic anhydride bumped badly when heated, it was found best to use several small portions of acetic anhydride instead of the larger quantity suggested by Blanc (25). Twenty grams of 1-*ortho*-carboxyphenylcyclohexylacetic acid and 10 g. of acetic anhydride in a small distilling flask were heated slowly in a metal-bath until the temperature of the mixture was 160°. During the process (which took one hour) acetic acid and acetic anhydride distilled over. The operation was repeated with three fresh 10-ml. portions of acetic anhydride. The temperature was then raised and the product was distilled over at atmospheric pressure. It was dissolved in benzene, washed free from acid, and dried over calcium chloride. The benzene was removed by distillation and the ketone was distilled under reduced pressure; yield, 13 g., or 85%; b.p. 128–129°/2 mm.; m.p. 58–59°. It crystallized from petroleum ether in the form of white plates.

Anal. Calc'd for $C_{14}H_{16}O$: C, 84.0; H, 8.1.
Found: C, 84.2; H, 8.2.

Semicarbazone. Prepared by refluxing the ketone with semicarbazide hydrochloride and sodium acetate in ethyl alcohol for two hours, recrystallized from hot ethyl alcohol-water in fine white needles, m.p. 211.5–212.5°.

Anal. Calc'd for $C_{15}H_{19}N_3O$: C, 70.0; H, 7.4; N, 16.3.
Found: C, 70.1; H, 7.4; N, 16.7.

Oxime. Prepared by heating the ketone with hydroxylamine hydrochloride in pyridine on a water-bath for three hours, according to the method of Cook *et al.* (14). The same oxime was produced by refluxing the ketone with hydroxylamine hydrochloride and sodium acetate in ethyl alcohol for four hours. Recrystallization from hot ethyl alcohol-water produced thin white needles, m.p. 137–138°.

Anal. Calc'd for $C_{14}H_{17}NO$: C, 78.1; H, 8.0; N, 6.5.
Found: C, 77.9; H, 8.1; N, 6.9.

Nitro oxime. The oxime was nitrated in cold concentrated sulfuric acid solution according to the method of Cook *et al.* (3) by the addition of powdered potassium nitrate. Recrystallization from acetone-water produced white needles, m.p. 187–188°.

Anal. Calc'd for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.2; N, 10.8.
Found: C, 64.4; H, 6.4; N, 11.0.

Nitro ketone. The ketone was nitrated as above. Recrystallization from acetone-water gave white plates, m.p. 192–192.5°. The same nitro ketone was produced when the above nitro oxime was hydrolyzed by refluxing with 10% sulfuric acid.

Anal. Calc'd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.2; N, 5.7.
Found: C, 68.6; H, 6.2; N, 5.8.

Spirocyclohexane-1,1'-indane (XIII). Ten grams of ketone was refluxed with 50 g. of amalgamated zinc, 40 ml. of glacial acetic acid, 30 ml. of water, and 50 ml. of concentrated hydrochloric acid for twenty hours. Ten grams more of amalgamated zinc was then added and the refluxing continued for 10 hours. During the entire process 10-ml. portions of hydrochloric acid were added at six hour intervals, four portions being thus added. The hydrocarbon was extracted with ether and the ether solution washed successively with water, sodium carbonate solution, and water. After drying over magnesium sulfate, the ether was evaporated and the hydrocarbon was distilled over sodium under reduced pressure; yield, 7.5 g., or 81%; b.p. 99–100°/2 mm., 132–133°/10 mm.; n_D^{18} 1.5483; n_D^{25} 1.5440; d_4^{25}0.9912; M_D calc'd 58.85; M_D obs. 59.29.

Anal. Calc'd for $C_{14}H_{18}$: C, 90.3; H, 9.7.
Found: C, 90.4; H, 9.8.

A sample of the hydrocarbon was refluxed in acetic acid with chromic acid for one hour. Most of the acetic acid was then removed *in vacuo* and the residue taken up with water. The crystallized acid was filtered off, dissolved in sodium hydroxide, treated with boneblack, and acidified. The *alpha,alpha*-pentamethylenehomophthalic acid produced melted at 155–155.5° and did not depress the melting point of an authentic sample.

Acetylspirocyclohexane-1,1'-indane (XIV). The hydrocarbon was acetylated according to the general method of Mosettig and van de Kamp (26) using nitrobenzene as the solvent. The same acetyl derivative was obtained in much better yield when purified petroleum ether (b.p. 40–60°) was used instead of nitrobenzene. The petroleum ether was purified by washing with concentrated sulfuric acid, water, sodium carbonate solution, and water. It was then dried over calcium chloride and distilled. Three grams of aluminum chloride was suspended in 15 ml. of petroleum ether, and 2 g. of hydrocarbon dissolved in 6 ml. of petroleum ether added. The mixture was cooled in ice-water and after the addition of 1.2 g. of acetyl chloride it was allowed to remain in the ice-water for one-half hour and at room temperature overnight. It was then poured upon ice and treated with 15 ml. of concentrated hydrochloric acid. The oil was extracted with ether, washed free from acid, and dried over magnesium sulfate. On evaporating the solvent, a gummy residue appeared, from which crystals were obtained when petroleum ether was added and the mixture chilled with dry ice. White, thin needles were secured by crystallization from hot ethyl alcohol-water; yield, 1.2 g., or 49%; m.p. 97–97.5°.

Anal. Calc'd for $C_{16}H_{20}O$: C, 84.2; H, 8.8.
Found: C, 84.4; H, 9.0.

Semicarbazone. Prepared by refluxing the acetyl compound with semicarbazide hydrochloride and sodium acetate in ethyl alcohol for three hours. Recrystallization from hot ethyl alcohol gave clusters of fine white needles, m.p. 231–231.5°.

Anal. Calc'd for $C_{17}H_{23}N_3O$: C, 71.5; H, 8.1; N, 14.7.
Found: C, 71.7; H, 8.4; N, 14.8.

Spirocyclohexane-1,1'-indanecarboxylic acid (XV). The acetylspirane was dissolved in methyl alcohol and an aqueous solution of sodium hypochlorite added. The solution was refluxed with additions of sodium hypochlorite from time to time until no cloudiness appeared on dilution with water. Acidification with hydro-

chloric acid and recrystallization from methyl alcohol produced long white needles, m.p. 239–240°.

Anal. Calc'd for $C_{15}H_{18}O_2$: C, 78.2; H, 7.9.
Found: C, 78.0; H, 8.0.

Oxidation and oximation of the hydrocarbons from the cyclodehydration of 1-beta-phenylethylcyclohexanol-1. The mixture of hydrocarbons obtained by Perlman, Davidson, and Bogert (1) by the cyclodehydration of 1-*beta*-phenylethylcyclohexanol-1 with 85% sulfuric acid and separated into fractions by them by distillation in an all-glass apparatus with a Widmer column under 10 mm. pressure was used in the following experiments.

Each fraction was dissolved in 6 volumes of glacial acetic acid and oxidized with 5 volumes of chromic acid solution (200 g. of chromic acid dissolved in 110 ml. of water and diluted with glacial acetic acid to 1 liter). The chromic acid solution was added dropwise with stirring to the hydrocarbon solution which was cooled to keep the temperature below 20°, a procedure similar to that used by Cook *et al.* (3). After the solution had stood for a week at room temperature, ethyl alcohol was added to reduce the excess of chromic acid and most of the acetic acid was removed *in vacuo*. Water was added and the mixture extracted twice with petroleum ether. The extract was washed with water, sodium carbonate solution, and water. After drying over magnesium sulfate, the solvent was removed by distillation and the ketones fractionated *in vacuo*. Oximes were prepared by refluxing with hydroxylamine hydrochloride in anhydrous pyridine as above. Isomeric oximes were then separated by fractional crystallization. In addition to the pure oximes listed below each fraction yielded low-melting mixtures of oximes from which it was difficult to isolate pure compounds.

Fraction 1 (n_D^{25} 1.5355) yielded a first crop of oximes from methyl alcohol which melted at 132–134.5°. Recrystallized from methyl alcohol, m.p. 136.5–137°.

Fraction 2 (n_D^{25} 1.5436) similarly yielded an oxime m.p. 134–136°, which melting point was not depressed by the above oxime m.p. 136.5–137°.

Fraction 3 (n_D^{25} 1.5490). The first crop of crystals from methyl alcohol melted at 145–150°. Recrystallization from acetone-water produced an oxime m.p. 186–187°. By the addition of a small amount of water to the methyl alcohol filtrate an oxime m.p. 123–124° was isolated.

Fraction 4 (n_D^{25} 1.5515) and fraction 5 (n_D^{25} 1.5527) each similarly yielded oximes m.p. 187–188° after recrystallization from methyl alcohol. Addition of water to the methyl alcohol filtrates yielded further material which when recrystallized from ethyl alcohol-water melted at 123–124°.

Identification of the oximes. Each oxime was nitrated as above by suspending in ice-cold concentrated sulfuric acid and adding portions of powdered potassium nitrate. They were then recrystallized from acetone-water. The nitro oximes were hydrolyzed to nitro ketones by refluxing with dilute sulfuric acid, and the nitro ketones were crystallized from acetone-water.

The oxime m.p. 123–124° yielded a nitro ketone m.p. 149–150°. This oxime is evidently the same as the oxime m.p. 124° reported by Cook *et al.* (3) as the oxime of *cis*-ketoöctahydrophenanthrene. The nitro ketone prepared by Cook *et al.* melted at 150–150.5°.

The oxime m.p. 136.5–137° proved to be that of the spirocyclohexane-1,1′-indanone. The melting point was not depressed when the substance was mixed with the oxime m.p. 137–138° of the spirocyclohexane-1,1′-indanone synthesized above. Both gave identical nitro oximes m.p. 187–188° and identical nitro ketones m.p. 192–192.5° on hydrolysis with 10% sulfuric acid.

The oxime m.p. 187–188° yielded a nitro ketone m.p. 222° (decomp.). This oxime is evidently the same as the oxime m.p. 187.5° suggested by Cook *et al.* as being that of spirocyclohexane-1,1′-indanone-3′.

Selenium fusion. One gram of spirocyclohexane-1,1′-indane and 3 g. of selenium were placed in a Pyrex test tube with a long piece of Pyrex tubing sealed on to serve as an air condenser. The mixture was heated in a Woods metal-bath for 20 hours at 300–320° and for 22 hours at 330–340° (bath temperature). The product was repeatedly extracted with hot ethyl alcohol and filtered free from selenium. After drying over magnesium sulfate, the alcohol was evaporated and the residue distilled under reduced pressure. About 0.7 g. distilled over. Attempts to form the picrate by treating with a hot saturated alcoholic solution of picric acid gave no picrate.

Sulfur fusion. One gram of spirocyclohexane-1,1′-indane and 0.5 g. of sulfur were heated in an apparatus similar to that of the selenium fusion for forty hours at 300° (bath temperature). The resulting hard mass was ground thoroughly with hot ethyl alcohol and filtered. Attempts to make a picrate by treating the alcohol solution with a hot saturated alcoholic solution of picric acid gave no picrate.

Catalytic dehydrogenation. The catalyst, 30% palladium-charcoal, was prepared according to the method of Zelinsky and Turowa-Pollak (27).

Liquid-phase dehydrogenation. A mixture of 0.8 g. of spirocyclohexane-1,1′-indane with 0.4 g. of catalyst was heated for 15 hours in a tube similar to that used in the selenium fusion. The heating was done with an electric heating coil of nichrome wire which kept the internal temperature at 330–340°. The mixture was extracted with acetone and filtered. After the solvent was evaporated, the residue was heated for 15 minutes on a steam-bath with a saturated ethyl alcohol solution of picric acid. On cooling, a small amount of a crystalline picrate formed. Recrystallized from ethyl alcohol, this was identified as phenanthrene picrate by its melting point 144°, not depressed by an authentic sample (m.p. 145°). Decomposition of the picrate with ammonium hydroxide and extraction of the hydrocarbon with ether, followed by recrystallization from ethyl alcohol, gave phenanthrene of m.p. 98°, not depressed by an authentic sample. The filtrate from the picrate was freed of solvent, ammonium hydroxide was added, and the oil was extracted with ether. Evaporation of the ether followed by oxidation with chromic acid in boiling glacial acetic acid, as above gave *alpha,alpha*-pentamethylenehomophthalic acid, showing that considerable spirane had been unacted upon by the palladium under the conditions of the experiment.

Vapor-phase dehydrogenation. The vapor-phase dehydrogenation was carried out in the apparatus shown in Fig. I. The 60 cm. Pyrex tube (A) of 10 mm. diameter, which was inclined at an angle of about 10° during the experiment, was packed with a mixture of equal weights of asbestos and palladium-charcoal, which extended 15 cm. down from the end of the dropping-funnel (B). The collecting vessel (C) was a side-arm Pyrex test tube 13 cm. long to which a stopcock (D) was sealed at the lower end. (E) was a mercury trap. Heating was accomplished electrically by means of the nichrome wire coil (F), which enclosed a glass thermometer well (G). The apparatus was designed to allow material to be repeatedly recirculated without the admission of air.

Dry nitrogen was passed into the apparatus through (H) to displace the air while the temperature was raised to 370–375°. The flow of nitrogen was stopped and hydrogen, washed with acid permanganate and dried over calcium chloride, was admitted to displace the nitrogen. The flow of hydrogen was then stopped and 2.5 g. of spirocyclohexane-1,1′-indane was added through the dropping-funnel (B) at the rate of 0.5 g. per hour. Material which collected in (C) was drawn off through

the stopcock (D) and recirculated. After two circulations, partial crystallization took place in the liquid condensing from the heated catalyst. The solid was melted down with an auxiliary heating coil and the entire material recirculated twice more. At this point the liquid in (C) was drawn off without melting the solid. The solid was then melted and removed for examination. It was found to be quite low-melting and weighed 0.7 g. By heating it on the steam-bath for 15 minutes with a saturated alcoholic solution of picric acid, 0.4 g. of picrate was obtained. Recrystallization from hot ethyl alcohol produced phenanthrene picrate m.p. 144–145°, not depressed by an authentic sample. Decomposition of the picrate with ammonium hydroxide as above yielded phenanthrene m.p. 100°, not depressed by an authentic sample.

The liquid portion which had been drawn off previously was recirculated at 400–420°. After three circulations, so much high-melting solid formed that it could not be conveniently sent through the apparatus again. The hydrogen in the reaction tube was now displaced by nitrogen and the dehydrogenation product was removed with acetone and filtered. The solvent was evaporated and the residue was recrystallized by dissolving it in purified "Skellysolve B" and chilling in an ice-salt mix-

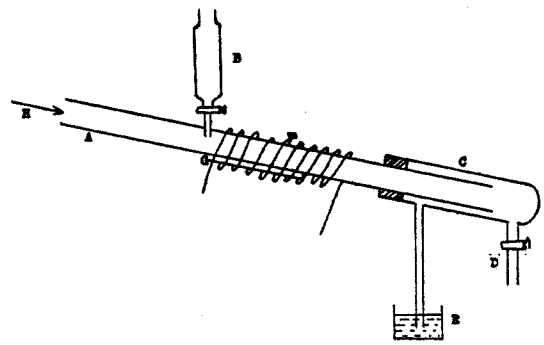


FIG. 1

ture. Four-tenths of a gram of solid was obtained which melted at 120–125°. Two recrystallizations from ethyl alcohol produced 0.15 g. of white plates which melted at 214°, which melting point was not depressed when the compound was mixed with an authentic sample of anthracene. Identification as anthracene was further confirmed by oxidation with chromic acid in boiling glacial acetic acid to anthraquinone. Addition of water to the acetic acid solution produced white needles which on recrystallization from ethyl alcohol melted at 285°. The melting point was not depressed when the compound was mixed with anthraquinone made by oxidizing anthracene in the same manner.

The filtrate of the "Skellysolve B" recrystallization, freed from solvent, gave a little *alpha,alpha*-pentamethylenehomophthalic acid showing that some of the spirane had not been acted upon. From the filtrate of the first recrystallization of the anthracene, 0.05 g. of phenanthrene was obtained.

SUMMARY AND CONCLUSIONS

1. Spirocyclohexane-1,1′-indane has been synthesized by a method which establishes its structure.

2. It is definitely shown that spirocyclohexane-1,1′-indane is one of the products of the cyclodehydration of 1-*beta*-phenylethylcyclohexanol-1, by isolating derivatives of the spirane from the mixture and comparing them with synthetic compounds of known structure.

3. The melting point of the oxime of spirocyclohexane-1,1′-indanone-3′ is 137–138°, and not 187.5° as reported by Cook *et al.*

4. Hydrophenanthrenes believed to have *trans* configurations because they can be changed to octahydrophenanthrenes with constants similar to those reported by van de Kamp and Mosettig for *trans*-octahydrophenanthrene may not *ipso facto* be *trans*. The constants reported by van de Kamp and Mosettig are probably for a mixture of compounds, mainly spirocyclohexane-1,1′-indane.

5. Spirocyclohexane-1,1′-indane undergoes rearrangement, with concurrent aromatization to phenanthrene and anthracene, when dehydrogenated over a palladium-charcoal catalyst. Postulation of structure of hydrophenanthrenes based on dehydrogenation to phenanthrene under the same conditions are suspect if the synthetic methods used can yield isomeric spiranes. This is especially true if the compound thought to be a hydrophenanthrene does not dehydrogenate under the influence of selenium or sulfur. Spirocyclohexane-1,1′-indane gives no aromatic products when fused with either selenium or sulfur.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. VI. THE OCCURRENCE OF CETYL PALMITATE IN CORALS

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Corals occur in almost unlimited quantities in the coastal waters of the tropical regions of the globe. In spite of their abundance, however, little if anything is known about the nature of their organic constituents. Silliman (1), in his classical study on the composition of corals, was the first to point out that in spite of their principally inorganic appearance the stony- or reef-corals contain considerable amounts of organic material. He found that the organic matter of a number of corals amounted to from four to eight per cent of the total, and that it was intimately united with inorganic material throughout the structure of the coral. Silliman's observations have been verified by the more recent studies of Clarke and Wheeler (2), who estimated from two to seven per cent of organic material in twenty-eight species of corals. Silliman also observed that corals contained some wax-like material which was separated from its inorganic surroundings by boiling the corals with water. It was found floating on the surface of the water in "transparent jelly-like masses of yellowish color." Silliman stated that "it was insoluble in alcohol, but readily so in ether, and the ethereal solution yielded a yellow solid resembling wax. It fuses below 200°F." The only other publications which contain some reference to organic constituents of stony corals are those of Montignie (3), who found the presence of sterol-like material indicated by certain color reactions, and of Yonge and collaborators (4), who demonstrated the presence of certain enzymes. No other information concerning the nature of the organic constituents of corals appears to be available at present.

During an investigation of the sterols of corals which is in progress at this laboratory it was found that corals contain significant quantities of wax-like material similar to that described by Silliman. As a rule it can be isolated in a crystalline form by concentrating the acetone extract of the crushed corals. From the staghorn coral, *Madrepora cervicornis*, the wax was obtained in a yield of 0.25%. The recrystallized product melted at 50–50.5°, and its composition and physical properties indicated that it was cetyl palmitate. This was borne out by the fact that saponification

led to the isolation of cetyl alcohol and palmitic acid. Similar results were obtained with the coral *Meandra areolata*. Data so far available indicate that the average content of cetyl palmitate of the stony- or reef-corals is from 0.25–0.5%.

EXPERIMENTAL

All melting points are corrected.

Isolation of cetyl palmitate from Madrepora cervicornis. Two thousand eight hundred and fifty grams of crushed corals was placed in a large Soxhlet apparatus and extracted with acetone for 24 hours. The acetone extract was then concentrated to about 300 cc. and cooled, whereby a copious crystalline precipitate was formed. After filtering, washing with dilute acetone, and drying *in vacuo*, it weighed 6.85 g. and hence represented 0.25% of the total. It was recrystallized six times from acetone. During the last recrystallizations the melting point remained constant at 50.0–50.5°. The refractive index was $n_D^{80°}$ 1.4414; Whitby's (5) value for cetyl palmitate is $n_D^{60°}$ 1.4429.

Anal. Calc'd for $C_{32}H_{64}O_2$: C, 79.93; H, 13.42.
Found: C, 79.33; H, 13.26.

Cetyl alcohol. A 1.0823 g. sample of the wax was refluxed for two hours with an excess of a 1% solution of potassium hydroxide in ethanol. The saponification-mixture was then separated in the usual manner into an alcohol and an acid fraction. The alcohol fraction, weighing 0.47 g., showed a constant m.p. 47.4–47.5° after three recrystallizations from acetone.

A larger quantity of the alcohol was fractionally distilled *in vacuo* from a small flask with a built-in Widmer column. Practically all the material distilled at constant temperature. The distillate melted at 49.2°. Recrystallizations from acetone did not raise this melting point. When mixed with an authentic sample of cetyl alcohol of m.p. 49.3–49.5° and setting point 48.6°, the alcohol melted at 49.5° and set at 48.6°

Anal. Calc'd for $C_{16}H_{34}O$: C, 79.25; H, 14.14.
Found: C, 79.17; H. 14.10.

Cetyl 3,5-dinitrobenzoate. A 0.5 g. sample of authentic cetyl alcohol and 0.8 g. of 3,5-dinitrobenzoyl chloride were dissolved in 25 cc. of dry pyridine and the mixture heated on the steam-bath for two hours. After cooling, the mixture was poured into a separatory funnel and diluted with 400 cc. of ether. Dilute sulfuric acid was then added to remove the pyridine, and the ether layer was washed first with a solution of sodium bicarbonate and then with water. After drying over anhydrous sodium sulfate, the ether was evaporated and the residue recrystallized twice from petroleum ether. The product showed a constant melting point of 72.3°. The 3,5-dinitrobenzoate of the coral alcohol was prepared in the same manner. It melted at 72.2° and gave no depression of the melting point when mixed with cetyl-3,5-dinitrobenzoate.

Anal. Calc'd for $C_{23}H_{36}N_2O_6$: C, 63.28; H, 8.31.
Found: C, 63.47; H, 8.24.

Palmitic acid. The acid obtained by the saponification of 1.0823 g. of coral wax weighed 0.650 g. Its molecular weight as determined by titration was 253.1; palmitic acid 256. After five recrystallizations from acetone the acid melted at 62.5–62.6°. When mixed with an authentic sample of palmitic acid of the same melting point, no depression of the melting point was obtained.

To complete the identification of the acid a larger sample was changed into the methyl ester which was then subjected to fractional distillation *in vacuo* in a flask with a built-in Widmer column. Practically all the material distilled at constant temperature. The distillate melted at 28.2°. Upon hydrolysis of the ester, palmitic acid was obtained which after recrystallization from acetone melted at 62.4–62.5°.

Anal. Calc'd for $C_{16}H_{32}O_2$: C, 74.95; H, 12.57.
Found: C, 75.26; H, 12.49.

SUMMARY

The staghorn coral, *Madrepora cervicornis*, contains between 0.25 and 0.5% of cetyl palmitate.

NEW HAVEN, CONN.

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE COLLEGE]

THE REACTION OF ETHYLENE OXIDE WITH GRIGNARD'S REAGENT

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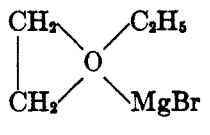
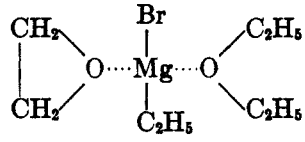
The formation of ethylene bromohydrin from ethylene oxide and ethylmagnesium bromide was explained by Blaise (1) by assuming the intermediate formation of $BrCH_2CH_2OMgBr$ by the splitting of the Grignard reagent between the magnesium and bromine. The following year (1903) Grignard (2) proposed a mechanism involving the formation of an "oxonium" compound, I, which was thought to react with water to form ethylene oxide, ethane, magnesium bromide, and magnesium hydroxide. The ethylene oxide and magnesium bromide would then undergo the Wurtz reaction to form ethylene bromohydrin. Grignard found that heating the reaction-mixture brought about a vigorous reaction which he called the "second phase" and that final hydrolysis gave an excellent yield of *n*-butyl alcohol. This "second phase" reaction was thought to consist of rearrangement of the oxonium compound, under the influence of heat, to form $C_2H_5CH_2CH_2OMgBr$. Studies in this field were extended using ethylene oxide and different Grignard reagents, by Henry (3), Delaby (4), and others.

Meisenheimer (5) contributed analytical data in support of Grignard's ideas and assigned formula II to the "oxonium salt" and $C_2H_5CH_2CH_2OMgBr$ to the product formed in the second phase.



I



II

In 1930, Ribas and Tapia (6) described the formation of the bromochlorohydrin of glycerine by the hydrolysis of an intermediate formed by treating an ether solution of magnesium bromide with epichlorohydrin. Two years later (7) the same authors presented analytical data to

[1] Abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1940.

support their view that the product formed by treating an ether solution of magnesium bromide with a molecular equivalent of ethylene oxide is identical with that obtained by Grignard (8) from ethylene bromohydrin and ethylmagnesium bromide. The assignment of the structure $BrCH_2CH_2OMgBr$ was based upon the fact that approximately one-half of the bromine could be titrated, in dilute nitric acid, as bromide ion. In order to obtain a satisfactory check between the experimental and calculated percentages of total bromine, bromide ion, and magnesium, they assumed that each molecule of $BrCH_2CH_2OMgBr$ held in combination approximately nine-tenths of a molecule of diethyl ether.

Ribas and Tapia (9) described also precipitates formed when ethylmagnesium bromide is treated with varying quantities of ethylene oxide and drew the conclusion that these were mixtures of $BrCH_2CH_2OMgBr$ and $BrCH_2CH_2OMgOCH_2CH_2Br$. In the same article, they mentioned the formation of butyl alcohol when the ether solution was removed from the precipitate formed by the reaction of one mole of ethylmagnesium bromide and one mole of magnesium bromide and then treated with more ethylene oxide. The precipitate formed by the action of ethylene oxide on Grignard reagents was thought to result from the reaction between the oxide and magnesium bromide formed in the Schlenk equilibrium. In equations, Ribas and Tapia used only the formula $(BrCH_2CH_2O)_2Mg$ for the precipitate, in spite of the fact that they considered it a mixture of this with $BrCH_2CH_2OMgBr$, and that their analytical results were interpreted as indicating the latter.

For the reaction of one mole of ethylmagnesium bromide and one mole of ethylene oxide they proposed:

$$[2C_2H_5MgBr \rightleftarrows (C_2H_5)_2Mg + MgBr_2] + 2(CH_2)_2O \longrightarrow (C_2H_5)_2Mg + (BrCH_2CH_2O)_2Mg$$

$$(C_2H_5)_2Mg + (BrCH_2CH_2O)_2Mg \xrightarrow{\text{heat}} (C_2H_5CH_2CH_2O)_2Mg + MgBr_2$$

$$(C_2H_5CH_2CH_2O)_2Mg + 2H_2O \longrightarrow C_2H_5CH_2CH_2OH + Mg(CH)_2$$

Their complete formulation of the reaction of one mole of Grignard reagent and two moles of ethylene oxide was as follows:

$$[2C_2H_5MgBr \rightleftarrows (C_2H_5)_2Mg + MgBr_2] + 4(CH_2)_2O \longrightarrow (C_2H_5CH_2CH_2O)_2Mg + (BrCH_2CH_2O)_2Mg \xrightarrow{4H_2O} 2C_2H_5CH_2CH_2OH + 2BrCH_2CH_2OH + 2Mg(CH)_2$$

The work which we wish to report indicates that the intermediate is a compound of the molecular formula $C_4H_8Br_2MgO_2$. This may be formed by treating magnesium bromide in ether solution with either one or two

moles of ethylene oxide. The structural formula suggested by Ribas can not be considered proved. It would seem to be confirmed by the formation of $(RCH_2CH_2O)Mg$ when $C_4H_8Br_2MgO_2$ is heated with R_2Mg. However, analysis indicates different types of attachment for the bromine atoms. Upon hydrolysis, one-half of the bromine is liberated in the ionic form.

The reaction of Grignard's reagent with one mole of ethylene oxide may be represented by the following equations:

(I) $$2RMgBr \rightleftarrows MgBr_2 + R_2Mg$$

(II) $$MgBr_2 + 2(CH_2)_2O \longrightarrow C_4H_8Br_2MgO_2$$

It is worthy of note that, although both $MgBr_2$ and R_2Mg are formed in the Schlenk equilibrium, ethylene oxide reacts with the bromide only, as long as it is present.

(III) $$C_4H_8Br_2MgO_2 + R_2Mg \xrightarrow{heat} (RCH_2CH_2O)_2Mg + MgBr_2$$

(IV) $$(RCH_2CH_2O)_2Mg + 2H_2O \rightarrow 2RCH_2CH_2OH + Mg(OH)_2$$

As further evidence of the mechanism of this reaction, the following results of experiments are submitted:

(a) $C_4H_8Br_2MgO_2$ was prepared from magnesium bromide and ethylene oxide. The precipitate was suspended in an ether solution of ethylmagnesium bromide and heated. Upon hydrolysis, an excellent yield of butyl alcohol resulted.

(b) Propylmagnesium bromide was treated in ether solution with one mole of ethylene oxide. The $C_4H_8Br_2MgO_2$ was filtered off, and the solution of dipropylmagnesium was heated with $C_4H_8Br_2MgO_2$ prepared from *n*-amylmagnesium bromide and ethylene oxide. *n*-Amylalcohol was the main product of hydrolysis.

(c) The $C_4H_8Br_2MgO_2$ obtained from propylmagnesium bromide was suspended in the ether solution of di-amylmagnesium obtained from *n*-amylmagnesium bromide. Heating and hydrolysis gave *n*-heptyl alcohol.

Dialkylmagnesium compounds, prepared by the dioxane precipitation method (10), react at room temperature with two moles of ethylene oxide to give excellent yields of alcohol.

(V) $$R_2Mg + 2(CH_2)_2O \longrightarrow (RCH_2CH_2O)_2Mg$$

$$(RCH_2CH_2O)_2Mg + 2H_2O \rightarrow 2RCH_2CH_2OH + Mg(OH)_2$$

As would be expected, the reaction of Grignard's reagent with two moles of ethylene oxide gives at room temperature both $C_4H_8Br_2MgO_2$

(equation II) and $(RCH_2CH_2O)_2Mg$ (equation V). Hydrolysis of these gives a mixture of bromohydrin and alcohol.

The preparation of $BrCH_2CH_2OMgBr$ (8) has been accomplished by treating ethylmagnesium bromide with bromohydrin.

$$\text{(VI)} \quad C_2H_5MgBr + BrCH_2CH_2OH \rightarrow BrCH_2CH_2OMgBr + C_2H_6$$

Analysis after the compound had been brought to constant weight in a vacuum desiccator did not indicate retention of ether. If this compound were to exist in quantity when Grignard's reagent and ethylene oxide react in equimolecular ratio, its formation would be expressed by the equation:

$$[2RMgBr \rightleftarrows MgBr_2 + R_2Mg] + 2(CH_2)_2O \longrightarrow$$

$$\text{(VII)} \qquad R_2Mg + (CH_2)_2O + BrCH_2CH_2OMgBr$$

Obviously, the dialkylmagnesium and ethylene oxide on the right hand side of this equation would react at room temperature to form $(RCH_2CH_2O)_2Mg$ (equation V). Hydrolysis of the mixture would be expected to give both alcohol and bromohydrin. All evidence available indicates the formation of bromohydrin only.

Tertiary alkylmagnesium bromides, when treated with one or two moles of ethylene oxide according to the standard procedure, yielded only ethylene bromohydrin, indicating small reactivity of these compounds with either $C_4H_8Br_2MgO_2$ or ethylene oxide. Whitmore (11) reported ethylene chlorohydrin as the main product when tert. butylmagnesium chloride was treated with ethylene oxide. When the filtrate from the tert. butylmagnesium bromide and ethylene oxide (2 moles) reaction was allowed to stand for several months in the presence of light and without heating, a small yield of 3,3-dimethylbutanol was obtained.

When one mole of benzylmagnesium chloride reacted with one mole of ethylene oxide, phenylpropyl alcohol was obtained without heating or standing. The amount of ethylene chlorohydrin produced was small. When two moles of ethylene oxide were heated with one mole of benzylmagnesium chloride, the results were practically the same as when one mole was used. It appears that either dibenzylmagnesium reacts at room temperature with $C_4H_8Cl_2MgO_2$ to form $(C_6H_5CH_2CH_2CH_2O)_2Mg$, or that benzylmagnesium chloride reacts directly with ethylene oxide to give $C_6H_5CH_2CH_2CH_2OMgCl$.

The Grignard reagents were prepared in the usual manner from the alkyl halide and pure magnesium turnings. Each Grignard reagent was treated in three different ways:

(A) Treated with one mole of ethylene oxide and then refluxed with benzene before hydrolysis.

(B) Treated with two moles of ethylene oxide and hydrolyzed without the addition of benzene or heating.

(C) The magnesium halide was precipitated by dioxane and the solution of dialkylmagnesium was treated with two moles of ethylene oxide.

The results of the three methods of procedure are compared in Table I. The theories presented require the formation of $(RCH_2CH_2O)_2Mg$ as the final intermediate in alcohol formation. This may be formed from either

TABLE I

YIELDS OF ALCOHOLS

	$R_2Mg + 2(CH_2)_2O$	$RMgX + 2(CH_2)_2O$ NO HEAT		$RMgX + (CH_2)_2O$ HEAT	
	% Yield of Alcohol	% Yield Halohydrin[b]	% Yield Alcohol[a]	% Yield Halohydrin[b]	% Yield Alcohol[a]
Bromoethane	88	45	72	11	79
1-Bromopropane	90	43	75	6	76
2-Bromopropane	85	45	70	7	74
1-Bromobutane	82	41	71	5	70
2-Bromobutane	70	51	65	9	65
1-Bromo-2-methylpropane	80	41	69	3	64
2-Bromo-2-methylpropane		50	None[c]	60	None
1-Bromopentane	75	40	60	10	69
2-Bromopentane	60	44	50	5	63
1-Bromo-3-methylbutane	70	41	56	4	59
1-Bromo-2-methylbutane	68	35	53	9	58
2-Bromo-2-methylbutane	None	48	None	42	None
2-Chloro-2-methylbutane	None	35	None	39	None
2-Bromo-3-methylbutane	45	41	46	10	40
1-Bromohexane	50	30	47	4	49
2-Bromopentane	55	47	40	6	43
2-Bromo-2-methylbutane		42	None	48	None
Bromobenzene	72	50	55	42	58
Bromocyclohexane	60	42	45	8	50
Benzyl chloride		5	79	3	73

[a] Calculated from alkyl halide.

[b] Calculated from ethylene oxide.

[c] The filtrate gave on long standing a nine per cent yield.

R_2Mg and ethylene oxide or R_2Mg and $C_4H_8Br_2MgO_2$. In complete agreement with theory, Table I reveals that the yields of alcohols are of the same order in all three methods of procedure, even though the amount of ethylene oxide required may be one or two moles.

Structures have not been definitely established for two of the alcohols listed as products of reaction in Table I. With 3,4-dimethylpentanol, alkaline permanganate oxidation gave 3,4-dimethylpentanoic acid, iden-

tical with the product obtained from 2-bromo-3-methylbutane by the malonic ester synthesis. Oxidation of 3,3-dimethylbutanol gave 3,3-dimethylbutanoic acid, which, by the melting point of its amide, was identified with the acid prepared by the successive oxidation of di-isobutylene with chromic acid and with sodium hypobromite (12).

Physical constants of the alcohols have been redetermined and are given in Table II, together with the melting points of derivatives (13).

TABLE II

PHYSICAL CONSTANTS OF ALCOHOLS

	B.P. (740 MM.) °C.	n_D^{23}	d_4^{24}	DERIVATIVES	M.P. °C.
Butanol	116–118	1.3993	0.807	α-Naphthylurethane	71
Pentanol	135–137	1.4100	.816	α-Naphthylurethane	65.5
3-Methylbutanol	130	1.4081	.812	α-Naphthylurethane	67
Hexanol	153–155	1.4131	.818	α-Naphthylurethane	59
3-Methylpentanol	151–152	1.4112	.823	α-Naphthylurethane	58
4-Methylpentanol	150–152	1.4132	.815	α-Naphthylurethane	60
3,3-Dimethylbutanol	141–143	1.4160	.814	3,5-Dinitrobenzoate	83.5
Heptanol	173–174	1.4231	.816	α-Naphthylurethane	62
3-Methylhexanol	161–162	1.4213	.817	α-Naphthylurethane	45.5
5-Methylhexanol	168–169	1.4251	.819	3,5-Dinitrobenzoate	54.5
4-Methylhexanol	168–169	1.4233	.821	α-Naphthylurethane	50
3,4-Dimethylpentanol	160–162	1.4261	.819		
Octanol	190–193	1.4303	.824	α-Naphthylurethane	66
3-Methylheptanol	101 (26 mm.)	1.4293	.821		
2-Phenylethanol	217–219	1.5258	1.027	α-Naphthylurethane	119
2-Cyclohexylethanol	88–90 (7 mm.)	1.4693	0.9185	3,5-Dinitrobenzoate	70.5
3-Phenylpropanol	233–235	1.5351	1.006	Phenylurethane	47

EXPERIMENTAL

Preparation of Grignard reagents. Twenty-four grams (one mole) of magnesium turnings and a crystal of iodine were placed in a dry two-liter three-necked round-bottomed flask fitted with a glycerine sealed stirrer, reflux condenser, and dropping-funnel. The flask was heated with a small flame until the iodine vaporized. It was allowed to cool while one mole of alkyl halide was weighed out. Two milliliters of the halide was added to the reaction-flask and the remainder was mixed with two hundred ml. of anhydrous ether. After starting the reaction with a few ml. of anhydrous ether, an additional fifty ml. of ether was placed in the flask and the ether solution of alkyl halide was added through the dropping-funnel at such a rate as to cause gentle refluxing. After addition was complete the mixture was stirred for two hours and allowed to stand overnight.

Reaction of one mole of Grignard reagent with one mole of ethylene oxide. The Grignard reagent prepared as above was cooled in an ice-salt-bath. One hundred milliliters of anhydrous ether was cooled to 0° and placed in a dropping-funnel with

a tight cork. One mole (44 g.) of ethylene oxide was measured out in a flask, previously calibrated, and cooled to 0°. The cooled ethylene oxide was mixed with the ether in the dropping-funnel and added cautiously to the Grignard reagent. As soon as addition was complete, the ice-salt-bath was removed and the mixture was allowed to come to room temperature while being stirred vigorously. The condenser was set for distillation and the flask was placed in a water-bath at 50° until about 250 ml. of ether had been removed and the contents became pasty. The condenser was again set for refluxing and 250 ml. of anhydrous benzene was added. Gentle refluxing on the water-bath was continued for six hours and the mixture was allowed to stand overnight. After hydrolysis with 100 ml. of water, the benzene layer was decanted. The pasty magnesium hydroxide was extracted three times with small portions of ether, neutralized with iced dilute hydrochloric acid, and again extracted three times with ether. The ether and benzene extracts were combined, dried over anhydrous sodium sulfate and fractionated from a Claisen flask modified by a fifteen-inch Vigreux column which was surrounded by a silvered and highly evacuated jacket.

Reaction of one mole of Grignard reagent with two moles of ethylene oxide. One mole of Grignard reagent was cooled to 0°. Eighty-eight grams of ethylene oxide was measured in a calibrated flask (chilled to 0°) and mixed with 150 ml. of cold ether in the dropping-funnel. After all of the ethylene oxide solution had been cautiously added, the reaction-flask was removed from the cold-bath and the mixture was stirred until it came to room temperature. After standing overnight, the mixture was hydrolyzed with 100 ml. of cold water. After the ether layer had been separated, the aqueous portion was extracted three times with ether, then made acid with cold dilute hydrochloric acid, and again extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether was distilled off. The residue was fractionated with the fifteen-inch column described in the previous experiment. In cases where the boiling points of the alcohol and bromohydrin were close together it was necessary to extract the alcohol fraction with water and thus reduce the total yield.

Reaction of dialkylmagnesium with two moles of ethylene oxide. Dioxane was added through the dropping-funnel to one mole of Grignard reagent at a rate causing gentle refluxing. The addition was continued until no more halides were precipitated as determined by adding a drop of dioxane to the clear supernatant liquid. The halide was removed by centrifuging the mixture in chilled corked tubes and the clear ether solution was decanted into a three-necked flask set up as for the preparation of Grignard reagent. After measuring the total of solution, a two-ml. aliquot was removed, made acid with 0.1 *N* HCl and back titrated with 0.1 *N* NaOH. The total yield of dialkylmagnesium was calculated, and two molecular equivalents of ethylene oxide in cold ether was added as previously described. The mixture was stirred for three hours and allowed to stand overnight. Hydrolysis, extraction, and fractionation were carried out as in the preceding experiment.

Reaction of tert. butylmagnesium bromide with two moles of ethylene oxide. Like the other tert. alkylmagnesium halides, tert. butylmagnesium bromide did not yield an alcohol when treated with two moles of ethylene oxide as described above. In one case, however, the mixture was allowed to stand overnight and the ether solution was removed from the white precipitate by decantation. After standing three months in a tightly stoppered flask, it was hydrolyzed with 50 ml. of water. The ether and water layers were separated and the latter extracted three times with small portions of ether. After drying, the combined ether extracts gave upon frac-

tionation 13 g. of 3,3-dimethylbutanol, which was identified by its boiling point (141°), analysis, and the melting point (83.5°) of the 3,5-dinitrobenzoate.

Reaction of one mole of $C_4H_8Br_2MgO_2$ with one mole of ethylmagnesium bromide. One hundred sixty grams of bromine was added, dropwise, to 24 g. of magnesium covered with 700 ml. of ether. The rate of addition was regulated to produce gentle refluxing. Stirring was continued for two hours after the addition of bromine was complete. Most of the ether was poured off and the precipitate was washed three times by decantation with 50-ml. portions of ether. The precipitate was then suspended in 200 ml. of anhydrous ether and one mole of an ether solution of ethylmagnesium bromide was added. Stirring was continued one hour. Three hundred milliliters was distilled off and replaced by an equal volume of benzene. After refluxing six hours, the mixture was allowed to stand overnight. It was then hydrolyzed, extracted, dried, and fractionated using the same technique as in the reaction of Grignard reagents with one mole of ethylene oxide. A seventy-three per cent yield (54 g.) of normal butyl alcohol was obtained.

Reaction of $C_4H_8Br_2MgO_2$ prepared from Grignard reagents with dialkylmagnesium from other Grignard reagents. To carry out experiments of this type, two-liter three-necked round-bottomed flasks were modified by sealing a stopcock into the bottom in such a manner that glass wool filters could be placed in the opening. By using these flasks, it was possible to remove the ether solution without exposing it or the precipitate to moisture, oxygen, or carbon dioxide of the air.

In one flask *n*-propylmagnesium bromide was treated with one mole of ethylene oxide in ether, as already described. In the second flask, *n*-amylmagnesium bromide was treated with the same amount of ethylene oxide. After completion of the reactions, the ether solutions were removed and the precipitates washed three times with anhydrous ether. The combined ether solution from *n*-propylmagnesium bromide was added to the $C_4H_8Br_2MgO_2$ from *n*-amylmagnesium bromide, while the ether solution from the latter was added to the $C_4H_8Br_2MgO_2$ in the first flask. Three hundred milliliters of ether was removed from each flask by distillation and replaced with an equal amount of benzene. The mixtures were finally refluxed for six hours before hydrolysis and fractionation. The ether solution from *n*-propylmagnesium bromide gave a sixty-one per cent yield of *n*-amyl alcohol while that from *n*-amylmagnesium bromide gave a forty-six per cent yield of *n*-heptyl alcohol.

Hydrolysis of $C_4H_8Br_2MgO_2$. One mole of magnesium and 500 ml. of anhydrous ether were placed in a three-liter three-necked round-bottomed flask fitted with a reflux condenser, glycerine sealed stirrer, and dropping-funnel. One mole of bromine was allowed to drop into the ether magnesium mixture at such a rate that gentle refluxing took place. After the addition of one-half of the bromine, 250 ml. of anhydrous ether was added through the reflux condenser. After all of the bromine had been added, the mixture was stirred for two hours. To the cooled $MgBr_2$ ether solution one mole of ethylene oxide in cold ether was added. The reaction-mixture was stirred for six hours, refluxed for one hour and allowed to stand overnight. Hydrolysis was accomplished with 50 ml. of water and the ether solution was decanted from the magnesium hydroxide. This was extracted three times with 50-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and distilled. The yield of 61% of bromohydrin based on ethylene oxide used was probably low due to its solubility in water.

Analysis of the intermediate compound from one mole of Grignard reagent and one mole of ethylene oxide. The preparation of the Grignard reagent (C_2H_5MgBr) and addition of ethylene oxide was accomplished as previously described. The mixture

was stirred for two hours and allowed to stand for an additional hour. The ether solution was decanted and the precipitate was washed four times with 100-ml. portions of anhydrous ether. It was transferred quickly to a weighing-bottle which was placed in a desiccator and evacuated with a water-pump for three hours and an oil-pump at 2 mm. for twelve hours. Total bromine was determined by sodium peroxide fusion in a Parr bomb and subsequent titration by the Volhard method. Bromide ion was determined by dissolving a weighed sample (0.2-0.4 g.) in 30 ml. of 1:5 nitric acid and titrating immediately by the Volhard method. Magnesium was determined as MgO after burning and ignition to constant weight using a Meeker burner. The Pregl micro method was used for the determination of carbon and hydrogen. Because magnesium carbonate was formed during the combustion it was necessary to remove the boat, weigh it, and ignite to constant weight. The loss in weight added to the increase in weight of the Ascarite tube gave the weight of carbon dioxide.

Anal. Calc'd for $C_4H_8Br_2MgO_2$: C, 17.62; H, 2.94; total Br, 58.85; Mg, 8.93; bromide ion, 29.4.

Found: C, 16.80; H, 3.14; total bromine, 56.40; Mg, 8.83; bromide ion, 27.30.

$C_4H_8Br_2MgO_2$ from one mole of tert. butylmagnesium bromide and one mole of ethylene oxide. The same technique was used as in the preceding case.

Anal. Calc'd for $C_4H_8Br_2MgO_2$: C, 17.62; H, 2.94; total Br, 58.85; Mg. 8.93; bromide ion, 29.4.

Found: C, 17.01; H, 2.94; total Br, 55.34; Mg, 9.21; bromide ion, 29.5.

$C_4H_8Br_2MgO_2$ from ethylene oxide. One mole of magnesium was prepared by adding the calculated amount of bromine to magnesium, covered with ether and cooled to 0°. Eighty-eight grams of ethylene oxide in cold ether was added. It was stirred for an additional two hours and allowed to stand overnight. The ether was decanted from the precipitate which was then washed four times with anhydrous ether and freed from ether by vacuum.

Anal. Calc'd for $C_4H_8Br_2MgO_2$; total Br, 58.85; Mg, 8.93; bromide ion, 29.34.

Found: total Br, 56.7; Mg, 8.61; bromide ion, 28.46.

Titration of an aliquot of the combined ether solutions showed that approximately forty-two per cent of the total bromine remained in solution. Experiments in which the amount of ethylene oxide was doubled gave a precipitate of the same composition.

Anal. Found: Total Br, 56.1; Mg, 8.68; bromide ion, 28.84.

The precipitate formed from ethylmagnesium bromide with one mole of ethylene bromohydrin. One mole of ethylene bromohydrin was added drop by drop to the stirred Grignard reagent. The reaction-mixture was stirred for three hours and allowed to stand overnight. The clear ether solution was decanted from the white precipitate, which was washed four times with anhydrous ether and brought to constant weight in a vacuum.

Anal. Calc'd for $C_2H_4Br_2MgO$ ($BrCH_2CH_2OMgBr$); total Br, 70.10; Mg, 10.65; bromide ion, 35.6.

Found: total Br, 64.20; Mg, 11.72; bromide ion, 34.00.

Because of the ease of hydrolysis, the product probably contained some $Mg(OH)_2$.

Proof of structure of 3,4-dimethylpentanol. Fifteen grams of 3,4-dimethylpentanol (from the Grignard reaction of 2-bromo-3-methylbutane) was mixed in a three-liter, three-necked flask with 100 ml. of water and 3 g. of sodium carbonate. A solution of 40 g. of potassium permanganate in 1500 ml. of water was added with stirring while the mixture was cooled to 4° in an ice-salt-bath. Stirring was continued twelve hours at room temperature and the manganese dioxide was removed by suction.

The filtrate was evaporated to 100 ml., cooled, covered with a layer of ether, and acidified with dilute sulfuric acid. After three extractions with ether, the combined extracts were dried over anhydrous sodium sulfate. Upon fractionation, 3 g. of an acid (b.p. 210°) was obtained. This was converted into the chloride, by heating with thionyl chloride, from which the anilide was prepared, m.p. 67°.

Eighty grams (0.5 mole) of malonic ester was added with efficient stirring to one-half mole of sodium ethoxide in 200 ml. of alcohol. Stirring was continued for one hour and then three-fifths mole (90.6 g.) of 2-bromo-3-methylbutane was added and the mixture was heated on the water-bath until neutral. After removal of most of the alcohol, the salt was dissolved in water and three extractions were made with 50-ml. portions of ether. The fraction boiling at 235–245° was collected and saponified with fifty per cent potassium hydroxide. The alkaline solution was extracted once with ether and acidified with dilute sulfuric acid. Extraction with ether and decarboxylation at 150–170° gave 3 g. of 3,4-dimethylpentanoic acid which distilled at 210–214°.

Anal. Calc'd for $C_7H_{16}O_2$: C, 64.61; H, 10.76.
Found: C, 64.69; H, 10.80.

The anilide (m.p. 67°) and amide (m.p. 95.5°) were prepared through the acid chloride.

Proof of structure of 3,3-dimethylbutanol. Five grams of 3,3-dimethylbutanol, (from di-tert. butylmagnesium and ethylene oxide) was oxidized by alkaline potassium permanganate, using the technique described in the preceding experiment with corresponding mole fractions. One gram of acid was collected at 177–180° and converted to the chloride (thionyl chloride) which gave an amide melting at 131°.

Ninety grams of di-isobutylene was oxidized over a ten-day period with chromic acid. The yield of 2,2-dimethylpentanone-4 (b.p. 122–126°) was 20 g. One hundred grams of ice and 52 g. of sodium hydroxide in 200 ml. of water were placed in a three-necked flask fitted with a glycerine sealed stirrer, dropping-funnel, and thermometer. Twenty-four milliliters of bromine was added with stirring over a period of one hour while the flask was cooled in an ice-salt-bath. Seventeen grams of 2,2-dimethylpentanone-4 was added in ten minutes and the mixture allowed to stand overnight. The thermometer was replaced by a condenser arranged for distillation and the mixture was stirred while distillation was carried out over a free flame. When no more oil came over, the contents of the flask were cooled and acidified with 60 ml. of concentrated sulfuric acid. After steam distillation, the oily product was separated from the water layer and redistilled, giving a yield of 10 g. of 2,2-dimethylbutanoic acid which was collected at 178–184°. The amide melted at 131.5° (11).

SUMMARY

1. We believe that evidence submitted in this paper proves the intermediate in the reaction between a Grignard reagent and ethylene oxide to be $C_4H_8Br_2MgO_2$ without an appreciable amount of $BrCH_2CH_2OMgBr$.

2. Analytical results indicate the formation of $C_4H_8Br_2MgO_2$ when magnesium bromide is treated with either one or two moles of ethylene oxide.

3. Primary and secondary R_2Mg react with $C_4H_8Br_2MgO_2$ only when heated, or on long standing, to give $(RCH_2CH_2O)_2Mg$.

4. Primary and secondary R_2Mg react with ethylene oxide at room temperature to give $(RCH_2CH_2O)_2Mg$.

5. The absence of alcohol formation when RMgBr is treated at *room temperature* with one mole of ethylene oxide precludes the formation of appreciable amounts of $BrCH_2CH_2OMgBr$ as an intermediate.

6. Tert. butyl, tert. amyl, tert. hexyl Grignard reagents yield only ethylene bromohydrin when treated with one or two moles of ethylene oxide as above. On long standing tert. butyl Grignard gave a small yield of 3,3-dimethylbutanol-1.

7. Benzylmagnesium chloride reacts readily with one or two moles of ethylene oxide *at room temperature* to give phenylpropyl alcohol. The fundamental reaction in this case is probably between $(C_6H_5CH_2)_2Mg$ and $(ClCH_2CH_2O)_2Mg$, although direct action of $C_6H_5CH_2MgCl$ with ethylene oxide is a possibility.

8. Proof of structure of two alcohols, 3,3-dimethylbutanol-1 and 3,4-dimethylpentanol-1 was given.

EAST LANSING, MICH.

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REMARKS ON THE SYNTHESIS OF SUBSTITUTED STILBENES AND DIPHENYLBUTADIENES

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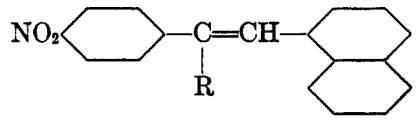
The synthesis of substituted stilbenes has recently become an interesting field of chemotherapeutical research, as members of this series have proved to be active as oestrogenic (1) or trypanocidal (2) agents. For some time, we have been occupied with the synthesis of lipophilic chemotherapeuticals (3), which are supposed to penetrate the waxy wall of the cells of certain bacteria. The substances in the group to be described here are all based on the same principle, *i.e.* the combination of an aromatically substituted unsaturated chain and a polar group, especially the amino group. Our results are, however, only preliminary and are published because this work can not be continued for the time being.

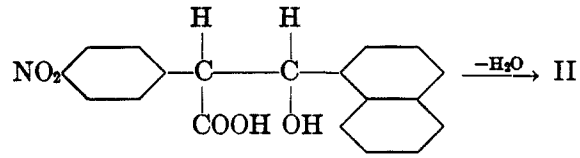
Of the many reactions which permit the synthesis of stilbene, only the method of Perkin can be generally applied. When α-naphthaldehyde was condensed with *p*-nitrophenylacetic acid by means of piperidine, only a 13% yield of α-(*p*-nitrophenyl)-β-(1-naphthyl)ethylene (I) was obtained, whereas the modification of Kuhn (4), who uses the lead salt of the acid, gave a 20% yield of I and at the same time 25% of α-(*p*-nitrophenyl)-β-(1-naphthyl)acrylic acid (II). As is known from the work of Ruggli (5) and Taylor (6), the structure of these acrylic acids corresponds to the *cis* form of the ethylene. One may therefore conclude that first the two *cis* and *trans* acids are formed, but that the *trans* form is much more easily decarboxylated than the *cis* isomer. As there is no sure example of the different behavior of such isomeric acids in decarboxylation, another explanation seems to us more acceptable: First, the two stereoisomeric hydroxy acids A and B are formed, usually in unequal amounts. There are now two possibilities for elimination of the hydroxyl group, (a) by splitting off water with an adjacent hydrogen atom, or, (b) with the carboxyl group. Assuming now, that the aromatic nuclei are held at maximal distance from each other, one must conclude that in form A the hydroxyl is eliminated together with the neighboring hydrogen because these two are trans to each other, whereas in form B, for the same reason, lactonization with the carboxyl trans to the hydroxyl is the favored reaction. Such a mechanism would parallel the known behavior of the stilbene dibromides (7): Only the

bromination-product of *cis*-stilbene readily loses hydrogen bromide to yield the corresponding bromoethylene, whereas the *trans* addition-product is very stable and occasionally regenerates the *trans*-stilbene.

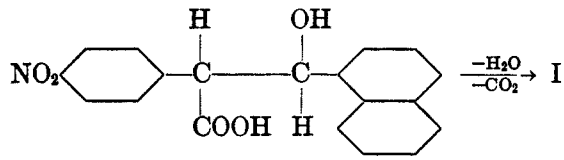


I. R = H

II. R = COOH

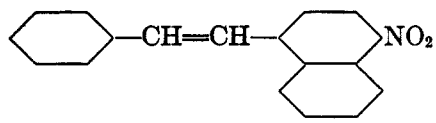


A.

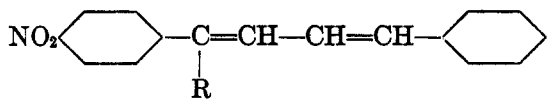


B.

1-Styryl-4-nitronaphthalene (III) was obtained by the method of Meerwein (8), through diazo coupling of cinnamic acid with 4-nitro-1-naphthylamine. Only the ethylene derivative was obtained (in 12% yield), and no trace of an isomer of II. The trans structure of III, in spite of the low melting point, 94°, is shown by the stability of the dibromide, which is not changed in boiling pyridine. 1-*p*-Nitrophenyl-4-phenyl-1,3-butadiene (IV) was synthesized by the two methods mentioned:



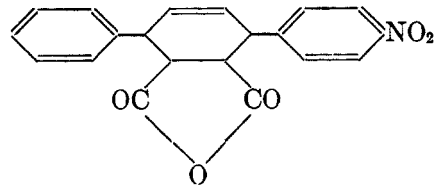
III



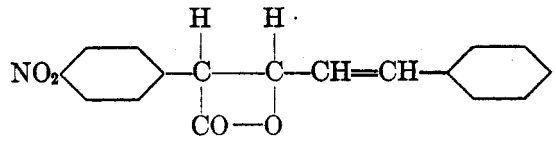
IV. R = H V. R = COOH

(a) The Perkin reaction between cinnamic aldehyde and *p*-nitrophenylacetic acid yielded about equal parts of IV (11%) and of the acid (V) (9%). The structure of IV is proved by the ready condensation with maleic anhydride, which gives, in quantitative yield 3-phenyl-6-*p*-nitrophenyl-1,2,3,6-tetrahydrophthalic anhydride (VI), and by the addition of four bromine atoms. On the other hand, the acid V, like α-phenylcinnamic acid (9), does not react with bromine, although the second double bond is not sterically hindered by a carboxyl group. After esterification of the acid, two bromine atoms are added.

(b) The diazo coupling between *p*-nitroaniline and cinnamylideneacrylic acid gave also exclusively the ethylene (IV) in 25% yield. No trace of V could be detected. This means, on the basis of the above developed theory, that the diazo reaction yields solely the lactone (VII), which spontaneously splits off CO_2. This assumption also is in accordance with the reaction-mechanism of Meerwein (8).



VI



VII

Reduction of the described nitro compounds was best effected by the method of Stoermer (10), although they are only sparingly soluble in alcohol. The amines are all brownish-yellow and difficult to purify. On the other hand, the nitro acids are easily reduced in water solution by ammonia and ferrous sulfate, and best precipitated as their hydrochlorides.

EXPERIMENTAL

1-(p-*Nitrophenyl*)-2-(α-*naphthyl*)*ethylene* (I). (a) α-Naphthaldehyde (11 g.) (11) and *p*-nitrophenylacetic acid (13 g.) were heated with 1 cc. of piperidine for two hours at 160°, the syrupy mass triturated with glacial acetic acid, and the brown crystals separated by filtration. After repeated recrystallizations from glacial acetic acid and butyl acetate, long brownish needles were obtained, m.p. 183°, yield, 3 g.

Anal. Calc'd for $C_{18}H_{13}NO_2$: C, 78.55; H, 4.7.
Found: C, 78.1; H, 4.9.

The dibromide was prepared in carbon tetrachloride, and crystallized from high-boiling petroleum ether in beautiful plates, m.p. 183°.

Anal. Calc'd for $C_{18}H_{13}Br_2NO$: C, 49.7; H, 3.0.
Found: C, 49.9; H, 2.9.

Reduction of the nitro group with stannous chloride in glacial acetic acid or with iron dust and hydrochloric acid in alcohol failed. Only the following method proved successful: Ten grams of the nitro compound was suspended in 250 cc. of boiling ethanol and a solution of 80 g. of ferrous sulfate and 400 cc. of concentrated ammonia in 400 cc. of water was added. The mixture was stirred and boiled for two hours. After twelve hours, the black precipitate was filtered, dried, and extracted with benzene. From this solution, after evaporation, 5 g. of the amino compound was obtained. On recrystallization from ethanol, yellow needles, m.p. 114°, were obtained.

Anal. Calc'd for $C_{18}H_{15}N$: N, 5.7. Found: N, 5.5.

(b) Fourteen grams of the aldehyde and 16.2 g. of *p*-nitrophenylacetic acid were added to a solution of lead oxide (10 g.) in acetic anhydride (18 g.), and the mixture heated at 140° for four hours. Crystallization set in spontaneously. The solid part was filtered and recrystallized once from glacial acetic acid, then from high-boiling petroleum ether with some benzene; m.p. and mixed m.p. 183°, yield, 5 g.

The filtrate from the ethylene derivative, on standing, deposited a yellow substance, which, after recrystallization from xylene, melted at 201° (II), yield, 7 g. The substance did not add bromine.

Anal. Calc'd for $C_{19}H_{13}NO_4$: C, 71.5; H, 4.1; N, 4.4.
Found: C, 71.0; H, 4.1; N, 4.4.

The acid (II) was esterified with diazomethane. The methyl ester was twice recrystallized from high-boiling petroleum ether, and melted then at 140°. It formed yellow blocks.

Anal. Calc'd for $C_{20}H_{15}NO_4$: C, 72.1; H, 4.5.
Found: C, 71.9; H, 4.5.

Reduction of the nitro acid was accomplished by dissolving the acid (2 g.) in an excess of concentrated ammonia and adding ferrous sulfate (10 g.) in the same solvent. After short boiling, the mixture was cooled and acidified with hydrochloric acid. The amino acid was purified by dissolving in hot ammonia and reprecipitating with hydrochloric acid. In this way, the pure hydrochloride was obtained in the form of silky, yellow needles, m.p. 254°.

Anal. Calc'd for $C_{19}H_{16}ClNO_2$: C, 70.2; H, 4.9.
Found: C, 70.8; H, 5.1.

1-Styryl-4-nitronaphthalene (III). 4-Nitro-1-naphthylamine (12) (24 g.) was suspended in 12% hydrochloric acid (100 cc.) and diazotized at 0° with 9 g. of sodium nitrite in 20 cc. of water. The diazo solution was added dropwise to cinnamic acid. Then cupric chloride (5.3 g.) and sodium acetate (27.5 g.) in water (25 cc.) were added; nitrogen was evolved at once. After stirring for one hour at 15°, the reaction-mixture was distilled with steam until the distillate became clear. The non-volatile residue formed a black tar, containing the desired nitro compound and some unreacted cinnamic acid. The mass was dissolved in ether, dried, and distilled *in vacuo*, b.p. 240–260° at 9 mm. The brown distillate, on trituration with acetone-petroleum ether, gave a yellow powder. This was recrystallized first from glacial acetic acid, then from petroleum ether. Strong, yellow lancets were obtained, m.p. 94°, yield, 3.5 g. Concentrated sulfuric acid gives first a blue, then a blue-violet color.

Anal. Calc'd for $C_{18}H_{13}NO_2$: C, 78.55; H, 4.7.
Found: C, 78.5; H, 5.0.

The dibromide, prepared as above, crystallized from high-boiling petroleum ether, m.p. 182°. It was recovered unchanged after four hours boiling in pyridine.

Anal. Calc'd for $C_{18}H_{13}Br_2NO_2$: C, 49.7; H, 3.0; N, 3.2.
Found: C, 49.2; H, 3.1; N, 3.1.

p-*Nitrophenylphenylbutadiene* (IV). (a) *p*-Nitrophenylacetic acid (18 g.), cinnamic aldehyde (13 g.), lead oxide (11 g.), and acetic anhydride (20 g.) were boiled together for five hours. The crude product was separated into a soda-soluble and a neutral part. The neutral substance (IV), after recrystallization from toluene, melted at 172°, yield, 2.7 g. With concentrated sulfuric acid, a red-brown color reaction was noted.

Anal. Calc'd for $C_{16}H_{13}NO_2$: C, 76.5; H, 5.2; N, 5.6.
Found: C, 76.1, 76.2; H, 5.2, 5.1; N, 6.0.

The acid (V) is insoluble in toluene and may be separated from IV also by means of that solvent. From butanol it crystallized in thin yellow needles, m.p. 256°, yield, 2.5. g. The acid did not react with bromine.

Anal. Calc'd for $C_{17}H_{13}NO_4$: C, 69.2; H, 4.4; N, 4.7.
Found: C, 69.4; H, 4.7; N, 5.0.

(b) Diazo coupling between *p*-nitroaniline (18 g.) and cinnamylideneacrylic acid (22 g.) (13)[1] in acetone (350 cc.), as described above, yielded, after steam distillation, brown crystals, which were purified with butyl acetate and high-boiling petroleum ether, m.p. and mixed m.p. 171–172°, yield, 8.0 g.

Reactions of p-*nitrophenylphenylbutadiene.* (a) With maleic anhydride: Two grams of the anhydride (6 equiv.) was melted on a water-bath with 0.8 g. of the diene, and afterwards heated for two hours to 110°. The melt was mixed with water and filtered. The product (VI) crystallized from acetic anhydride in nearly colorless prismatic rods, m.p. 213°, yield quantitative.

Anal. Calc'd for $C_{20}H_{15}NO_5$: C, 68.8; H, 4.3; N, 4.0.
Found: C, 69.0; H, 4.6; N, 4.3.

(b) With bromine: When excess bromine in carbon tetrachloride was added, a clear solution was first obtained, but immediately afterwards a red-brown precipitate appeared. The addition-product was recrystallized from a mixture of xylene and high-boiling petroleum ether (1:2), and formed clusters of colorless needles, m.p. 245–246°.

Anal. Calc'd for $C_{16}H_{13}Br_4NO_2$: C, 33.6; H, 2.3.
Found: C, 34.3; H, 2.7.

(c) Reduction to 1-*p*-aminophenyl-4-phenyl-1,3-butadiene: By the same method described for (I), 10 g. of the nitro compound yielded 8 g. of the amino product. From toluene, glistening needles, m.p. 167°, were obtained. The brown color changes to yellow in contact with hydrochloric acid. It proved rather difficult to obtain a pure sample for analysis.

Anal. Calc'd for $C_{16}H_{15}N$: N, 6.3. Found: N, 6.3; 6.0.

For characterization, the amino compound was acylated with trichloroacetyl chloride in toluene-pyridine solution. The derivative melts at 177–178° and forms bright yellow rods from butanol.

Anal. Calc'd for $C_{18}H_{15}Cl_3NO$: C, 59.0; H, 3.8; N, 5.9.
Found: C, 59.3; H, 4.0; N, 6.2.

*Reactions of 1-*p-*nitrophenyl-4-phenyl-1,3-butadiene-1-carboxylic acid* (V). The

[1] The acid is best recrystallized from glacial acetic acid.

methyl ester, which was prepared with diazomethane, formed soft, yellow needles, which, after recrystallization from high-boiling petroleum ether, melted at 134°.

Anal. Calc'd for $C_{18}H_{15}NO_4$: C, 69.9; H, 4.85.
Found: C, 69.6; H, 4.7.

The ester was warmed with excess bromine in carbon tetrachloride. The syrupy residue which was left after evaporation of the solvent crystallized on trituration with methanol. From glacial acetic acid, beautiful colorless crystals of the tetragonal system, m.p. 248–249° were obtained.

Anal. Calc'd for $C_{18}H_{15}Br_2NO_4$: C, 46.05; H, 3.2.
Found: C, 45.7; H, 3.0.

Reduction of the acid was accomplished as described above for (II). The amino acid, which was first precipitated as hydrochloride, was recrystallized from diluted pyridine, m.p. 258°.

Anal. Calc'd for $C_{17}H_{15}NO_2$: C, 77.0; H, 5.7.
Found: C, 77.1; H, 6.1.

SUMMARY

The synthesis of some substituted stilbenes and diphenylbutadienes by the methods of Perkin and of Meerwein is described and the possible stereochemical mechanism is discussed.

REHOVOTH, PALESTINE.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

THE PREPARATION OF SOME DERIVATIVES OF RETENOXAZOLE AND RETENIMIDAZOLE AND A STUDY OF THE REACTION MECHANISM[1]

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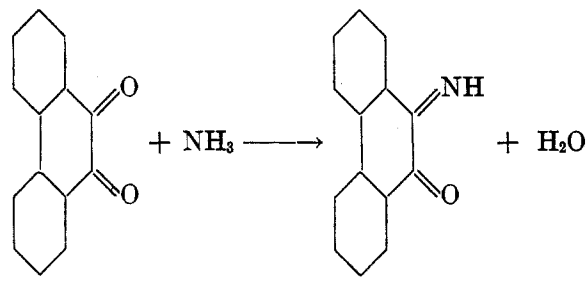
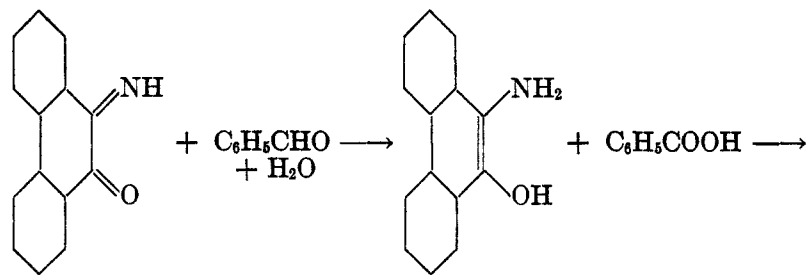
The reaction of phenanthraquinone with benzaldehyde and aqueous ammonia to form 2-phenylphenanthroxazole was first noted by Japp and Wilcock (1). The mechanism of this reaction has not been clearly established. Hence it was thought advisable to extend the earlier work, and by making a more thorough study of the intermediates, to establish the reaction mechanism. Since some of the previous work had a direct bearing on the work done in this investigation, a brief review is included.

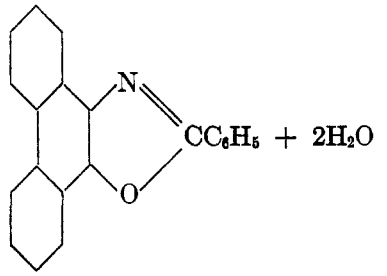
Japp and Wilcock suggested that the reaction involved as the first step the formation of phenanthraquinoneimine.



A hydrolytic oxidation between the imine and benzaldehyde with the formation of 10-amino-9-phenanthrol was next postulated. The latter compound then underwent the Ladenburg ring-closure with benzoic acid to form the oxazole.

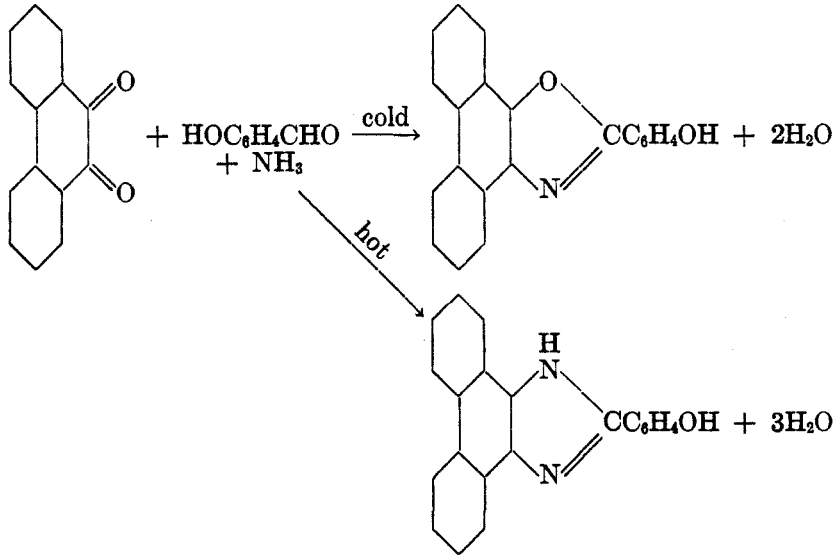


[1] An abstract of a thesis submitted by Saul I. Kreps in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.



Later Japp and Wilcock (2) noted that other aromatic aldehydes reacted, under the same conditions, as readily as benzaldehyde. Furfuraldehyde also condensed, but the corresponding phenanthroxazole was obtained in poor yields. In attempting to extend this condensation to acetaldehyde they had no success. They further noted that salicylaldehyde condensed with phenanthraquinone and ammonia to form 2-(2′-hydroxyphenyl)-phenanthrimidazole and not the expected phenanthroxazole. Japp and Streatfeild (3) investigated the anomalous action of salicylaldehyde and found that the hydroxyaryl aldehydes condensed with phenanthraquinone and ammonia to yield 2-aryl phenanthrimidazoles, while the corresponding methoxyaryl aldehydes formed both oxazole and imidazole.

Sircar and Sircar (4) modified the method of Japp by dissolving the phenanthraquinone and aromatic aldehyde in the minimum of hot amyl alcohol and passing ammonia through the solution. They observed that certain nitroaryl and bromohydroxyaryl aldehydes also formed 2-aryl phenanthrimidazoles. Sircar and Ray (5) showed that at high temperatures the hydroxyaryl, bromohydroxyaryl, and nitroaryl aldehydes formed imidazoles; while oxazoles were formed at lower temperatures. They assumed two distinct reaction trends depending upon the temperature employed for the condensation.



With benzaldehyde at both low and high temperatures only the oxazole was formed. They stated however that the course of the reaction was not dependent upon the character of the aldehyde, intimating that at high enough temperatures all aromatic aldehydes would form imidazoles.

Sircar and Sen (6) reported more conclusive evidence that the course of the reaction was affected by the temperature used. Working with acenaphthoquinone, aromatic aldehydes, and ammonia, they were able to distinguish four groups of aldehydes, each showing a different reactivity. The first group form only oxazoles at temperatures near 0°, while at higher temperatures only imidazoles were formed. The second group formed mixtures of the corresponding oxazoles and imidazoles at 0° and only imidazoles at higher temperatures. The third group formed only imidazoles even at 0°. The fourth group gave no reaction cold, and when heated yielded only imidazoles.

The formation of both oxazoles and imidazoles in some cases led Sircar and Sen to assume that in those reactions the acenaphthoxazoles were formed first, and by subsequent replacement of the oxygen atom by the amino group yielded the corresponding imidazole. They attempted the conversion of 2-(2′-nitrophenyl)acenaphthoxazole to the corresponding imidazole by heating the oxazole with aqueous ammonia at 130° in a sealed tube. After thirty hours, an increase in nitrogen content of 1.5% was found. However they were not able to isolate any of the imidazole. Such a conversion would probably involve hydrolysis of the oxazole ring, followed by replacement of OH by NH_2 and a subsequent ring-closure with the elimination of water. Apparently, no study has been made on the ease of hydrolysis of any of the acenaphthoxazoles. However, Japp and Wilcock attempted the hydrolysis of 2-phenylphenanthroxazole by heating with concentrated hydrochloric acid at 200°, but no hydrolysis was noted.

The postulate that phenanthroxazoles were necessary intermediates in the formation of the corresponding imidazoles is untenable for two reasons: (a) the extreme difficulty of splitting the phenanthroxazole ring; and (b) the rapid formation of phenanthrimidazoles from phenanthraquinone, certain aromatic aldehydes, and ammonia at moderate and even low temperatures.

The only other synthesis of a 2-aryl phenanthrimidazole has been reported by De and Ghosh (7). They obtained 2-phenylphenanthrimidazole by the reaction of benzamidine with the hydrochloride of 9-amino-10-phenanthrol at 190–200°.

It did not seem possible to draw any definite conclusions from the reported work concerning the mechanism of the formation of oxazoles and

imidazoles from ortho quinones. The mechanisms suggested have not been tested and no independent evidence has been brought forward to confirm or dispute them. Previous workers have stressed the action of ammonia with the quinone, and have assumed this to be the essential reaction in the formation of oxazoles. They have neglected the possibility that the action of ammonia on the aldehyde to form a hydrobenzamide might also be an important step in the reaction. It was decided therefore to make a thorough study of this type of reaction, using retene quinone, aromatic aldehydes, and ammonia. The study consisted of six parts: (A) the reaction of ammonia with retenequinone; (B) the reaction of retenequinoneimine with aromatic aldehydes; (C) the reaction of retenequinone with hydrobenzamide; (D) the reaction of retenequinoneimine with hydrobenzamide; (E) the action of ammonia on 2-aryl retenoxazoles; and (F) the preparation of a series of 2-aryl retenoxazoles.

TABLE I

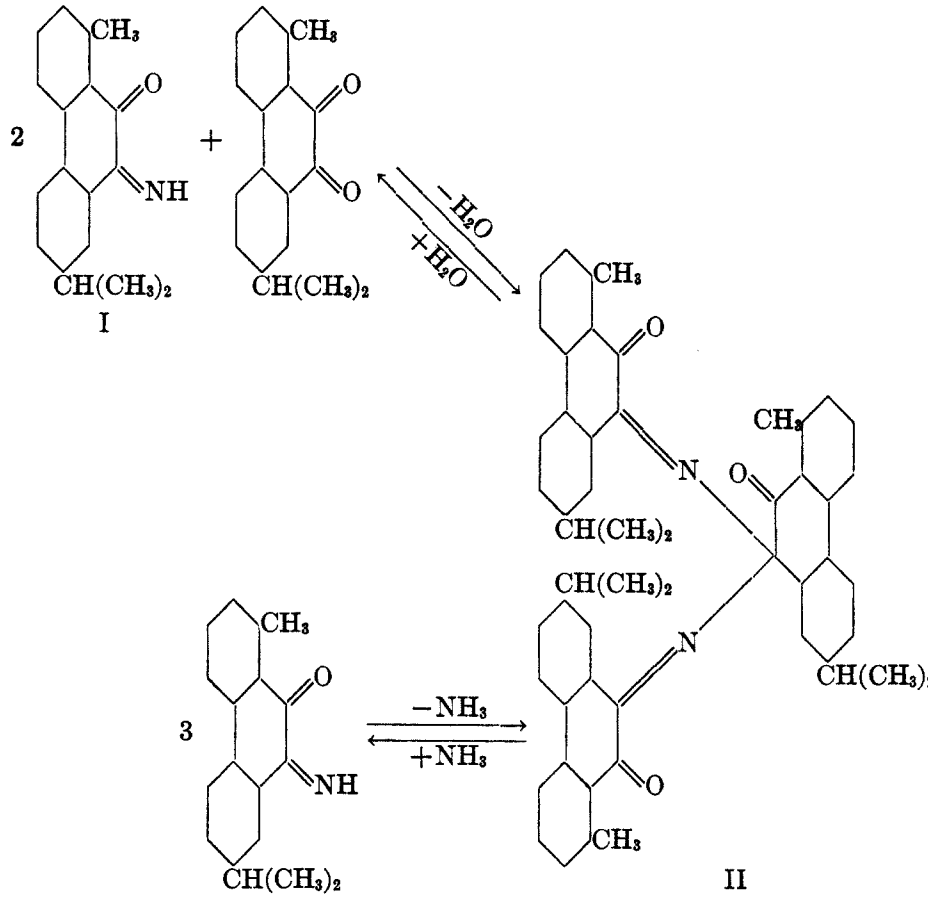
ACTION OF AMMONIA ON RETENEQUINONE

TIME	PRODUCTS	M.P. °C.	% N FOUND
60 min.	II	123	3.80
60 min.	II	120	3.92
45 min.	Mixture I and II	111–113	4.72
30 min.	I	107–108	5.10

Retenequinoneimine (I) was prepared by treating a chloroform solution of the quinone with an alcoholic solution of ammonia (8). When the reaction was carried out by passing ammonia through a suspension of the quinone in alcohol, other products were also obtained. From one run of this type, carried out at 5°, a product was isolated that melted sharply at 125° and contained 3.62% of nitrogen. The most reasonable structure assignable to this product was a hydrobenzamide type of structure II.

Another compound was isolated when this reaction was carried out in hot alcoholic solution. Melting points were indefinite but analyses indicated a molecular complex of one mole of the quinoneimine and one mole of the quinone.

It was found that as the time of addition of ammonia to alcoholic quinone solutions increased, the nitrogen content of the resulting product decreased. Thus for a series of reactions carried out at room temperature, the results shown in Table I were obtained. This might be explained on the basis of the following reactions:



To test the mechanism of Japp and Wilcock, benzaldehyde and *p*-hydroxybenzaldehyde were treated with retenequinoneimine under various conditions. No reaction occurred between benzaldehyde and the quinoneimine in the absence of a solvent, even on warming the mixture. In dry toluene, after refluxing for three hours, only a 1.4% yield of 2-phenylretenoxazole was obtained. A small amount of ammonia was given off during the refluxing.

No reaction was observed between the quinoneimine and *p*-hydroxybenzaldehyde in absolute alcohol after three days. After standing for thirty days, a small amount of product (6% yield) was obtained which was found to be a mixture of 2-(4′-hydroxyphenyl)retenoxazole and 2-(4′-hydroxyphenyl)retenimidazole. In hot absolute alcohol ammonia was liberated, and after three hours a sixteen per cent yield of the oxazole and imidazole was obtained. In dry toluene, after refluxing for forty-five

minutes, only a trace of product could be found. The aldehyde was recovered almost quantitatively and only a trace of ammonia was liberated during the reaction.

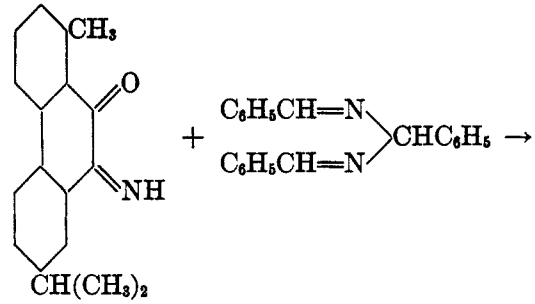
It was noted that reaction-products were isolated only in those cases were ammonia was liberated. This indicated partial hydrolysis of the quinoneimine by slight traces of water present in the solvents, or partial alcoholysis of the quinoneimine. The presence of the quinone, aldehyde, and free ammonia then established the conditions for the formation of the oxazole and the imidazole. These results pointed to the fact that the quinoneimine was not the only necessary intermediate for the reaction.

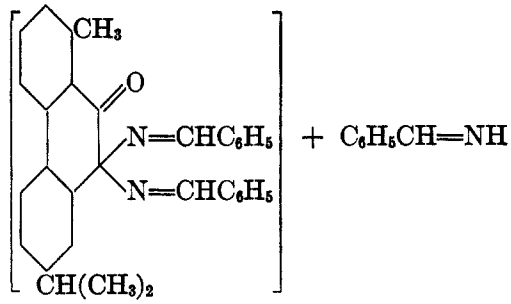
The possibility that hydrobenzamide might be formed in the reaction-mixture led to a study of the reaction of hydrobenzamide with retenequinone in various solvents. Oxazole formation was noted only in those cases where ammonia and benzaldehyde were liberated, indicating that the hydrobenzamide first underwent hydrolysis or alcoholysis, and then oxazole formation resulted. When hydrobenzamide and retenequinone were refluxed for three hours in isoamyl alcohol, a sixty per cent yield of 2-phenylretenoxazole was obtained. Ammonia was liberated steadily during the reaction. When the reaction was carried out in dry toluene, no product was isolated, and the quinone was recovered nearly quantitatively. After refluxing retenequinone and hydrobenzamide in dry toluene for three hours, a 2.1% yield of the oxazole was obtained. Ammonia was evolved in both cases.

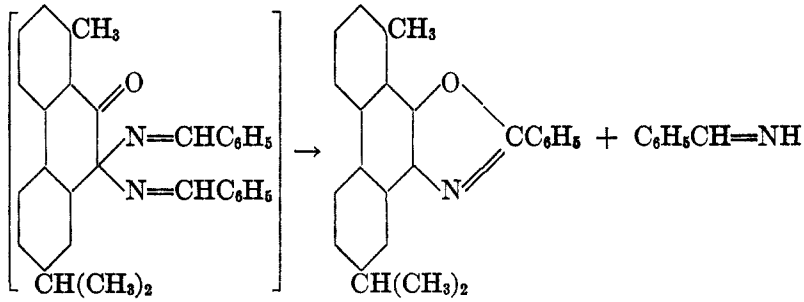
Hydrobenzamide alone in dry toluene liberated only slight traces of ammonia. In one run, 0.019 moles of hydrobenzamide liberated 0.0002 moles of ammonia after refluxing for three hours, indicating the extent of hydrolysis to be 0.5% within that period.

The observed increase in the amount of ammonia liberated in the quinone-hydrobenzamide mixture is accountable by the reaction of these traces of ammonia liberated from hydrobenzamide with the quinone, water and retenequinoneimine being formed. The traces of moisture thus formed cause increased hydrolysis of hydrobenzamide. Concurrent with this increased liberation of ammonia is an increase in the yields of oxazole. The low yields of oxazole observed can be correlated with the slight extent of hydrolysis within the period of the reaction. It would appear that any proposed mechanism which limited itself to the formation of only one necessary intermediate, quinoneimine or hydrobenzamide, would fail to meet the requirements imposed by experimental results. To test the possibility that both might be necessary intermediates, the interaction of retenequinoneimine and hydrobenzamide was studied. The reactions were carried out in dry toluene to avoid such complicating side reactions as hydrolysis and alcoholysis. When retenequinoneimine and hydrobenz-

amide were refluxed in dry toluene, the solution turned dark green in about six minutes but no ammonia was liberated. After another four minutes the solution became light yellow and ammonia was given off. One run, stopped after ten minutes, gave a seventy-eight per cent yield of oxazole. In another run, 0.010 moles of retenequinoneimine and 0.010 moles of hydrobenzamide were refluxed for three hours in dry toluene. The oxazole was isolated in a yield of ninety-six per cent (0.0096 mole) and 0.0057 moles of ammonia was evolved during the run. These results indicated the following mechanism.







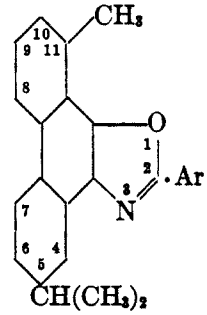
The benzaldimine formed would then be converted into hydrobenzamide and ammonia.

$$3\ C_6H_5CH{=}NH \rightarrow (C_6H_5CH)_3N_2 + NH_3$$

In this series of reactions it will be noted that for each mole of oxazole formed, 0.66 moles of ammonia would be liberated. The ratio of ammonia to oxazole would be 0.66. The ratio actually determined was 0.60. The rapidity of the reaction and the nearly quantitative yields obtained offered further confirmation of the proposed mechanism. The syntheses of oxazoles by the methods of Japp and Wilcock and Sircar and Sircar are best explained by the formation of the quinoneimine and the hydrobenzamide of the aromatic aldehyde used, followed by their further reaction according to the scheme shown above.

To test the assumption of Sircar and Sen that the oxazole was formed first and imidazole then resulted by the replacement of the oxygen by the imino group, 2-phenylretenoxazole was heated with aqueous ammonia at 170–180° and 500 lbs. pressure for forty-nine hours. The starting material was recovered almost quantitatively. Melting points, mixed melting points, and analyses all indicated that no conversion had occurred. Similar treatment of 2-(2′-hydroxyphenyl)retenoxazole likewise resulted in no conversion. When a sample of the latter was heated at 240–250° for fifty hours under 1100–1300 lbs. pressure, almost complete decomposition resulted but no trace of the imidazole was found. This failure to convert oxazole to imidazole, even with the salicylaldehyde product, whose imidazole was formed in the cold, indicated that the oxazole cannot be the necessary intermediate for imidazole formation. These compounds must be formed independently and through different mechanisms.

The remaining part of this study was devoted to the preparation of a series of 2-aryl retenoxazoles and several of the corresponding imidazoles. The compounds which for convenience were called 2-arylretenoxazoles, may also be called 2-aryl-5-isopropyl-11-methylphenanthroxazoles.



The method of Sircar and Sircar was modified in certain respects. Isolation of the products was simpler when the condensations were carried out in absolute ethyl alcohol rather than in isoamyl alcohol and the yields were higher in many cases. The condensations were also carried out in boiling toluene. The best results were obtained when equivalent amounts

of the retenequinone and aldehyde were dissolved in the boiling solvent and a rapid stream of dry ammonia was passed through the refluxing solutions for a short time, usually no longer than thirty minutes. The condensations were also carried out at room temperature as well as cold, using either ethyl or isoamyl alcohol as the solvent. Ammonia was passed through the suspension of retenequinone in the solvent containing the aldehyde until the quinone was entirely dissolved, or until the product precipitated to a solid mass. The yields were lower than those obtained from hot solutions.

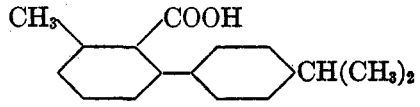
In no case did a change in temperature alter the nature of the products obtained. Heated, benzaldehyde, *p*-tolualdehyde, *o*-chlorobenzaldehyde, *m*-nitrobenzaldehyde, *p*-dimethylaminobenzaldehyde, *p*-diethylaminobenzaldehyde, vanillin, anisaldehyde, veratraldehyde, piperonal, and furfuraldehyde formed only oxazoles. Salicylaldehyde and *p*-hydroxybenzaldehyde gave, both hot and cold, mixtures of the corresponding oxazoles and imidazoles. When such mixtures were obtained from hot reactions, the oxazoles were usually found in greater quantities than the imidazoles. In cold reactions this also held true except with the salicylaldehyde condensation carried out in cold isoamyl alcohol.

Some condensations were also carried out by the method of Japp and Wilcock. Retenequinone, the aldehyde, and an excess of aqueous ammonia were heated together in an autoclave. Using benzaldehyde at temperatures up to 230° and pressures of 1000 lbs., only the oxazole was obtained. The yields were high but not quantitative. With salicylaldehyde at temperatures up to 200° and 580 lbs. pressure, a mixture of oxazole and imidazole was obtained. A larger relative percentage of imidazole was obtained than in runs in boiling ethyl or isoamyl alcohol, but the overall yield was low due to decomposition of the products at the temperatures used. With *m*-nitrobenzaldehyde, only the oxazole was obtained at 200° and 670 lbs. pressure. These results are at variance with those reported by Sircar and Ray, and Sircar and Sen. This may be due to a difference in the chemical behavior of retenequinone and phenanthraquinone and acenaphthoquinone. Sircar used the last two compounds in his work.

It will be noted that the retenoxazoles are formulated in an arbitrary manner in this paper, with the nitrogen atom of the heterocyclic ring always attached to the 9-position of the retene structure. The reactions leading to the formation of this ring are also indicated as taking place at this position. All attempts to establish the absolute structure of these compounds were unsuccessful. It was planned to convert the retenoxazoles to either 9- or 10-retenol, the final product depending upon the relative positions of the nitrogen and oxygen atoms of the oxazole ring.

However these compounds resisted hydrolysis even under the most rigorous conditions.

The arbitrary formulas assigned were considered the most probable after an examination of the work of Lux (9), who found 3-methyl-4'-isopropylbiphenyl-2-carboxylic acid among the decomposition products of retene. This acid was esterified only with difficulty, due



to the steric hindrance offered by the methyl and isopropylphenyl groups which occupied the positions adjacent to the carboxyl group. Such steric hindrance might also be a factor in inhibiting reactions with the quinoid oxygen in the 10-position and reaction would then occur preferentially at the 9-position. The fact that only one oxazole was obtained in each case can be explained only on the basis of such an assumption.

This work is being continued and extended to the mechanism of imidazole formation by Day and co-workers.

EXPERIMENTAL

Analysis. The semi-micro Kjeldahl method was used for the nitrogen determinations. The distillate was absorbed in 4% boric acid solution, and titrated to a methyl red end-point, according to the method of Meeker and Wagner (10).

Molecular Weights. The Rast method of determining molecular weights by the depression of the melting point of *d*-camphor was used, according to the directions of Shriner and Fuson (11).

Retenequinone. Fifty grams (0.21 moles) of retene (Eastman practical grade) was suspended in 2 l. of glacial acetic acid. Ninety-two grams (0.92 moles) of chromic anhydride was dissolved in the minimum of cold water. This solution was diluted with an equal quantity of glacial acetic acid and added dropwise, over a period of two hours, to the well stirred retene suspension. The reaction-mixture was cooled when necessary to keep the temperature below 40°. After the addition was completed, the reaction-mixture was stirred for two hours. It was then diluted with 4 l. of distilled water and allowed to stand for one-half hour. The precipitated retenequinone was removed by filtration and washed with cold water until the washings were colorless. The crude product was dried in air and then recrystallized twice from chloroform; m.p. 197.5° (corr.). This method gave an excellent product and purification through the bisulfite addition-product was not necessary. The yield was 50% of the theoretical, based on the quantity of retene used.

Preparation of retenequinoneimine. [After Bamberger and Hooker (8).] Ten grams of retenequinone was dissolved in 400 cc. of chloroform and 400 cc. of a saturated solution of ammonia gas in absolute alcohol was added. This was allowed to stand, tightly stoppered, at room temperature for five days. The solution was evaporated as rapidly as possible at room temperature and the crystalline product obtained was separated from the small amount of gums formed. Slow evaporation, particularly in moist air, produced poor results. The product was recrystallized

from absolute alcohol saturated with dry ammonia gas and was obtained as yellow needles. Prolonged heating was avoided. M.p. 108–110° (corr.); yield, 60%.

Anal. Calc'd for $C_{18}H_{17}NO$: N, 5.32. Found: N, 5.25.

The reaction of retenequinone with ammonia. (a) Ten grams of retenequinone was suspended in 250 cc. of absolute alcohol and anhydrous ammonia gas was passed through the solution for thirty minutes. The temperature rose during the addition from 18° to 40° and then fell to 13°. The red solution was filtered from unreacted retenequinone and was diluted with an equal volume of water. The resulting yellow precipitate was filtered from the colloidal suspension. All attempts to break the colloidal suspension which invariably resulted at this stage were futile. The crude product was recrystallized from ethyl alcohol (max. temp. 40°) and was obtained as yellow needles, m.p. 104–105° (corr.).

Anal. Calc'd for $C_{18}H_{17}NO$: N, 5.32. Found: N, 5.28.

(b) Five grams of retenequinone was suspended in 200 cc. of absolute alcohol and the suspension was cooled to 5°. Anhydrous ammonia was added for seven and one-half hours; the temperature rose to 16° and then fell to 11°. The dark red solution was filtered and was then diluted with an equal volume of distilled water. The precipitated product was recrystallized from ethyl alcohol and was obtained as yellow plates, with a greenish-gold tinge, m.p. 125° (corr.), (Compound II).

Anal. Calc'd for $C_{54}H_{48}N_2O_3$: N, 3.63. Found: N, 3.62.

(c) Ten grams of retenequinone was dissolved in 250 cc. of boiling absolute alcohol and ammonia gas was passed through the refluxing solution for forty-seven minutes. The dark red solution was poured into 500 cc. of cold distilled water and the precipitated yellow product was isolated by filtration. After recrystallization from ethyl alcohol, it was obtained as shining golden plates, m.p. 159–169° (corr.), (Compound III).

Anal. Calc'd for $C_{36}H_{33}NO_3$: N, 2.66. Found: N, 2.55.

(d) Other runs were carried out in the same manner. The results shown in Table I were obtained by suspending 10 g. of retenequinone in 250 cc. of absolute alcohol and adding ammonia for the desired period. The solutions were filtered, diluted with an equal volume of distilled water, and the resulting product recrystallized from ethyl alcohol.

The reaction of retenequinoneimine with benzaldehyde. Five grams (0.019 moles) of retenequinoneimine and 2.0 cc. (0.019 moles) of benzaldehyde were dissolved in 50 cc. of dry toluene and refluxed for three hours. Ammonia was evolved slowly over the entire period. The solution was chilled and the precipitated product was filtered from the liquid. By fractional crystallization from ethyl alcohol, a small amount of 2-phenylretenoxazole was separated from retenequinone. Evaporation of the toluene liquor yielded no further oxazole but only benzaldehyde and retenequinone. Recovered retenequinone, 76%; yield of oxazole, 1.4%; m.p. of the 2-phenylretenoxazole, 171–173° (corr.).

The reaction of retenequinoneimine with p-*hydroxybenzaldehyde.* (a) One gram of retenequinoneimine and 0.6 gram of *p*-hydroxybenzaldehyde were dissolved in 100 cc. of absolute alcohol. After forty-eight hours standing at room temperature, a slight positive test for ammonia was obtained. After eight days, a very slight precipitate was observed in the flask. After thirty days the precipitate was filtered from the solution, extracted with 50 cc. of hot alcohol, and then recrystallized from dioxane. The product was obtained as tan plates, m.p. above 300°, yield, 6%.

Anal. Calc'd for $C_{25}H_{21}NO_2$: N, 3.81, for $C_{25}H_{22}N_2O$: N, 7.65.
Found: N, 7.13.

(b) Two grams of retenequinoneimine and 1.1 g. of *p*-hydroxybenzaldehyde were dissolved in 100 cc. of absolute alcohol and the mixture was refluxed for three hours. Ammonia was given off. The reaction-mixture was chilled and the precipitated product was removed. It was extracted with ethyl alcohol and then recrystallized from dioxane. M.p. above 300°, yield, 16%. Analysis showed that the product consisted mostly of the corresponding imidazole. Evaporation of the mother liquor under reduced pressure yielded retenequinone and *p*-hydroxybenzaldehyde but no further product was found.

(c) One gram of retenequinoneimine and 0.6 g. of *p*-hydroxybenzaldehyde were dissolved in 100 cc. of dry toluene and the mixture was refluxed for forty-five minutes. A small amount of ammonia was liberated. On chilling, an orange product was obtained which was entirely soluble in ethyl alcohol. It was identified as retenequinone. Evaporation of the mother liquor yielded more retenequinone and *p*-hydroxybenzaldehyde.

The reaction of retenequinone with hydrobenzamide. (a) Five grams (0.019 moles) of retenequinone and 5.46 g. (0.019 moles) of hydrobenzamide were dissolved in isoamyl alcohol and the mixture was refluxed for two hours. Ammonia was evolved during this period. After standing overnight, the precipitated solid was removed by filtration and recrystallized from ethyl alcohol. It was identified as 2-phenylretenoxazole, m.p. 170° (corr.), mixed m.p. with 2-phenylretenoxazole, 170° (corr.); yield, 60%.

(b) The reaction was repeated in 150 cc. of dry toluene and after refluxing for one hour, the solution was cooled. A small amount of ammonia was given off during the refluxing period. Chilling the solution yielded unchanged quinone. The solution was evaporated and retenequinone and hydrobenzamide were recovered. In the last residues, lophine was isolated and identified by its melting point, 275° (corr.), mixed m.p. with an authentic sample of lophine, 275° (corr.). Recovery of retenequinone was 96% complete.

(c) The reaction was repeated in 100 cc. of dry toluene. After refluxing for three hours, during which period ammonia was given off, the reaction-mixture was chilled and precipitated retenequinone was removed. By evaporation of the mother liquor under reduced pressure and fractional crystallization from ethyl alcohol, 2-phenylretenoxazole was isolated, m.p. 172° (corr.); yield, 2.1%.

The reaction of retenequinoneimine with hydrobenzamide. (a) Two and one-half grams (0.010 moles) of retenequinoneimine and 2.82 g. (0.010 moles) of hydrobenzamide were dissolved in 50 cc. of dry toluene and the mixture refluxed for exactly three hours. As ammonia formed it was collected in 50 cc. of 4% boric acid solution; and after the refluxing period the system was swept out for thirty minutes by a stream of dry air to complete the collection of ammonia. The trapped ammonia was titrated to a methyl red end-point with standard hydrochloric acid, after the method of Meeker and Wagner. During the refluxing period, color changes were observed in the reaction-mixture. After six minutes of refluxing, the solution turned a very dark green. During this period no ammonia was evolved. After another four minutes the solution became a light yellow and ammonia was evolved.

After refluxing for three hours and sweeping out for thirty minutes, the reaction-mixture was made slightly acid with hydrochloric acid, chilled for twelve hours and filtered. By repeated evaporation and chilling, more product was obtained. After recrystallization from dioxane, it was identified as 2-phenylretenoxazole, m.p. 172° (corr.); yield, 96%; 0.0096 moles.

Titration of the ammonia as described above indicated a yield of 0.0057 moles.

(b) The reaction was repeated with the same quantities of reactants. The color changes were observed to occur exactly as described above. The reaction-mixture was chilled after refluxing for ten minutes and acidified with hydrochloric acid. 2-Phenylretenoxazole was obtained as the product. After recrystallization from dioxane, it melted at 172° (corr.), yield, 78%.

The hydrolysis of hydrobenzamide. Hydrobenzamide (5.64 g.; 0.019 moles) was dissolved in 100 cc. of dry toluene and refluxed for three hours. The quantitative procedure described in the foregoing section for the determination of ammonia was followed. Titration of the ammonia given off with standard hydrochloric acid to a methyl red end-point indicated that 0.0002 moles of ammonia were liberated.

Attempted conversion of 2-aryl retenoxazoles to 2-aryl retenimidazoles. (a) Five grams of pure 2-phenylretenoxazole was mixed with 250 cc. of aqueous ammonia (28%) and heated in the autoclave for forty-nine hours at 170–180° and 400–500 pounds pressure. The solid product was then separated from the ammoniacal liquor. Evaporation of the liquor left no organic residue. The solid was recrystallized from acetone. Yield, 4.8 g., 96% recovery of 2-phenylretenoxazole, m.p. 173° (corr.), mixed m.p. with a sample of 2-phenylretenoxazole, 172° (corr.).

Anal. Calc'd for $C_{25}H_{21}NO$: N, 3.99. Found: N, 4.04.

(b) Five grams of pure 2-(2′-hydroxyphenyl)retenoxazole was mixed with 250 cc. of aqueous ammonia and heated for fifty hours at 170–180° and 900–1150 lbs. pressure. Ninety-four per cent of the original material was recovered. After recrystallization from dioxane, the melting point was 242° (corr.).

Anal. Calc'd for $C_{25}H_{21}NO_2$: N, 3.81. Found: N, 3.87.

(c) Five grams of pure 2-(2′-hydroxyphenyl)retenoxazole was mixed with 250 cc. of aqueous ammonia and heated for fifty hours at 240–250° and 1100–1300 lbs. pressure. The compound was completely destroyed under these conditions.

Attempts to hydrolyze 2-aryl retenoxazoles. (a) Two grams of 2-phenylretenoxazole and 40 cc. of concentrated hydrochloric acid were heated in pressure flasks for 100 hours at 130–140°. At the end of this period, the compound was removed from the mixture and washed with water until free of acid. Recovery was 100%. The compound was slightly yellow, m.p. 171–172° (corr.). After recrystallization from ethyl alcohol, the compound melted at 172° (corr.).

Anal. Calc'd for $C_{25}H_{21}NO$: N, 3.99. Found: N, 4.03.

(b) Hydrolysis of 2 g. of 2-phenylretenoxazole by 40 cc. of 95% acetic acid, at 140–150° for 100 hours was attempted. The same technique described in part (a) was used. The compound was appreciably soluble in acetic acid. Recovery on cooling, 90%. Careful addition of water to the filtrate yielded more of the product. Total recovery, 98%, m.p. 172° (corr.), mixed m.p. with 2-phenylretenoxazole, 172° (corr.).

(c) Hydrolysis of 1 g. of 2-(3′-nitrophenyl)retenoxazole (m.p. 238°) by 20 cc. of concentrated hydrochloric acid at 130–140° was also attempted. The recovered solid showed some evidence of decomposition; m.p. 220–237°, with slight decomposition. After recrystallization from ethyl alcohol, the melting point was 238.5° (corr.). Recovery, 98%. No further product could be found.

Preparation of 2-aryl retenoxazoles and 2-aryl retenimidazoles. The method of Sircar and Sircar was used, modified in certain respects. Ten grams (0.038 moles) of retenequinone and 0.038 moles of the appropriate aldehyde were dissolved in 100–150 cc. of the solvent. This mixture was heated to boiling and anhydrous ammonia gas was passed through the refluxing mixture for thirty minutes, except in those cases where the product precipitated from the reaction-mixture in a shorter

time. The solution was cooled and filtered and the crude product was washed with cold ethyl alcohol to remove colored impurities. By evaporation of the mother liquor under reduced pressure more of the product was usually obtained.

The reaction was also carried out cold, by suspending the retenequinone in a solution of the aldehyde in the solvent. Anhydrous ammonia gas was passed through the solution for thirty minutes or until the product precipitated from the reaction-mixture. The general procedure was then followed as outlined above.

The method of Japp and Wilcock was also employed in some cases. The retenequinone and aldehyde were mixed with an excess of aqueous ammonia and heated in a stainless steel autoclave at high temperatures. At the end of this period the product was removed, ground up into a fine powder, and purified.

2-Phenylretenoxazole (IV). This compound was prepared by the method of Sircar and Sircar, using hot isoamyl alcohol as the solvent. It was recrystallized from dry alcohol, yield, 24%.

The compound was also prepared by the method of Sircar and Sircar from cold ethyl alcohol, yield, 16%. The method of Japp and Wilcock was also used. The mixture was heated for six hours at 230° and 1000 lbs. pressure, yield, 90%.

2-(3'-Methylphenyl)retenoxazole (V). The compound was prepared by the method of Sircar and Sircar, from retenequinone and *m*-tolualdehyde dissolved in 100 cc. of boiling absolute ethyl alcohol. A solid precipitated before the reaction was completed. The product was recrystallized from dioxane and obtained as needles with a pink tinge, yield, 43%.

2-(2'-Chlorophenyl)retenoxazole (VI). The compound was prepared from retenequinone and *o*-chlorobenzaldehyde dissolved in 100 cc. of boiling isoamyl alcohol. It was recrystallized from dioxane, yield, 33%.

2-(3'-Nitrophenyl)retenoxazole (VII). This compound was prepared from retenequinone and *m*-nitrobenzaldehyde dissolved in 100 cc. of boiling absolute ethyl alcohol. The yellow product precipitated from the reaction-mixture after twenty minutes. It was recrystallized from dioxane, yield, 55%. This compound was also prepared by the method of Japp and Wilcock. The mixture was heated for six hours at 200° and 670 lbs. pressure, yield, 96%.

2-(4'-Dimethylaminophenyl)retenoxazole (VIII). This compound was prepared from retenequinone and *p*-dimethylaminobenzaldehyde dissolved in 100 cc. of boiling absolute ethyl alcohol. It was obtained as lemon yellow prisms, showing a slight green fluorescence, after recrystallization from dioxane, yield, 52%.

2-(4'-Diethylaminophenyl)retenoxazole (IX). This compound was prepared from retenequinone and *p*-diethylaminobenzaldehyde dissolved in 100 cc. of boiling isoamyl alcohol. It was recrystallized from dioxane, yield, 30%.

2-(2'-Hydroxyphenyl)retenoxazole (X) *and 2-(2'-hydroxyphenyl)retenimidazole* (XI). These compounds were prepared from retenequinone and salicylaldehyde dissolved in 100 cc. of boiling absolute alcohol. The products began to separate out of the reaction-mixture at the end of ten minutes, although the addition of ammonia was continued for the full thirty minute period. The products were separated by fractional crystallization from dioxane. By cooling the dioxane slowly to room temperature, the oxazole was obtained; it was recrystallized from dioxane, yield, 63%. By evaporating the dioxane mother liquor to a small volume and chilling, the imidazole was obtained. This was recrystallized from ethyl alcohol, yield, 7%.

The compounds were also prepared from retenequinone and salicylaldehyde in cold isoamyl alcohol. The general procedure was followed. By chilling the reac-

tion-mixture overnight, the crude product was obtained. The components were separated by fractional crystallization from ethyl alcohol. Yield of oxazole, 2%; of imidazole, 30%.

The preparation was also carried out in hot isoamyl alcohol. Separation was effected by fractional crystallization from dioxane. Yield of oxazole, 20%; of imidazole, 1%.

The method of Japp and Wilcock was also used. It was noted that the salicylaldehyde and aqueous ammonia reacted immediately upon mixing to form a gummy yellow precipitate. After heating the mixture for five hours at 200° and 580 lbs. pressure, the products were separated by fractional crystallization from dioxane and were at the same time separated from gums and carbon caused by extensive decomposition at the temperature of the reaction. Yield of the oxazole, 32%; of the imidazole, 12%.

2-(4'-Hydroxyphenyl)retenoxazole (XII) *and 2-(4'-hydroxyphenyl)retenimidazole* (XIII). The compounds were prepared from retenequinone and *p*-hydroxybenzaldehyde, dissolved in 100 cc. of boiling absolute ethyl alcohol. The general procedure was followed. After ten minutes, the mixture had set into a solid mass. The product was removed from the cool mixture by filtration and was washed with cold alcohol. Evaporation of the mother liquor produced no further product. The crude product was recrystallized from dioxane and was obtained as small tan plates, m.p. above 300°. The color persisted through further recrystallization and could not be removed by treatment with decolorizing charcoal. Nitrogen analysis indicated that a mixture of the oxazole and imidazole was present.

Attempts at fractional crystallization and fractional extraction with a variety of solvents including dioxane, benzene, toluene, chloroform, acetone, and alcohol were ineffectual due to the similar solubilities of XII and XIII. Separation was finally effected by dissolving the mixture in a large volume of hot dioxane and passing dry hydrogen chloride into this hot solution. The hydrochloride of the imidazole was precipitated and filtered from the hot solution. Further addition of hydrogen chloride to the clear hot filtrate did not produce further precipitation. On cooling this solution, the pure oxazole was obtained, yield, 16%.

The imidazole hydrochloride was boiled with dioxane to remove any contaminating oxazole. It was obtained as buff colored plates, m.p. above 300°.

Anal. Calc'd for $C_{25}H_{22}N_2O \cdot HCl$: N, 6.95. Found: N, 6.81.

The base was obtained by boiling the hydrochloride in 5% aqueous sodium hydroxide for two hours. The solid was separated by filtration, washed with water and alcohol and then recrystallized from dioxane. It was obtained as small, shining, tan plates, yield, 19%.

These compounds were also prepared cold by the method of Sircar and Sircar, using 100 cc. of chloroform as the solvent. Evaporation of the solution to dryness was necessary to recover the product. It was extracted with a mixture of alcohol and acetone, under reflux for one hour, and then recrystallized from dioxane. Analysis for nitrogen indicated that the product was a mixture of the oxazole and imidazole, of approximately the same composition as the mixture obtained from hot alcohol. Total yield, 26%.

2-(4'-Hydroxy-3'-methoxyphenyl)retenoxazole (XIV). This compound was prepared from retenequinone and vanillin, dissolved in 100 cc. of boiling absolute ethyl alcohol. The product was obtained after chilling the reaction-mixture in the ice box for two days. It was recrystallized from dioxane, yield, 71%.

2-(4'-Methoxyphenyl)retenoxazole (XV). This compound was prepared from

TABLE II

2-ARYL RETENOXAZOLES AND 2-ARYL RETENIMIDAZOLES

COMPOUND	M.P. °C. CORR.	CRYST. FORM	EMPIRICAL FORMULA	NITROGEN %		MOL. WT.	
				Calc'd	Found	Calc'd	Found
IV 2-Phenylretenoxazole	172	needles	$C_{25}H_{31}NO$	3.99	4.07	351	347
V 2-(3′-Methylphenyl)retenoxazole	164	needles	$C_{26}H_{33}NO$	3.83	3.84	365	364
VI 2-(2′-Chlorophenyl)retenoxazole	155–156	needles	$C_{25}H_{30}ClNO$	3.63	3.76	386	395
VII 2-(3′-Nitrophenyl)retenoxazole	238.5	yellow prisms	$C_{25}H_{30}N_2O_3$	7.06	7.00	396	412
VIII 2-(4′-Dimethylaminophenyl)retenoxazole	232	yellow prisms	$C_{27}H_{36}N_2O$	7.11	7.09	394	403
IX 2-(4′-Diethylaminophenyl)retenoxazole	188	yellow prisms	$C_{29}H_{40}N_2O$	6.63	6.54	422	408
X 2-(2′-Hydroxyphenyl)retenoxazole	243	buff needles	$C_{25}H_{31}NO_2$	3.81	3.99	367	371
XI 2-(2′-Hydroxyphenyl)retenimidazole	220–221	needles	$C_{25}H_{32}N_2O$	7.65	7.72	366	375
XII 2-(4′-Hydroxyphenyl)retenoxazole	>300	buff plates	$C_{25}H_{31}NO_2$	3.81	3.64	367	372
XIII 2-(4′-Hydroxyphenyl)retenimidazole	>300	buff plates	$C_{25}H_{32}N_2O$	7.65	7.63	366	371
XIV 2-(4′-Hydroxy-3′-methoxyphenyl)retenoxazole	186–187	yellow prisms	$C_{26}H_{33}NO_3$	3.53	3.58	397	416
XV 2-(4′-Methoxyphenyl)retenoxazole	172–173	needles	$C_{26}H_{33}NO_2$	3.67	3.70	381	398
XVI 2-(3′,4′-Dimethoxyphenyl)retenoxazole	204	buff needles	$C_{27}H_{35}NO_3$	3.41	3.44	411	415
XVII 2-(3′,4′-Methylenedioxyphenyl)retenoxazole	198.5	buff needles	$C_{26}H_{31}NO_3$	3.54	3.50	395	412
XVIII 2-(α-Furfuryl)retenoxazole	162–163	needles	$C_{22}H_{19}NO_2$	3.97	3.99	353	338

retenequinone and anisaldehyde dissolved in 100 cc. of boiling absolute ethyl alcohol. The same procedure was used as for the vanillin condensation. The product was recrystallized from dioxane, yield, 55%.

2-(3',4'-Dimethoxyphenyl)retenoxazole (XVI). This compound was prepared from retenequinone and veratraldehyde dissolved in 100 cc. of boiling absolute ethyl alcohol. The same procedure was followed as for the vanillin condensation. It was recrystallized from dioxane, yield, 60%.

2-(3',4'-Methylenedioxyphenyl)retenoxazole (XVII). This compound was prepared from retenequinone and piperonal dissolved in 100 cc. of boiling absolute ethyl alcohol. The same procedure was used as for the vanillin condensation. The product was crystallized from dioxane, yield, 62%.

2-(α-Furfuryl)retenoxazole (XVIII). This compound was prepared from retenequinone and furfuraldehyde dissolved in 100 cc. of boiling absolute ethyl alcohol. At the end of thirty minutes, the reaction-mixture had set into a solid mass. After recrystallization from dioxane and then from alcohol, the compound was obtained as small, white needles, yield, 40%.

PHILADELPHIA, PA.

SUMMARY

1. The reaction of retenequinone and ammonia has been studied.

2. A critical study has been made of the mechanisms previously assigned to the reaction of *o*-quinones and aromatic aldehydes in the presence of ammonia to form oxazoles and imidazoles.

3. A new mechanism, in agreement with experimental findings, has been developed to explain the formation of 2-aryl retenoxazoles from retenequinone, aromatic aldehydes, and ammonia.

4. A series of 2-aryl retenoxazoles and 2-aryl retenimidazoles has been prepared.

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SOME REACTIONS OF 5-CHLOROMERCURI-2-FURFURYL ALCOHOL[1]

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The simple furans, especially those with saturated substituent groups, are so sensitive towards acidic reagents employed in nuclear substitution that such reactions usually lead either to low yields or complete decomposition. This difficulty can often be circumvented by indirect substitution involving an intermediate mercuration step (1). The present work is an extension of this method to the sensitive compound 2-furfuryl alcohol, from which only one substitution-product, 5-nitrofurfuryl alcohol, has been reported (2). The successful preparation of mercurated furfuryl alcohol as outlined in this paper thus provides a means of obtaining such compounds as 5-bromo- and 5-aceto-furfuryl alcohol, which cannot yet be obtained by bromination or by the Friedel and Crafts reaction. The oxidation of mercurated furfuryl alcohol likewise leads through mercurated furfural to products obtainable by replacement of the halomercuri group.

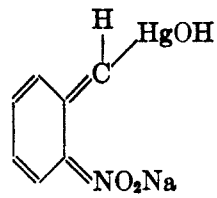
When furfuryl alcohol, I, was mercurated by the prescribed procedure (1) the product was chiefly an infusible non-crystallizable precipitate. If, however, a threefold excess of the alcohol was employed, a 50% yield of 5-chloromercurifurfuryl alcohol, II, was obtained and the production of infusible material was minimized. The object in using this excess of alcohol was, of course, to reduce poly- in favor of mono-substitution, but the infusible material evidently contains more than simple substitution-products. Evidence for this lies in the observation that it is partially soluble in dilute alkali; the solution when carefully acidified with hydrochloric acid yields 5-chloromercurifurfuryl alcohol. A part of the infusible precipitate must therefore be an intermediate of type III, by analogy with similar intermediates which have been isolated (1, 3) in both the furan and thiophene series.

The foregoing description concerning preparation of 5-chloromercurifurfuryl alcohol indicates its characteristic property of solubility in alkali. When it was treated with one equivalent of 5% sodium hydroxide it dissolved at once, but a compound, presumably the hydroxymercuri deriva-

[1] Presented at the Detroit meeting of the American Chemical Society, September, 1940.

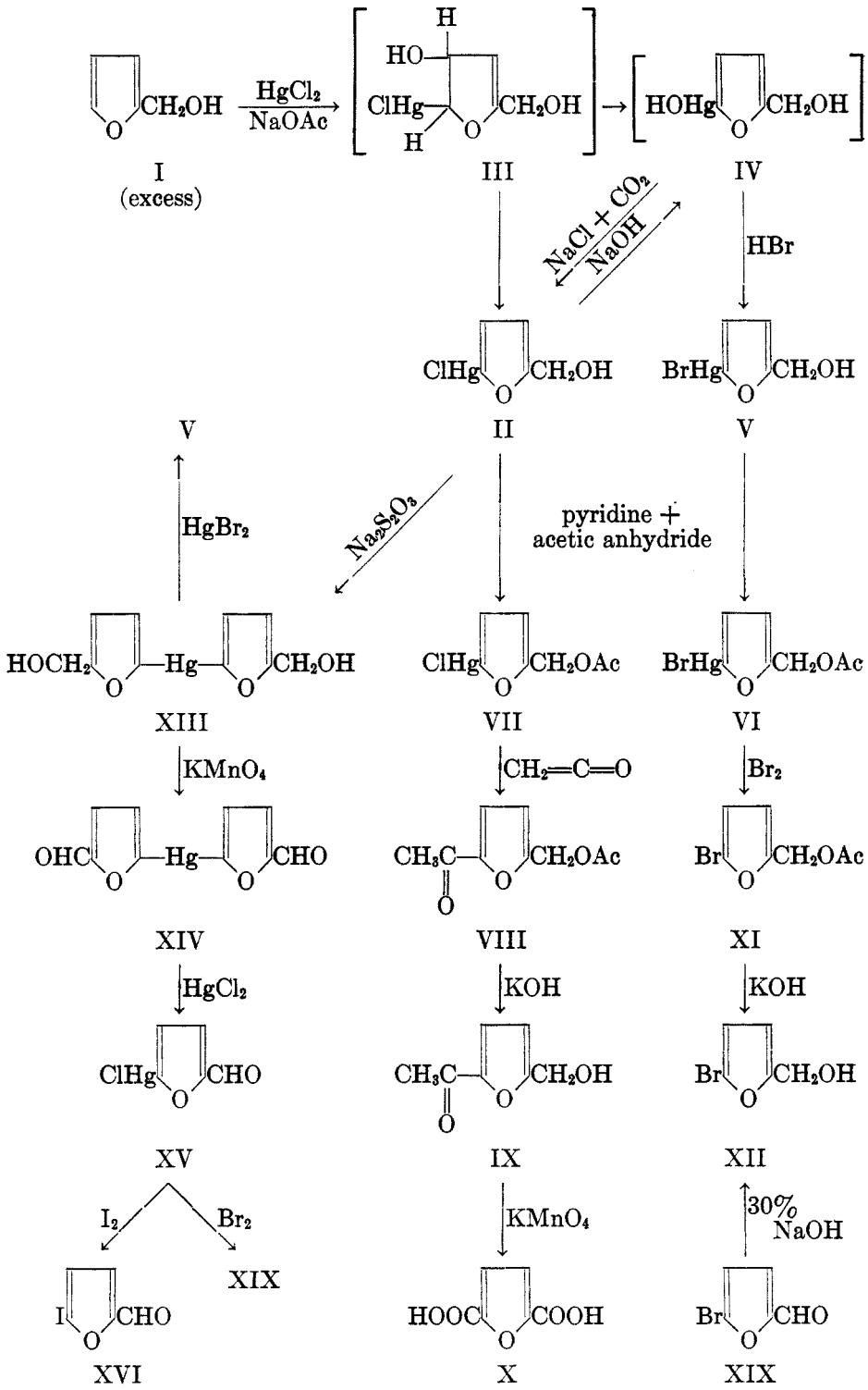
tive, IV, precipitated immediately. This compound could not be purified satisfactorily for analysis, owing to its tendency to retain the elements of potassium or sodium chloride and to decompose with formation of mercurous salt. It was somewhat soluble in water and very soluble in excess alkali, from which solution the chloromercuri derivative could be regenerated by cautious addition of hydrochloric acid. Since the odor of furfuryl alcohol during such treatment attested the extreme lability of the C—Hg linkage in this compound, a better regeneration of the chloromercuri derivative, II, was effected with carbon dioxide in a solution saturated with sodium chloride.

This solubility of chloromercurifurfuryl alcohol was at first somewhat surprising to us. We have since found that this is an extreme instance of a general though little-known property of hydroxymercurials. Thus phenylmercuric chloride dissolves with some difficulty by heating in 10% alkali and, if the solution be diluted sufficiently, the hydroxymercuri derivative does not precipitate. The solubility of RHgOH types depends, however, upon the presence of coordinating groups. This is especially noticeable in the case of α-methoxymercurials, many of which are so easily dissolved in sodium hydroxide that a neutralization equivalent can be carried out with a compound such as 1-chloromercuri-2-methoxycyclohexane (4). The furyl nucleus must also have this property, since furylmercuric chloride (1) is very soluble in 5% aqueous sodium hydroxide, from which it can be recovered unchanged by careful acidification with hydrochloric acid. In this connection, we see no reason to assume with Reissert (5) that the ready solubility of *o*-nitrobenzylmercuric chloride results from formation of an acinitro salt, since this characteristic solubility



could be explained equally satisfactorily as due to the effect of the coordinating nitro group on the hydroxymercuri linkage. It must be admitted, however, that such an unelaborated concept does not explain the report that *o*-nitrophenylmercuric chloride (6)[2] as well as some α-methoxymercurials are not soluble in alkali, nor that an excess of alkali is required to retain 5-hydroxymercurifurfuryl alcohol in solution.

[2] More recent work in this laboratory indicates that *o*-nitrophenylmercuric chloride can be dissolved in warm alkali and reprecipitated from this solution with hydrochloric acid.


CH₂OH
HgCl₂
NaOAc
HO
H
ClHg
CH₂OH
H
HOHg
CH₂OH
I
(excess)
III
IV
NaCl + CO₂
NaOH
HBr
ClHg
CH₂OH
BrHg
CH₂OH
II
V
V
HgBr₂
Na₂S₂O₃
pyridine +
acetic anhydride
HOCH₂
Hg
CH₂OH
ClHg
CH₂OAc
BrHg
CH₂OAc
XIII
VII
VI
KMnO₄
CH₂=C=O
Br₂
OHC
Hg
CHO
CH₃C
CH₂OAc
Br
CH₂OAc
XIV
VIII
XI
HgCl₂
KOH
KOH
ClHg
CHO
CH₃C
CH₂OH
Br
CH₂OH
XV
IX
XII
I₂
Br₂
KMnO₄
30%
NaOH
XIX
I
CHO
HOOC
COOH
Br
CHO
XVI
X
XIX

When the alkaline solution of chloromercurifurfuryl alcohol was treated with hydrobromic acid the product contained both bromine and chlorine. A better method of preparing bromomercurifurfuryl alcohol, (V), involved repeated treatment of chloromercurifurfuryl alcohol, (II), with sodium bromide in ethanol. Both II and V were smoothly acetylated with acetic anhydride in pyridine to yield 5-bromomercurifurfuryl acetate, (VI), and 5-chloromercurifurfuryl acetate, (VII).

This compound VII was desired in order that it might be treated with ketene to produce 5-acetofurfuryl acetate, (VIII), from which the corresponding alcohol, (IX), could be prepared. This step seemed necessary because no product could be obtained by reaction of II with ketene in acetone except for a small amount of VII. When the acetate, (VII), was

TABLE I

PREPARATION OF 2-FURYL METHYL KETONE IN VARIOUS SOLVENTS BY THE ACTION OF KETENE UPON 2-CHLOROMERCURIFURAN

RUN	SOLVENT	MOLES KETENE	% YIELD 2-FURYL METHYL KETONE	M.P. 2,4-DINITROPHENYLHYDRAZONE, °C.	YIELD KETENE POLYMER, GRAMS
1	Acetone	0.536	34.5	165–174	0.64
			27.0	212–214[a]	
2	Diethyl sulphide	0.57	20.9	190–194	0.39
3	Glycol dimethyl ether	0.346	13.8	189–192	0.23
4	Pyridine	0.36	None		21.5
5	Acetone + hydroquinone	0.56	34.5	164–168	0.59
6	Carbon tetrachloride	0.528	11.8	200–215	None
7	Chloroform	0.624	31.7	199–203	None

[a] Purified crude dinitrophenylhydrazone from Expt. 1 by crystallization.

likewise treated with ketene in acetone none of the product VIII could be isolated.

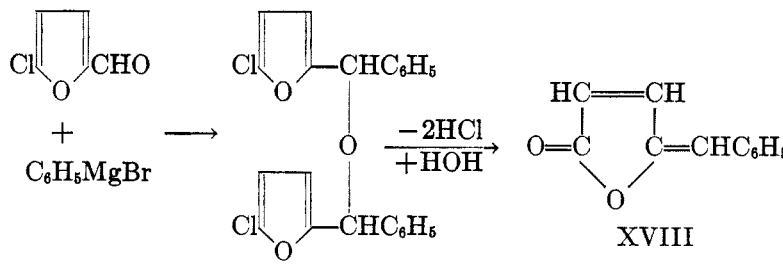
The method (7) was, however, known to be erratic and seemed to warrant further investigation. The work of Rice and Greenberg (8) suggested that solvents other than acetone might reduce the tendency towards ketene polymerization. Table I shows, by comparison of apparent furyl methyl ketone 2,4-dinitrophenylhydrazone yields with the crude melting points, that solvents such as carbon tetrachloride and chloroform are most satisfactory for this reaction of organomercurials with ketene. The latter solvent is to be preferred because it dissolves organomercurials with greater ease than does carbon tetrachloride.

When chloroform was used as solvent in the reaction between chloromercurifurfuryl acetate, (VII), and ketene, a 14% yield of 5-acetofurfuryl acetate, (VIII), was obtained. In addition to VIII considerable furfuryl

acetate was obtained, which was not unexpected owing to the lability of the C—Hg linkage in these mercurials. Compound VIII was identified by saponification to acetofurfuryl alcohol (IX), by preparation of its oxime, and oxidation to dehydromucic acid, (X).

The bromination of 5-chloromercurifurfuryl acetate, (VII), produced an oil containing both chlorine and bromine. It was better, therefore, to use 5-bromomercurifurfuryl acetate, (VI), in order to obtain a fair yield of pure 5-bromofurfuryl acetate, (XI). This ester had a pleasant fruity odor. It was slowly saponified at room temperature to give the odorless, low-melting solid 5-bromofurfuryl alcohol, (XII). This compound was extremely unstable and difficult to purify. After futile attempts to stabilize XII with urea or with hydroquinone, it was found that conversion to the bromomagnesium alkoxide by means of the Grignard reagent, followed by regeneration of the alcohol with dilute acetic acid, rendered XII much more amenable to purification techniques. Nevertheless, the isolated compound was exceedingly unstable. It decomposed slowly at room temperature, and immediately at 65°, to form a greenish-black tar. It was more stable in solution; indeed, it survived a five-hour reflux period in benzene containing suspended sodium acetate. It seems, however, to be a property of halofurans that decomposition is autocatalytic. Hence the presence of sodium acetate, which effectively removes traces of halogen acid, might be expected to retard decomposition.

A deliberate attempt to decompose bromofurfuryl alcohol, (XII), either spontaneously or with sulfuric acid, to produce acetylacrylic acid has thus far not been successful. This would be the expected product in view of the formation of benzalcrotonolactone, (XVIII), from the ether of chlorofuryl phenyl carbinol (9), (XVII). The fact that XVIII will not add hydrogen halide whereas acetylacrylic acid undergoes this addition may contribute to the failure to isolate the latter compound from 5-bromofurfuryl alcohol, (XII). It was observed that the decomposition of XII in sulfuric acid did not produce the hydrogen halide observed in the comparable reaction with XVII.



XVII XVIII

Oxidation of bromofurfuryl alcohol failed to yield a characterizing derivative, but the structure of this compound was proved by synthesis *via* the Cannizzaro method from 5-bromofurfural, (XIX). This reaction did not succeed using an equivalent quantity of 30% sodium hydroxide, but was effected when a large excess of this alkali and a trace of hydrogen peroxide was employed. The demonstrated catalytic effect of peroxide on the Cannizzaro reaction (10) is significant here because furfurals, unlike benzaldehydes, do not form peroxides in the air. Thus, furfurals do not autooxidize to furoic acids as benzoic acids are formed from benzaldehydes.

No chloromercurifuroic acid could be isolated when 5-chloromercurifurfuryl alcohol was oxidized with permanganate, although a 1–2% yield of 5-chloromercurifurfural was obtained. This aldehyde, (XV), was more conveniently obtained by the following series of reactions. Chloromercurifurfuryl alcohol, (II), with sodium thiosulfate gave a good yield of *bis*-5-hydroxymethyl-2-furylmercury, (XIII). The structure of this compound was demonstrated by conversion with mercuric bromide to bromomercurifurfuryl alcohol, (V), in a state of purity which demonstrated that passage from one halomercuri derivative to another is best effected in this series through the R_2Hg intermediate. When *bis*-5-hydroxymethyl-2-furylmercury was oxidized with permanganate, a 22% yield of *bis*-5-formyl-2-furylmercury was obtained, which could be converted quantitatively with mercuric chloride to 5-chloromercurifurfural, (XV).

This compound, XV, was identified by bromination to 5-bromofurfural (11), (XIX), and was further characterized by iodination to 5-iodofurfural, (XVI). The latter substance melted 18° higher than the compound to which Scheibler and co-workers (12) assigned this structure. Since their compound was prepared from a substance which they describe as triacetoxyfurfural (although the analysis is none too satisfactory for this designation) it is possible that their compound is either a β-substituted furfural or an impure sample of the iodofurfural which we have prepared. Our compound has been converted to 5-iodofuroic acid by a Cannizzaro reaction, in which the fraction containing the iodofurfuryl alcohol was discarded because of the evident extreme instability of this compound.

EXPERIMENTAL

5-Chloromercuri-2-furfuryl alcohol. To a solution of 815 g. (3 moles) of mercuric chloride, and 1632 g. (12 moles) of sodium acetate trihydrate in 15 liters of water was added 882 g. (9 moles) of freshly distilled, water-soluble furfuryl alcohol. After stirring for thirty-five hours, the crude product, 789 g., m.p. 144°, was filtered off. Extraction with boiling alcohol and subsequent recrystallization from the same solvent yielded 490 g., m.p. 144.5–145.5°. This 49% yield of pure product may be

augmented both by evaporation of the crystallizing liquors, and by solution of the ethanol-insoluble residue, remaining after ethanol extraction of the crude product, in 4% sodium hydroxide (150 cc. per 20 g.). After filtering and chilling this alkaline solution it was stirred while exactly one equivalent of 4% hydrochloric acid was added dropwise. These additional yields, m.p. 137–138°, were difficult to purify, but were suitable for the preparation of the R_2Hg compounds.

Anal. Calc'd for $C_5H_5ClHgO_2$: C, 18.0; H, 1.51.
Found: C, 17.8; H, 1.54.

When the alcohol was dissolved in 1 equivalent of 5% sodium hydroxide an immediate precipitate appeared. This precipitate, m.p. 155–157°, was soluble in an excess of alkali. Although it was undoubtedly the hydroxymercuri compound, it contained small amounts of sodium and halogen and has not yet been satisfactorily purified for analysis. When its water solution was saturated with sodium chloride and treated with carbon dioxide, pure 5-chloromercurifurfuryl alcohol was precipitated. The alcohol could likewise be obtained by acidifying the alkaline solution with hydrochloric acid, although the odor of furfuryl alcohol was always apparent. The lability of this C—Hg linkage was likewise demonstrated by treating a pyridine solution of the alcohol II with an equivalent of trityl chloride. The product, trityl furfuryl ether, m.p. 138–140° was identified by mixed melting point (13).

5-Chloromercurifurfuryl acetate. An unsatisfactory yield of this compound can be obtained by treating an acetone solution of the alcohol with gaseous ketene. It is more conveniently prepared by treating 33.3 g. (0.1 mole) of chloromercurifurfuryl alcohol in 47 g. (0.6 mole) of pyridine (dried over barium oxide) with 41 g. (0.4 mole) of acetic anhydride at 0° for four days. Subsequent addition of 1% hydrochloric acid until the pyridine was neutralized produced a precipitate weighing 36.5 g. (97% yield) melting at 126–127°. This yielded 29 g. m.p. 131–131.5°, after crystallization from 7:1 benzene-petroleum ether (b.p. 60–70°). Subsequent crystallization did not raise the melting point.

Anal. Calc'd for $C_7H_7ClHgO_3$: C, 22.4; H, 1.87; Hg, 53.5; Cl, 9.5.
Found: C, 22.3; H, 1.86; Hg, 53.6; Cl, 9.1.

bis-*5-Hydroxymethyl-2-furylmercury.* To a solution of 337 g. (1.34 mole) of sodium thiosulfate pentahydrate in 900 cc. of water was added 150 g. (0.453 mole) of 5-chloromercuri-2-furfuryl alcohol at once with vigorous agitation. After standing for twenty-two hours the precipitate was filtered off and re-treated with the same quantity of fresh thiosulfate solution. The resulting mixture was filtered after twelve hours. A weight of 106 g. (theoretical, 88.6 g.) and melting point of 130–135° indicated an incomplete reaction. Crystallization from 2:1 methanol-ethyl acetate yielded 55 g., m.p. 147.5–148.5° (yield, 62%) which was sufficiently pure for most purposes. Repeated crystallization from this solvent, and from benzene raised the melting point to 153–154°.

Anal. Calc'd for $C_{10}H_{10}HgO_4$: C, 30.4; H, 2.56.
Found: C, 30.4; H, 2.65.

The compound was also obtained in 61% yield when 5-chloromercurifurfuryl alcohol in methanol was treated with an excess of diazomethane (14).

5-Bromomercuri-2-furfuryl alcohol. a. From *bis*-5-hydroxymethyl-2-furylmercury. A solution of 0.39 g. (0.001 mole) of the R_2Hg compound with 0.36 g. (0.001 mole) of mercuric bromide in 8 cc. of ethanol was refluxed for ninety minutes. Vacuum evaporation of the solvent left 0.74 ., m.gp. 124–130°. Crystallization from 1:1 chloroform-ethanol yielded 0.63 g., m.p. 139–140°. Yield of this pure material was therefore 84%.

Anal. Calc'd for $C_5H_5BrHgO_2$: C, 15.9; H, 1.33.
Found: C, 15.8; H, 1.43.

b. From 5-chloromercuri-2-furfuryl alcohol. A solution of 33.3 g. (0.1 mole) of the alcohol in 450 cc. of 95% ethanol was treated with 20.6 g. (0.2 mole) of sodium bromide in 25 cc. of water. Vacuum evaporation of the solvent, followed by thorough washing of the residue with water yielded a solid, m.p. 137–138° which still contained chlorine. Repetition of the entire process yielded a crude product, m.p. 138°, in 70.8% yield.

5-Bromomercuri-2-furfuryl acetate. This preparation, identical with that outlined for the chloro compound except that hydrobromic acid was used to neutralize the pyridine, yielded a crude product melting at 90–95° which was crystallized from 1:7 benzene-petroleum ether (b.p. 60–70°) to the constant melting point 108–109°. Yield of the purified product was 88%.

Anal. Calc'd for $C_7H_7BrHgO_3$: C, 20.0; H, 1.67.
Found: C, 20.4; H, 1.81.

5-Bromofurfuryl acetate. A solution of 7.18 g. (0.017 mole) of 5-bromomercuri-2-furfuryl acetate in 150 cc. of chloroform stirred at 0° was treated dropwise but rapidly with 2.75 g. (0.017 mole) of bromine in 30 cc. of chloroform. After the addition, the precipitated mercuric bromide was filtered off and the filtrate washed successively with 50 cc. of saturated sodium sulfite, 50 cc. of 10% sodium carbonate, and twice with water. Distillation of the solution dried with magnesium sulfate, finally at 110–112° (17–18 mm.) gave 2.39 g. which was redistilled at 106–107° (13 mm.) to yield (58% of theoretical) a colorless oil having a pleasant fruity odor, d_{25}^{25}, 1.51; n_D^{25}, 1.4991; M_D Calc'd 42.69, Found 42.57.

Anal. Calc'd for $C_7H_7BrO_3$: Br, 36.5. Found: Br, 36.7.

5-Bromofurfuryl alcohol. a. From bromofurfuryl acetate. A solution of 2.54 g. (0.01 mole) of the acetate and 2.6 g. (0.05 mole) of potassium hydroxide in 11 cc. of methanol and 14 cc. of water was let stand for four days until the odor of the acetate was very slight. The methanol was removed at 10 mm., and the aqueous residue extracted with ether. The ether solution, dried with magnesium sulfate, was evaporated to leave 1.78 g. of orange-colored oil. This was crystallized under nitrogen repeatedly from 1:8 ether-petroleum ether (b.p. 40–60°) from +20° to −80°. After eight crystallizations and final evacuation at 0° to remove solvent the compound weighed 0.54 g. and melted at 43–44°. This wasteful process was improved as described below. The resulting compound was extremely unstable; it became slightly green after a short time and then rapidly decomposed to a green tar. The green, slightly decomposed samples gave a red solution when dissolved in alcohol. Addition of 1% of hydroquinone or urea lowered the melting point without stabilizing the compound. Boiling with excess sodium acetate in benzene for five hours did not decompose the substance, which was recovered unchanged. Decomposition over a one day period in either concentrated sulfuric acid or 85% phosphoric acid did not yield a recognizable product. When an ether solution of the alcohol was refluxed overnight with acetyl chloride, a good yield of bromofurfuryl acetate was obtained by steam distillation. The alcohol could be dissolved in water at 60° but would not crystallize on cooling although it could be recovered by ether extraction. Such a homogeneous water solution could be refluxed for some hours without destruction of the substance. However when more than would dissolve in the water was heated to 65° under water the undissolved portion decomposed instantly with formation of a green tar; the aqueous solution gave a dinitrophenylhydrazone test and iodoform test (comparable tests with furfuryl alcohol were negative) but no product could be

isolated. When the alcohol was refluxed in ethanol solution for two days and the solvent subsequently removed at 12 mm., the residue distilled at 91–94°, 12 mm. This compound is being investigated; it seems not to contain a carbonyl group and is not soluble in water or in saturated sodium bicarbonate solution. Because of difficulty in freeing bromofurfuryl alcohol from solvent without decomposing it, the analyses were not good.

Anal. Calc'd for $C_5H_5BrO_2$: Br, 45.2. Found: Br, 44.2.

b. From 5-bromofurfural. The disappearance of bromofurfural in this Cannizzaro reaction was followed by testing the supernatant ether solution for the characteristic yellow color with aniline acetate. A suspension of 17.5 g. (0.1 mole) of bromofurfural in 100 cc. of ether was stirred with 400 cc. of 30% sodium hydroxide. The time of reaction varied from one to four days, but the reaction could be brought quickly to completion by addition of a drop of 30% hydrogen peroxide. When the test for bromofurfural was negative, water was added to dissolve the sodium bromofuroate, and the alkaline solution extracted five times with ether, after which it was acidified, yielding 76% of the possible amount of 5-bromofuroic acid. The ether extract, washed with ferrous ammonium sulfate solution, sodium bisulfite, and water, was dried with magnesium sulfate to which was added a little charcoal. The ether solution was then treated with 0.1 mole of filtered ethylmagnesium bromide in ether. Treatment with phenylmagnesium bromide for two days gave the same results. After two hours this was poured into iced dilute acetic acid. The ether solution obtained by five-fold extraction of this hydrolysate was washed with 2% alkali, dried with magnesium sulfate to which charcoal was added, and evaporated at 10 mm. to yield 7.12 g. (80%) of bromofurfuryl alcohol melting at 35°. This was purified by solution in 10 cc. of benzene and seeding of the solution rendered turbid by addition of 60 cc. of petroleum ether (b.p. 26–30°) to yield 5.25 g., m.p. 43–44°. A mixed melting point with the compound obtained from the mercurial was not lowered.

2-Furyl methyl ketone 2,4-dinitrophenylhydrazone. This preparation was used to check the effect of solvents on the reaction of mercurials with ketene. Into a solution of 2-chloromercurifuran in the selected dry solvent maintained at 64° was passed ketene from an Ott lamp at the rate of 0.06–0.08 mole per hour for eight hours. The solvent was then removed under reduced pressure and the residue steam distilled until the distilling liquid no longer gave a dinitrophenylhydrazone test. The distillate was extracted with ether which, after drying, was evporated to leave a residue of ketone. This was weighed and then converted to the 2,4-dinitrophenylhydrazone by the method of Iddles and Jackson (15). A sample of pure furyl methyl ketone treated by this procedure gave a crude melting point of 210–212° and a high melting point of 223° after repeated crystallization from 3:1 ethyl acetate-ethanol. The results shown in Table I indicate that carbon tetrachloride or chloroform are the best solvents for the reaction. It may be noted that addition of hydroquinone to the solvent acetone did not increase the yield of ketone nor decrease the yield of polymer.

Anal. Calc'd for $C_{12}H_{10}N_4O_5$: C, 49.6; H, 3.47.
Found: C, 49.0; H, 3.70.

5-Acetofurfuryl acetate. A solution of 11.2 g. (0.03 mole) of 5-chloromercuri-2-furfuryl acetate in 165 cc. of chloroform dried with calcium chloride was treated with ketene (0.6 moles) at 64° for twelve and one-half hours. The chloroform solution was then filtered and the solvent removed under reduced pressure. The residue was steam distilled until the distillate gave a negative dinitrophenylhydrazone test.

The ether extract of the distillate was dried and evaporated to yield 3.23 g. of oil, which was fractionated at 11–12 mm. to give 1.47 g., b.p. 73–74° and 1.13 g., b.p. 100–140°. The latter fraction was purified by crystallization from 1:1 methanol-petroleum ether (b.p. 40–60°) and melted at 44–46°, 0.87 g. or 14% of theoretical. Three further crystallizations from a methanol-petroleum ether-ethyl ether mixture raised this melting point to 46.5–47°.

Anal. Calc'd for $C_9H_{10}O_4$: C, 59.3; H, 5.53.
Found: C, 59.2; H, 5.84.

Oxidation with alkaline permanganate gave a 2% yield of dehydromucic acid, identified by its yellow ferric chloride test and by conversion with diazomethane to its dimethyl ester, m.p. 107–108° after crystallization from water.

5-Acetoxymethyl-2-furyl methyl ketone semicarbazone. When the ester was treated with an excess of semicarbazide at pH 8, the precipitated semicarbazone melted at 169–170°. Two crystallizations from 4:1 benzene-ethanol raised this to 173–174°.

Anal. Calc'd for $C_{10}H_{14}N_3O_4$: C, 50.0; H, 5.82.
Found: C, 50.3; H, 5.79.

5-Acetofurfuryl alcohol. A 62% yield was obtained by saponifying the acetate with one equivalent of potassium hydroxide in 1:1 methanol-water for two days. Removal of the methanol *in vacuo* and extraction with ether gave 0.05 g. of solid, m.p. 42°, after this dried solution was evaporated. This compound was crystallized from 1:3 methanol-petroleum ether (b.p. 40–60°) and melted at 43–44°. A mixed melting point with the original acetate was lowered 20°.

Anal. Calc'd for $C_7H_8O_3$: C, 60.0; H, 5.75.
Found: C, 59.6; H, 5.82.

Oxidation of this compound with iodine in alkaline solution at 25° gave iodoform.

bis-*5-Formyl-2-furylmercury* (XIV). Finely powdered potassium permanganate (40.6 g., 0.257 mole) was gradually added over a three-hour period to a stirred solution of 50.7 g. (0.128 mole) of *bis*-5-hydroxymethyl-2-furylmercury in 1900 cc. of permanganate-purified acetone. When no unchanged permanganate remained after thirty-six hours, the mixture was filtered and the filtrate evaporated at 10 mm., leaving a residue, m.p. 128–133°. This residue was extracted twice with 475 cc. of saturated sodium sulfite made slightly acidic with acetic acid.

The bisulfite extracts were treated with sodium carbonate, giving 17.4 g. of the dialdehyde, m.p. 238–240° (22.5% of theoretical). Repeated crystallization from dioxane raised the melting point to 262–263°. After boiling with hydrochloric acid, the aniline acetate test, characteristic of furfural, was obtained.

Anal. Calc'd for $C_{10}H_6HgO_4$: C, 30.8; H, 1.55.
Found: C, 30.8; H, 1.63.

The compound slowly dissolved in a methanol solution of hydroxylamine. Vacuum evaporation of the solution left a solid, which was dissolved in 1% aqueous alkali and reprecipitated with carbon dioxide, giving 52% yield of a compound which was presumably the oxime, m.p. 114–116°, although we were unsuccessful in attempts to purify this compound for analysis.

5-Chloromercurifurfural. A 5% yield of the aldehyde m.p. 211–212° was obtained by oxidizing an alkaline solution of the alcohol with one equivalent of permanganate. A better method of preparation involved refluxing equivalent quantities of *bis*-5-formyl-2-furylmercury and mercuric chloride in ethanol for five hours. A 96% yield of crude product m.p. 200° was decreased to 66% after crystallization from 1:1 ethanol-chloroform m.p. 218–219°.

Anal. Calc'd for $C_5H_3ClHgO_2$: C, 18.1; H, 0.91.
Found: C, 18.5; H, 1.50.

5-Bromofurfural was obtained from this compound by treating a chilled chloroform suspension with one equivalent of bromine. After vacuum evaporation of the chloroform and steam distillation of the residue, the ether extract of the distillate gave on evaporation a 62% yield, m.p. 82°. A mixed melting point with the bromofurfural prepared from furfural was not lowered.

5-Iodofurfural. To a suspension of 1 g. (0.003 mole) of 5-chloromercurifurfural in 15 cc. of dioxane (distilled from sodium benzophenone) was added 0.76 g. (0.003 mole) of iodine in 24 cc. of dioxane. After ninety-six hours the dioxane was removed at 10 mm. and the residue steam distilled, yielding 0.46 g. m.p. 98–102°. This was washed with 5% potassium iodide solution and crystallized from acetone-water and dioxane-water, m.p. 127.5°, weight 0.31 g. or 46%.

Anal. Calc'd for $C_5H_3IO_2$: C, 27.0; H, 1.36; I, 57.2.
Found: C, 27.0; H, 1.43; I, 57.2.

A mixture of 0.16 g. (0.0008 mole) of this compound with 4 cc. of 30% sodium hydroxide solution containing a trace of peroxide yielded, after four days, 0.03 g. (32%) of 5-iodofuroic acid, m.p. 197°, which was crystallized from 1:1 benzene-petroleum ether (b.p. 60–70°), m.p. 197–198°. A mixed melting point carried out by Dr. Henry Gilman with the compound prepared from 2,5-diiodofuran (16) was not depressed. It was found in this connection that these samples must be introduced about 5° below the melting point in order to avoid decomposition. This accounts for the melting point 192° previously reported for this compound.

The authors are grateful to Miss Gladys Stonestreet and Miss Joan Romeyn for aid in the microanalyses, and to Dr. F. N. Peters, Quaker Oats Company, for generous supplies of the starting materials used in this investigation.

SUMMARY

1. Monomercurated furfuryl alcohol and furfural have been prepared and characterized.

2. 5-Acetofurfuryl alcohol and 5-bromofurfuryl alcohol have been prepared from these mercurials. The latter compound has also been synthesized from 5-bromofurfural.

3. 5-Iodofurfural has been prepared from 5-chloromercurifurfural.

TORONTO, CANADA.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY AND THE CENTRAL EXPERIMENT STATION, BUREAU OF MINES]

TELLURIUM COMPOUNDS AS FRIEDEL-CRAFTS CATALYSTS. THE OXIDATION OF ORGANIC COMPOUNDS WITH TELLURIUM DIOXIDE[1]

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Using toluene and acetyl chloride as the organic reactants, Dermer and his collaborators (1) recently studied the relative effectiveness of several metallic chlorides in the Friedel-Crafts synthesis (2) of *p*-methylacetophenone. As these workers (1) reported that tellurium dichloride and tetrachloride had been observed for the first time to function as Friedel-Crafts catalysts, it appears desirable to record some preliminary experiments of a similar nature that were made several years ago. The results of these earlier experiments were not published because the investigation, although temporarily abandoned, was incomplete.

FRIEDEL-CRAFTS REACTIONS

The senior author observed in 1935 that a Friedel-Crafts reaction occurs between benzene and benzyl chloride in the presence of tellurium dioxide. The chief product was diphenylmethane, but some material of higher boiling point was formed. It was found also that benzyl bromide and benzene behave similarly in the presence of tellurium dioxide.

When benzyl chloride and tellurium dioxide were warmed on a steam-cone in the absence of benzene a vigorous reaction ensued and a gumlike material was formed. Presumably, the product, which apparently was of high molecular weight, resulted from self-condensation of benzyl chloride according to the equation

$$xC_6H_5CH_2Cl \rightarrow C_6H_5(CH_2C_6H_4)_{x-1}CH_2Cl + (x-1)HCl.$$

It is possible also that chlorine-free compounds were formed by ring closure involving the terminal chloromethyl group. Similar autocondensation products have been produced from benzyl chloride with several metallic halides (3), from benzyl fluoride with hydrogen fluoride (4), and from

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beta-bromomethylnaphthalene with ferric oxide (5). It was observed (6) previously that a different type of reaction occurs in the presence of selenium dioxide, the benzyl chloride being converted into benzaldehyde.

Benzophenone (isolated as the phenylhydrazone) was prepared by refluxing a solution of benzene, benzoyl chloride, and tellurium tetrachloride for 3 hours, but the yield was low. No evidence of the formation of *o*-benzoylbenzoic acid was obtained when a mixture of phthalic anhydride, benzene, and tellurium tetrachloride was refluxed for 2 hours. Whether these results indicate that tellurium compounds are more effective with reactive alkyl halides than with acid chlorides and anhydrides or that tellurium dioxide is preferable to the tetrachloride was not determined. In this connection it should be noted that Dermer and co-workers (1) were able to prepare *p*-methylacetophenone from toluene and acetyl chloride in the presence of either tellurium dichloride or tellurium tetrachloride.

Several exploratory experiments were made by the authors to determine whether olefins react in the presence of tellurium halides. That a reaction occurred when tellurium tetrachloride was added to either cyclohexene or styrene was evidenced by discoloration and a rise in temperature. The reaction in the styrene experiment was so vigorous that some of the mixture ran out of the flask; the material that remained behind was black and gummy. Considerable quantities of tellurium were deposited when either cyclohexene or a benzene solution of styrene was refluxed with tellurium tetrachloride. Although homogeneous fractions could not be separated in these experiments, products of high molecular weight were formed, and polymerization probably occurred.

The results of several experiments indicate that tellurium compounds, although possibly useful in some instances, have certain limitations as Friedel-Crafts catalysts. The benzoyl chloride and phthalic anhydride experiments mentioned above indicate that tellurium tetrachloride is relatively ineffective for certain condensation reactions. Another limitation arises from the ease with which organotellurium compounds are formed. For example, Morgan and Drew (7) observed that tellurium tetrachloride reacts with acetic anhydride to give $TeCl_2(CH_2COOH)_2$. High yields of $ROC_6H_4TeCl_3$ and $(ROC_6H_4)_2TeCl_2$ were obtained (8) by treating phenetole or anisole with tellurium tetrachloride in the presence of large quantities of chloroform, a potential Friedel-Crafts reactant.

Oxidations with Tellurium Dioxide

In recent years selenium dioxide has been studied extensively (9) as an oxidizing agent for certain classes of organic compounds. One reason for this interest is the fact that this novel oxidizing agent is specific in its action

on certain groups, such as methylene groups in ketones and in some olefins (10). An example is the oxidation of acetophenone by selenium dioxide to phenylglyoxal in good yields (11). The purpose of some of the work reported herein was to ascertain whether tellurium dioxide also could be used advantageously as an oxidizing reagent. Tellurium dioxide might be expected to play an analogous role because of the positions occupied by tellurium and selenium in the periodic table, also because both oxides are reduced (12) by hydrazine, hydroxylamine, and certain organic substances such as glucose and phenylhydrazine.

One difficulty attending the use of tellurium dioxide as an oxidant for organic compounds, an obstacle not encountered with the corresponding selenium compound, is its insolubility in water and organic solvents. For this reason some solvents (alcohol, dioxane, and acetic acid) often employed in selenium dioxide oxidations were found to be useless, even at their boiling points, when tellurium dioxide was used. Nitrobenzene, pyridine, ether, and acetic anhydride also failed to dissolve appreciable amounts of tellurium dioxide, and at its boiling point acetic anhydride was slowly oxidized.

Tellurium dioxide appears to be less active and less useful as an oxidizing agent for organic compounds than selenium dioxide. The extent to which this unreactivity may be attributed to its sparing solubility is not known. In most of the present experiments solvents were not used, and relatively high temperatures were necessary to effect oxidation. Several oxidation experiments were made with selenium dioxide for comparison; in all instances the selenium oxide effected oxidation more readily and at considerably lower temperatures. Benzoin was the only compound studied that was oxidized satisfactorily by tellurium dioxide to one main product (95% yield of benzil). The ineffectiveness of tellurium dioxide as an oxidant for organic compounds is in harmony with the results of Hageman (13), who heated aqueous solutions of tartaric, citric, oxalic, succinic, malic, gallic, and lactic acids with tellurium dioxide at about 70° for 1 to 3 months and observed that tellurium was deposited only in the tartaric acid experiments.

EXPERIMENTAL

Friedel-Crafts reaction with benzyl chloride. Tellurium dioxide[3] reacted vigorously with benzyl chloride when heated on a steam-cone; an ether extraction of the reaction-mixture yielded only a gumlike substance and a tellurium compound, possibly the tetrachloride. In the presence of tellurium dioxide (10 g.), benzyl chloride (11.5 g.) and benzene (55 cc.), when refluxed for 72 hours, reacted to give, as the low-boiling products, 6 g. of diphenylmethane [oxidized to benzophenone with

[3] From the oxidation of pulverized tellurium with nitric acid. The dioxide thus prepared was washed with much water and dried.

selenium dioxide (6, 9b) and identified as the phenylhydrazone] and an oil that was distilled up to 380°.

Oxidation of ketones. No reaction occurred between *p*-chloroacetophenone and tellurium dioxide in boiling alcohol, or without solvent at 100°. Tellurium was gradually deposited when 1.6 g. of the dioxide was kept in 5 cc. of boiling *p*-chloroacetophenone for 3 hours; by extracting the reaction-mixture with alkali a low yield of *p*-chlorobenzoic acid was obtained. In control runs, selenium dioxide reacted readily with the same ketone in boiling alcohol, or at 100° without a solvent.

Benzoin was oxidized slowly and incompletely in boiling alcohol; however, after it was heated for 3 hours at 190° without solvent a 95% yield of benzil was obtained. Desoxybenzoin also was oxidized (at 200°), but the product (m.p. 162–170° after many crystallizations) was not identified.[4]

Anthrone reacted with tellurium dioxide in boiling alcohol in 10 hours, and without solvent at 200° in one-half hour, to give colorless needles melting at 242–250° (decomposition). A mixture of the product and dianthrone (m.p. 245–250° with decomposition) prepared from anthracene by oxidation with nitric acid (14) melted at 248–257° with decomposition. As indicated by the melting points listed below, dianthrone apparently is formed also by the oxidation of anthrone with selenium dioxide in boiling alcohol.

	M.P., °C.	MIXED M.P. WITH (A), °C.
(A) Dianthrone prepared by oxidation of anthracene with nitric acid (14)	245–250, dec.	—
(B) Tellurium dioxide product	242–250, dec.	248–257, dec.
(C) Selenium dioxide product	240–250, dec.	241–250, dec.

Oxidation of hydroquinone. Distillation of a mixture of hydroquinone, tellurium dioxide, and water failed to cause reaction; when selenium dioxide was substituted for the tellurium compound, quinone passed over (yield about 30%). When hydroquinone was heated with tellurium dioxide without a solvent at 190° it was oxidized readily, but quinone was not isolated on steam distillation.

Oxidation of alcohols. Benzyl alcohol, at its refluxing temperature, was oxidized slowly by tellurium dioxide to benzaldehyde, which was identified as the phenylhydrazone. Under these conditions selenium dioxide also effects this transformation slowly and with a poor yield (15).

Benzhydrol (9.2 g.) and tellurium dioxide (5 g.) were heated at about 280° for 1 hour and then refluxed for 1 hour. Upon distillation, 4.3 g. of oil was collected below 300°, and 2 g. at 300–355°. Treatment of the fraction boiling below 300° with phenylhydrazine gave benzophenonephenylhydrazone. The fraction boiling at 300–355° solidified on cooling; after several crystallizations from acetic acid, benzene, and ligroin, colorless crystals melting at 209–210° were obtained. To determine whether the product was 1,1,2,2-tetraphenylethane, this hydrocarbon was prepared by the method of Norris, Thomas and Brown (16). The product obtained by treating an ethyl acetate solution of benzhydryl bromide with zinc melted at 204–208° after

[4] It was suggested by the referee that this product might be isodidesyl, m.p. 160–161°, which has been obtained by mild oxidation of desoxybenzoin by iodine and alkali (17).

numerous crystallizations from alcohol, acetic acid, benzene, and ligroin. The melting point of this material was raised slightly by the addition of the high-melting benzhydrol oxidation-product.

Oxidation of hydrocarbons. Diphenylmethane, although oxidized to benzophenone in excellent yield by selenium dioxide (6, 9b) at 200–210°, was scarcely attacked by tellurium dioxide when refluxed (260°) for 1 hour. Anthracene also was virtually unaffected [a good yield of anthraquinone is obtained with selenium dioxide (9b) at 165–170°] by refluxing with tellurium dioxide.

Miscellaneous oxidations. Oxidation of mandelic acid with tellurium dioxide proceeded readily at 170–200°. Benzaldehyde (the principal product) and phenylglyoxylic acid were isolated, as the phenylhydrazones, but the yields were poor. When a mixture of mandelic acid and tellurium dioxide was heated at about 150°, benzaldehyde and water distilled.

An aqueous solution of *p*-chloromandelic acid, tellurium dioxide, and sodium hydroxide deposited only negligible amounts of tellurium when heated at 70°. Similar results were obtained when a hydrochloric acid solution of *p*-aminoacetophenone and tellurium dioxide was heated at the same temperature.

SUMMARY

Reactions of the Friedel-Crafts type occurred when benzene solutions of benzyl chloride and benzyl bromide were refluxed in the presence of tellurium dioxide. Evidence was obtained to indicate that tellurium tetrachloride can be used also in the Friedel-Crafts synthesis of ketones.

The oxidation with tellurium dioxide of several types of organic compounds that are amenable to oxidation with selenium dioxide was studied. Although effective in some instances, tellurium dioxide appears to be less reactive and less useful as an oxidizing reagent for organic compounds than selenium dioxide.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

THE AMIDES OF THE 3-(*p*-BROMOBENZOYL)-3-METHYL-ACRYLIC ACIDS

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I. THE COMPOUNDS DERIVED FROM AMMONIA

The object of this investigation was the preparation of a series of amides of a typical α,β-unsaturated γ-ketonic acid. Interest centers in the study of the ring-chain tautomerism and the possibility of isomerism in the *cis* compounds where the spatial juxtaposition of the two functional groups permits and facilitates the formation of cyclic structures. While a limited amount of pertinent work has been done on nitrogen derivatives of certain of the ortho aldo and keto benzoic acids, very little has yet been reported in connection with the closely analogous *cis*-β-acyl and β-aroylacrylic acids and their derivatives.

The 3-bromobenzoyl-3-methylacrylic series was selected for the initial investigation in this field for the following reasons: The open-chain and cyclic esters and the acid chloride of the *cis* acid have already been made and studied, as well as the *trans* compounds, which are necessarily open-chain and which are desirable for purposes of reference (1). The 3-methyl group has a definite stabilizing influence on the configurations and permits the existence of both *cis* and *trans* forms, but nevertheless allows interconversions between the two types to take place under suitable conditions. The tendency to form cyclic derivatives in this series is marked but not as strong as in the 2,3-dimethyl series (2). The 3-methyl group has a noticeable damping effect on the reactivity of the α,β-unsaturated ketone system and to some extent hinders addition reactions. The para bromine atom favors the formation of crystalline derivatives, thus facilitating manipulations.

The action of aqueous ammonium hydroxide on the open-chain and pseudo methyl esters (I and II) and on the acid chloride (III) of 3-bromobenzoyl-3-methylacrylic acid gave in each case the same product, which has been formulated as the lactamol[2] (cyclic amide) or 5-hydroxypyr-

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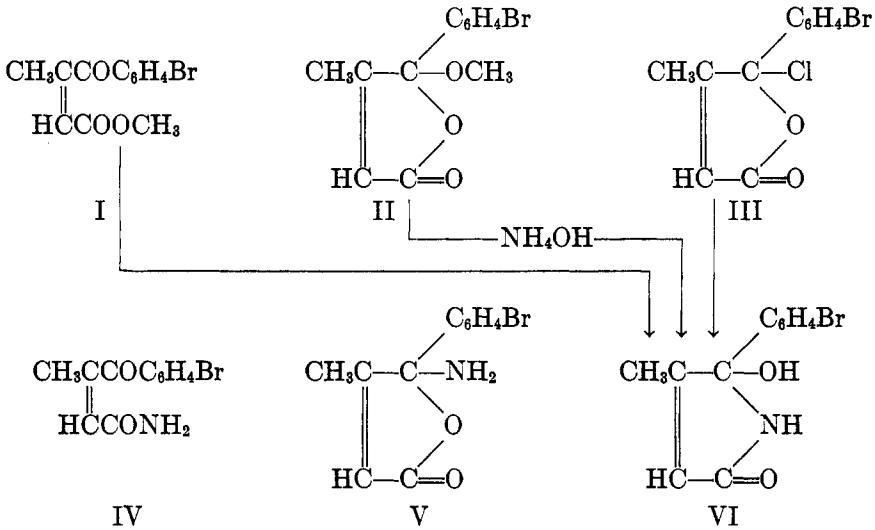
[2] The meaning of the term lactamol is self evident (*cf.* the term lactonol, Ref. 2b, footnote 3).

rolinone (VI). The alternative structural possibilities which must be considered are the open-chain true amide form (IV) and the cyclic pseudo amide or lactonamine (V) (better expressed perhaps as a 5-amino-2-furanone[3]). All of these three types of formulation (IV—VI) have been suggested for various compounds reported in the literature (*cf.* 3) but in few cases has there been given real proof of structure and in several cases it seems probable that the formulations assumed are erroneous (some of these are being reinvestigated in this laboratory). The structure we have assigned to this amide (VI) is based on the following considerations, some of which alone do not constitute good evidence but nevertheless add to the total and are consistent with the picture suggested.

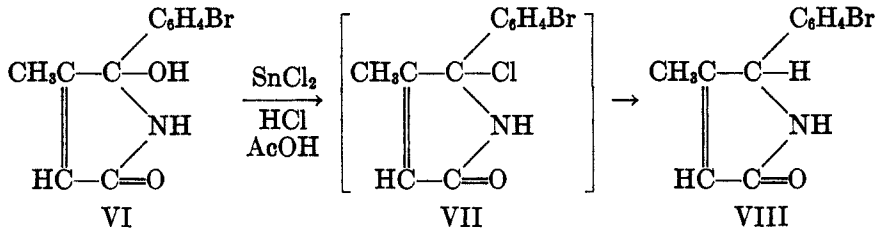


The amide is readily soluble in sodium hydroxide, in contrast with the *trans* amide (XI), which is not, and it is precipitated unchanged by acid. This property is consistent with formula VI. The weak acidity of the hydroxyl is comparable with that in the 2-hydroxy-3-furanones[3] (4) and is characteristic of the anilides in the *o*-benzoylbenzoic acid series (3h) which are supposed to be of the same cyclic type. Also, it is characteristic of a series of hydroxypyrrolidones which have recently been prepared from the enol lactone of β-benzoylpropionic acid (3k).

The resistance of the amide towards reduction with zinc and acetic acid or sodium hydrosulfite is an argument against the open-chain formula (IV) with its reactive conjugated 1,4-dicarbonyl system. Stannous

[3] The term furanone is obviously a misnomer. More properly it should be dihydrofuranone and numbered to indicate the positions involved. However, since a true furanone is impossible and since the abbreviated term has been extensively used (4), it will be retained here, but the expanded and proper term dihydrofuranone will be used whenever it is necessary to indicate the carbons involved.

chloride in hydrochloric and acetic acids, however, reduces the amide easily, eliminating an oxygen atom and giving a compound which is evidently the unsaturated lactam or α-pyrrolinone (VIII). This product gives a rapid reaction with Tollens' reagent as do the oxygen analogs, for example, 3,4-dimethyl-5-xenylfuranone-2 (2). Evidently the reduction has proceeded through the chloride (VII) and follows a course parallel with the reduction under similar conditions of oxygen analogs such as 2,3-dimethyl-3-xenoylacrylic acid which is believed to function in the cyclic form (2). The alternative cyclic formulation for the amide, as the 5-aminofuranone (V), would not be consistent with these facts because in that case reductive elimination of the nitrogen rather than the oxygen would be expected.

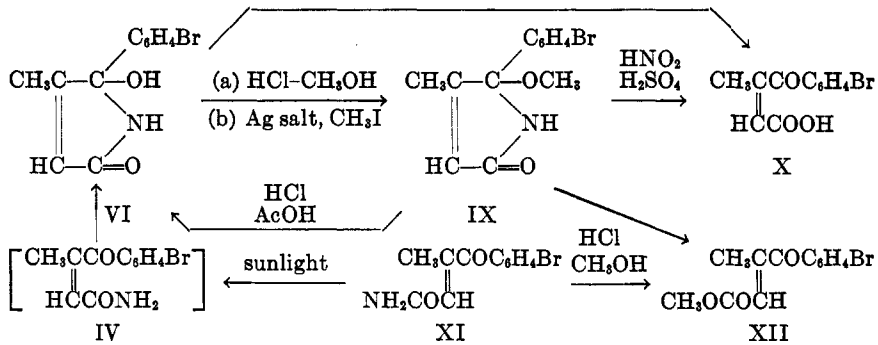


VI VII VIII

Methylation with methanolic hydrogen chloride readily converted the amide into a methyl ether (IX) which was easily hydrolyzed by conc'd hydrochloric and acetic acids. This methylation was not brought about by the action of dimethyl sulfate on the sodium salt, but it was effected in very small yield by the action of methyl iodide on the silver salt. Diazomethane, on the other hand, was without any action on the compound. These results cannot be explained on the basis of the 5-aminofuranone formula (V), are consistent with the properties which would be expected of a 5-hydroxypyrrolinone such as VI, but, of course, do not in themselves preclude the open-chain structure (IV). Analogous results are obtained with some of the 2-hydroxy-3-furanones (4) and are partly duplicated in the case of some of the *cis* aroylacrylic acids which function as 5-hydroxy-2-furanones (2). The failure to react with diazomethane clearly indicates a weakly acidic or hindered hydroxyl analogous to the hydroxyl in the 2-hydroxy-3-furanones (4). The methylation of the silver salt may (and probably does) involve the cyclic structure just as appears to happen in the methylation of the silver salts of certain of the 2-hydroxy-3-furanones (4).

The stability of the amide VI under hydrolytic conditions supports the hydroxypyrrolinone formulation (the open-chain amide IV should be easily hydrolyzable, as also should the aminofuranone form V). Unfortunately, the amide is sensitive, and is converted under many of the acid hydrolytic conditions into a complex high-melting nitrogen-containing

substance which is non-crystalline. Hydrolysis was finally effected by nitrous acid in conc'd sulfuric acid, and gave the *cis* acid (X).



Under extended treatment of the amide or its methyl ether with methanolic hydrogen chloride, inversion as well as methanolysis occurred, giving the *trans* ester (XII), which was obtained also directly from the *trans* amide (XI) by methanolysis under similar conditions. In this reaction inversion must precede methanolysis, since it is known that the *cis* acid and the *cis* (open-chain) ester are both converted into the cyclic (or pseudo) *cis* methyl ester under these conditions and, therefore, could not have been involved in intermediate steps. We are studying this reaction further in the hope of finding out something more about the mechanism of the changes.

Attempts to acylate or benzoylate were unsuccessful, as also were attempts to make the chloride (VII) with phosphorus pentachloride. Thionyl chloride reacted but caused chlorination of the methyl group, as will be described below.

Attempts to invert the *cis* amide to the *trans* isomer through the action of sunlight on a chloroform solution containing iodine as a catalyst were without avail, blocked perhaps by the stabilizing influence of the cyclic structure. This result calls to mind the inversion of the open-chain *cis*-3-bromobenzoyl-2- and -3-methylacrylic esters and the 2- (but not the 3-) methyl acid (1) to the *trans* isomers under these conditions. The failure of the 3-methyl acid to undergo inversion perhaps is due, as suggested, to the dominance of the cyclic structure in solution (1d).

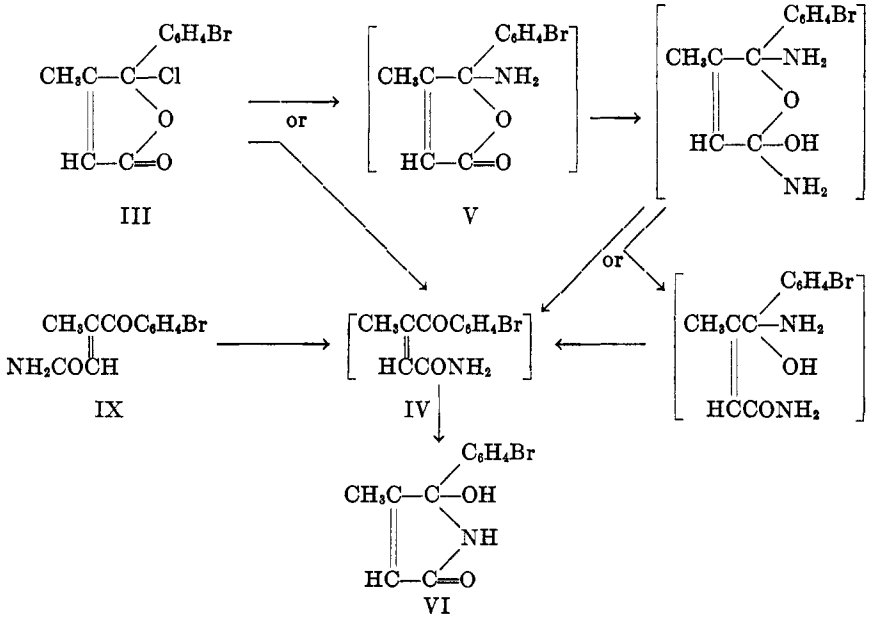
Ozonization of the methyl ether (IX) was carried out in the hope of isolating a nitrogen-containing fragment. Actually, such a compound was obtained, but in insufficient quantity for study. The chief products were *p*-bromobenzoic acid and *p*-bromophenyl methyl diketone, $BrC_6H_4COCOCH_3$.

In connection with these experiments the *trans* amide (XI) was made by the action of ammonium hydroxide on the *trans* acid chloride. It is insoluble in sodium hydroxide, in contrast with the *cis* isomer (VI). It

undergoes methanolysis to give the *trans* ester (XII), but acetic and hydrochloric acids convert it into an amorphous nitrogen-containing product similar to that obtained from the *cis* compound. Sunlight converts it into the *cis* amide (VI), which has been shown to be cyclic. Evidently the hypothetical open-chain isomer (IV) which must first be formed in the reaction undergoes spontaneous cyclization to the hydroxypyrrolinone form (VI).

Assuming the correctness of the formulation VI for the *cis* amide, it follows from the above described facts that the hypothetical open-chain form (IV) is inherently unstable and has a stronger tendency to cyclize than does the *cis* acid itself.

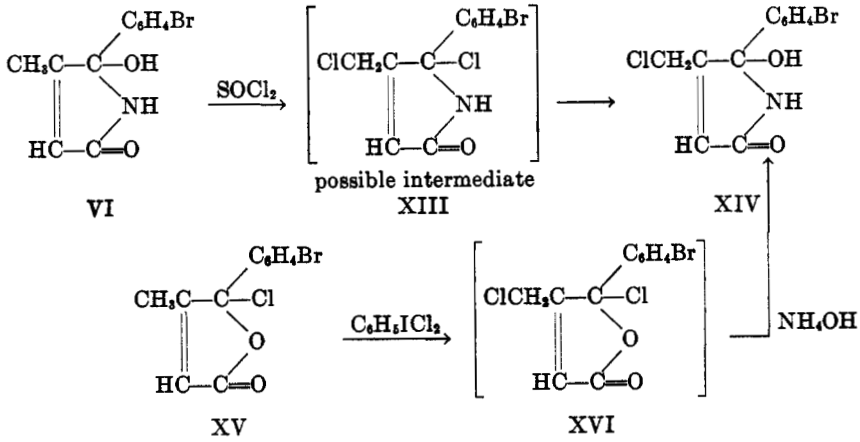
The reaction between ammonia and the pseudo acid chloride[4] (III) may proceed either by a 1,2-mechanism to give the aminofuran (V) as the primary product, or, as seems less likely, 1,4 to give first the open-chain amide (IV). Rearrangement or cyclization, respectively, must then follow. The transformation of the aminofuranone (V) into the hydroxypyrrolinone (VI) might involve first addition and elimination of ammonia to give the open-chain form (IV) as intermediate. The open-chain form (IV), produced either in this way or directly by a 1,4-reaction, would certainly cyclize to the hydroxypyrrolinone (VI), as must happen in the transformation of the *trans* isomer into VI by the action of sunlight alone. The following diagram outlines these possibilities, which are typical.



[4] Of course, the reaction might be expressed more simply in terms of a mobile tautomerism between the open-chain and cyclic forms of the chloride as in the case of succinoyl chloride, but it seems probable that here the cyclic structure (III) is fixed (*cf.* 1a).

Incidentally, it should be noted that actual migration or 1,3-shift of an amino group might occur in reaction, for example, from the 5 to the 2 positions of the cyclic form (V) to give momentarily the open-chain form (IV). However, there is little reason to suppose this, particularly since the anilino and the N-methylanilino groups do not migrate, as will be shown later (4c).

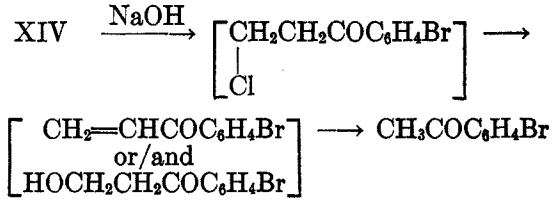
In attempting to make the 5-chloro-2-pyrrolinone by treating the cyclic *cis* amide (VI) with thionyl chloride, substitution of chlorine for hydrogen took place instead of replacement of the hydroxyl, and a crystalline monochloro derivative (XIV) was obtained. There is ample analogy for this type of reaction where thionyl chloride acts as a chlorinating agent, for example, the chlorination of hydroxycodeinone by this reagent (5). Presumably, in the reaction under discussion, the replacement of the hydroxyl was also involved to give XIII but attempts to isolate the dichloro compound failed. The reaction is formulated as follows:



The chloro amide (XIV) was prepared in a second way by the action of phenyl iododichloride on the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (XV), followed by treatment with ammonium hydroxide.

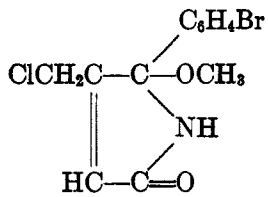
The proof of the position of the chlorine in the final product (XIV) was demonstrated as follows. Oxidation with potassium permanganate gave *p*-bromobenzoic acid, excluding the possibility that the chlorine was in the aryl group. Reduction with stannous chloride eliminated the chlorine and one oxygen and gave the unsaturated lactone or α-pyrrolinone (VIII) which had already been obtained from the parent amide (VI), thus showing the chlorine to be in an aliphatic combination. Alkaline hydrolysis gave *p*-bromoacetophenone, which was isolated and identified; this reaction evidently involved hydrolytic cleavage at the double bond (a reversal of

aldol condensation) followed by hydrolysis or elimination of hydrogen chloride, and a second hydrolytic cleavage to give *p*-bromoacetophenone, as follows:



If the chlorine had been on the ethylene linkage, hydrolytic cleavage could not have produced *p*-bromoacetophenone but might have given *p*-bromopropiophenone [which actually has been obtained in a similar hydrolysis of *cis*-3-bromobenzoyl-3-methylacrylic acid itself (1a)].

The chloro amide XIV shows reactions which are parallel with those of the parent amide VI, and which support the cyclic formulation. The compound is soluble in dilute sodium hydroxide and may be recovered unchanged on acidification. It is converted into the easily hydrolyzable methyl ether (XVII), and as mentioned above, is easily reduced by stannous chloride to the α-pyrrolinone, VIII.



XVII

The above mentioned chlorinations at the methyl group are of interest as demonstrating an activity at this point which is due presumably to conjugation through the intervening ethylene linkage with the carbonyl group.

EXPERIMENTAL[5]

5-(p-Bromophenyl)-5-hydroxy-4-methylpyrrolinone-2 (VI). A solution 70 g. of freshly prepared acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (III) in 250 cc. of dry dioxane was mechanically stirred and treated with 225 cc. of 16 *N* ammonium hydroxide, added gradually. The mixture was stirred for 3.5 hours at room temperature followed by refluxing for 1.5 hours. The solution was then cooled and evaporated in an air stream to remove the bulk of the dioxane. When the precipitation appeared to be complete, the product was filtered, washed with

[5] All melting points reported in this paper are "corrected". We are indebted to Mrs. James A. L. Mathers for many of the microanalyses.

water, and dried in a vacuum desiccator; yield 67 g. (96%). It was purified by repeated crystallization from 60% ethanol, from benzene, and from water, and melted at 174.5° (decomp.).

Anal. Calc'd for $C_{11}H_{10}BrNO_2$: C, 49.3; H, 3.8; N, 5.2.
Found: C, 49.2; H, 4.0; N, 5.1, 5.3.

Poorer yields were obtained when the *cis* acid chloride (III) was allowed to stand in saturated alcoholic ammonia for 48 hours.

The open-chain methyl ester (I) suspended in 16 *N* ammonium hydroxide reacted completely in 48 hours (and partially in 36 hours) to give the amide (VI). The pseudo ester (II) required longer standing, 70 hours, to complete the reaction (some unchanged material could be recovered after standing for only 48 hours).

Hydrolysis. A mixture of conc'd acetic acid to which a small amount of conc'd hydrochloric acid had been added, had no action on the amide (VI) at room temperature, but at refluxing temperature under the same conditions or with conc'd acetic acid continually saturated with hydrogen chloride, a high-melting amorphous solid which contained nitrogen was produced. Alkaline hydrolysis (refluxing 10% sodium hydroxide) gave non-crystalline products. The amide was dissolved in cold conc'd sulfuric acid and treated with sodium nitrite [the method of Bouveault (6)], the mixture then being warmed until evolution of gas ceased, and finally diluted with water; the *cis* acid (X) was produced in 50% yield.

Methanolysis of 10 g. of the amide (VI) by refluxing with 250 cc. of methanol and 30 cc. of conc'd hydrochloric acid for 3.5 hours, followed by evaporating in an air stream and cooling, gave as the first crop 2.2 g. of material which was identified as the *trans* ester (XII); yield 22%. Further evaporation gave 5.5 g. of crude solid which was filtered and washed with 10% sodium hydroxide; it was purified and identified as the methyl ether (IX); yield 25%. From the alkaline filtrate upon acidification 3 g. (30%) of unreacted amide was recovered. Wide variation in conditions, concentrations, and period of refluxing failed to improve the yield of the *trans* ester.

Reduction of the amide (VI) with zinc and conc'd acetic acid at 70° for a few minutes was without action but refluxing produced a high-melting amorphous material. Sodium hydrosulfite in 80% ethanol (refluxing for 1 hour) was without effect.

Chlorination with phosphorus pentachloride under various conditions gave only resinous products.

Diazomethane was without action, as also was dimethyl sulfate acting on a 10% sodium hydroxide solution.

Acylation with acetic anhydride or acetyl chloride at room temperature gave largely unchanged material, but under more drastic conditions (refluxing) or using pyridine, only a high-melting amorphous product was obtained.

Benzoylation. A mixture of 0.4 g. of the amide (VI) in 3 cc. of pyridine and 3 cc. of benzoyl chloride was allowed to stand at 0° for 20 hours. Hydrolysis gave 0.26 g. of product, which was washed with sodium carbonate and crystallized from methanol. It melted at 205–206°. (*Anal.* Calc'd for $C_{26}H_{20}BrNO_5$: C, 61.6; H, 3.95; N, 2.8. Found: C, 61.5, 61.3; H, 3.9, 3.9; N, 2.75). Treatment of this product with 10% sodium hydroxide (1 hour at 70–80°) was without action. This compound has not yet been identified.

5-(p-Bromophenyl)-5-methoxy-4-methylpyrrolinone (IX). This ether was prepared best by controlling the conditions of methanolysis of the amide (VI) as follows. The ratio of reactants was 4 g. of the amide, 60 cc. of methanol, and 1 cc. of conc'd hydrochloric acid. The mixture was refluxed 1 to 2 hours and allowed to stand for 3–12 hours. Water was then added up to the point of precipitation, and the solution was evaporated in an air stream until precipitation appeared to be complete. The

product was filtered and washed with 10% sodium hydroxide and water, small amounts of unchanged amide being removed (on the order of 1%). The yields varied from 95–99%. The compound crystallized from 60% ethanol and melted at 118–119°.

Anal. Calc'd for $C_{12}H_{12}BrNO_2$: C, 51.1; H, 4.3; N, 5.0; Br, 28.4; OCH_3, 11.0.
Found: C, 51.3; H, 4.1; N, 5.2, 5.0; Br, 28.2; OCH_3, 11.2.

The ether was also prepared as follows: A solution of the amide in sodium hydroxide was neutralized to the point of precipitation with dilute nitric acid, and silver nitrate was added, causing precipitation of the silver salt, which was filtered, washed with methanol, and digested (shaking) with methanol and methyl iodide for 2 hours. Largely unchanged material was recovered (90–95%), and a 5–10% yield of the methyl ether was isolated by taking advantage of its insolubility in alkali.

Hydrolysis was effected by the action of a 10:1 conc'd acetic-hydrochloric acid mixture upon standing for 24 hours at room temperature. The amide VI was obtained in quantitative yield. Using the sulfuric-nitrous acid method (6) as described above under the free amide (VI), the *cis* acid (X) was obtained in 60% yield.

Methanolysis of 0.4 g. with methanol and conc'd hydrochloric acid (refluxing for 3.5 hours) gave 0.1 g. (25%) of *trans*-3-bromobenzoyl-3-methylacrylic ester (XII).

Reaction with thionyl chloride. No reaction occurred on standing at room temperature but refluxing for 1 hour caused demethylation and also chlorination at the 4-methyl group to give XIV (see below).

Ozonization of 2 g. in 40 cc. of dry chloroform at 0° for 5 hours was followed by evaporation of the solvent, hydrolysis with water, and extraction with sodium bicarbonate and ether. From the sodium bicarbonate layer on acidification, 0.025 g. of *p*-bromobenzoic acid precipitated and was identified. From the ether solution, 0.55 g. of yellow crystals was obtained and then distilled in the vacuum oven. This was identified as *p*-bromophenyl methyl diketone [known (7); identified by melting point and analysis: Calc'd for $C_9H_8BrO_2$: C, 47.6; H, 3.1. Found: C, 47.6, 47.8; H, 3.2, 3.3]. From the non-acidic residues of the experiment a small amount of crystalline material was obtained by evaporation in the vacuum oven at 125°. It melted at 189–190°. Analysis indicated the formula to be C_8H_8BrNO, but not enough material was obtained for study.

5-(p-Bromophenyl)-4-methyl-2,5-dihydropyrrolone-2 (VIII). A solution of 0.5 g. of the amide (VI) in 10 cc. of conc'd acetic acid was added slowly to a freshly prepared suspension of 4 g. of stannous chloride in a mixture of 20 cc. of conc'd acetic and 5 cc. of conc'd hydrochloric acids, with stirring at room temperature for 1 hour. The mixture was diluted with water and extracted with ether. Upon evaporation of the ether and extraction of the acidic residue with sodium carbonate, a white crystalline residue remained, which was washed with hot methanol; yield 35%. After vacuum evaporation onto a cold finger, followed by repeated crystallization from methanol, it melted at 184–186°.

Anal. Calc'd for $C_{11}H_{10}BrNO$: C, 52.4; H, 4.0; N, 5.55.
Found: C, 52.3; H, 4.2; N, 5.5.

The compound gave an immediate positive test with Tollens' reagent, whereas the parent amide (VI) did not react at all under the same conditions.

5-(p-Bromophenyl)-4-chloromethyl-5-hydroxypyrrolinone-2 (XIV). Thionyl chloride was added dropwise to 1 g. of the amide (VI) until no further reaction occurred, and then 10 cc. of benzene was added, followed by ligroin (about 50 cc.) added dropwise with scratching until crystallization set in. The mixture was concentrated by an air stream to complete crystallization and the product was then filtered and washed with ligroin; yield 95%; melting point 152–154° (decomp.). Repeated crys-

tallization from benzene raised the melting point to 183–184° (decomp.), and then crystallization from 75% acetic acid raised it to 218–219° (decomp.).

Anal. Calc'd for $C_{11}H_9BrClNO_2$: C, 43.7; H, 3.0; N, 4.6.
Found: C, 43.8, 43.7; H, 3.3, 3.05; N, 4.9.

An alternative preparation was as follows: Five grams of freshly prepared acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (1a) in 10 cc. of dry chloroform was treated with 5 g. of phenyl iododichloride (8), refluxing for 3 hours. The solution was then evaporated in a current of air. The resulting oil (containing iodobenzene) was treated directly with 25 cc. of 16 *N* ammonium hydroxide and the mixture was allowed to stand for 16 hours. The pasty mass was leached with warm 10% sodium hydroxide and the alkaline layer was decanted, cooled in ice, and acidified with hydrochloric acid. After precipitation was deemed complete, the product was filtered, washed with water, and dried; yield, 4.1 g. (80%).

The same product was obtained when a sample of the methyl ether of the amide (IX) was treated with thionyl chloride (refluxing), followed by hydrolysis.

The compound dissolved in 10% sodium hydroxide and was precipitated unchanged by hydrochloric acid. Reduction by stannous chloride in acetic-hydrochloric acid solution at room temperature in the way described above produced the dihydropyrrolone (VIII). Zinc and conc'd acetic acid (stirring 1 hour at room temperature) was without action. Oxidation of 0.2 g. with 10 cc. of aqueous 10% sodium hydroxide and potassium permanganate, followed by treatment with sulfur dioxide, gave 0.05 g. of *p*-bromobenzoic acid.

Hydrolytic fission by steam distilling 0.9 g. in 50 cc. of 10% sodium hydroxide until 500 cc. of distillate collected, gave a solid volatile product (0.12 g; 20%) which melted at 49–50° and was identified as *p*-bromoacetophenone by comparison with an authentic sample.

The methyl ether (XVII) was prepared in several ways. Thionyl chloride was added dropwise to 1 g. of the amide (VI) until no further reaction occurred, the excess then being evaporated *in vacuo* at 50°. To this was added 8 cc. of 2 *N* sodium methoxide in methanol, then 5 cc. of methanol. (In another experiment, 10 cc. of 10% methanolic potassium hydroxide was used instead, and with equal success). The sodium chloride was filtered off and the filtrate was cooled and acidified with conc'd hydrochloric acid. The solution was then concentrated (air blast) and filtered when crystallization appeared to be complete; yield nearly pure, 1 g. (97%). This was purified by heating in benzene with decolorizing carbon to remove persistent color, and was crystallized by adding ligroin to the filtrate and concentrating. Repeated crystallization from 50% methanol gave a product of m.p. 159.5–161°.

Anal. Calc'd for $C_{12}H_{11}BrClNO_2$: C, 45.5; H, 3.5; OCH_3, 9.8.
Found: C, 46.0, 45.5; H, 3.4, 3.2; OCH_3, 9.6.

In another experiment the crude freshly prepared chlorination-product was treated with 20 cc. of methanol (acid conditions through generation of hydrogen chloride) with equally good results.

In another preparation, a solution of 1 g. of the chloro derivative (XIV) in 20 cc. of methanol and 0.3 cc. of conc'd hydrochloric acid was refluxed for 1.5 hours and allowed to stand for 24 hours. After cooling and concentrating in a current of air, a crystalline mass was obtained. This was crystallized by dissolving in 10 cc. of methanol and adding water dropwise with scratching and seeding; the product was washed on the filter with 10% methanol; yield, 8.7 g. (86%).

Hydrolysis of 0.3 g., upon standing for 24 hours in 10:1 conc'd acetic-hydrochloric acid, gave 0.25 g. (83%) of the chloro amide (XIV). Heating with aqueous sodium hydroxide, as with the chloro amide itself (XIV), gave *p*-bromoacetophenone.

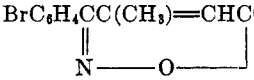
trans-*3*-(p-*Bromobenzoyl*)-*3-methylacrylic acid amide* (XI). The mixture made by treating 1 g. of the *trans* acid with 1 g. of phosphorus pentachloride and evaporating the bulk of the phosphorus oxychloride, was taken up in 3 cc. of dry dioxane (decanting from unchanged phosphorus pentachloride), and was then cooled and treated dropwise with an excess of 16 *N* ammonium hydroxide (with vigorous stirring). The mixture after standing for 16 hours was diluted with water and the resulting crystalline and nearly pure product was filtered off (0.7 g. or 70%). Repeated crystallization from benzene gave an analytical sample melting at 136.5–137.5°.

Anal. Calc'd for $C_{11}H_{10}BrNO_2$: C, 49.3; H, 3.8; N, 5.2.
Found: C, 49.1; H, 3.8; N, 5.45.

A solution of 0.1 g. of the amide (XI) in 15 cc. of methanol was exposed for 5 hours to the action of bright sunlight, and on concentration of the solution, an 85% yield of the *cis* isomer (cyclic, VI) was obtained.

The *trans* amide (XI) is insoluble in 10% sodium hydroxide. Methanolysis in a 15:1 methanol-conc'd hydrochloric acid mixture (refluxed for 10 hours) gave the *trans* methyl ester (XII). Hydrolysis of 0.2 g. in 10 cc. of conc'd acetic acid and 7 drops of conc'd hydrochloric acid (refluxed for 1 hour) gave an amorphous high-melting product.

3-(p-*Bromobenzoyl*)-*3-methylacrylic acid oxime anhydride*,



A solution of 0.7 g. of either the open-chain or pseudo *cis* ester of 3-bromobenzoyl-3-methylacrylic acid in 10 cc. of methanol was treated with 1 g. of hydroxylamine hydrochloride in 3 cc. of water, and then 10% sodium carbonate until the reaction became basic to litmus. Water and methanol alternately were added until solution of the materials involved was complete. After standing for 60 hours, crystals appeared. Using the cyclic or pseudo ester, the reaction was slower than with the open-chain isomer. After repeated crystallization from 60% ethanol, the product melted at 142–143°.

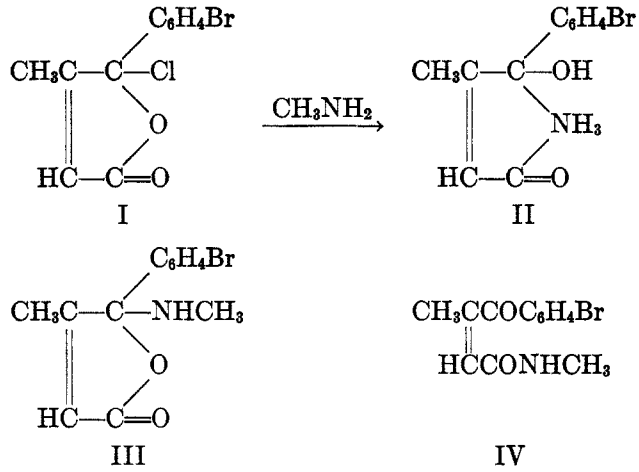
Anal. Calc'd for $C_{11}H_8BrNO_2$: C, 49.65; H, 3.0; N, 5.3.
Found: C, 49.56; H, 2.9; N, 5.2.

II. THE COMPOUNDS DERIVED FROM METHYLAMINE

The amides made from methylamine have been studied in order to determine the effect of an aliphatic group at the nitrogen on the tendency to form ring compounds. It was expected that the N-methyl group would have little influence and that the compounds of this series would prove, as they did, to be analogous to those derived from ammonia.

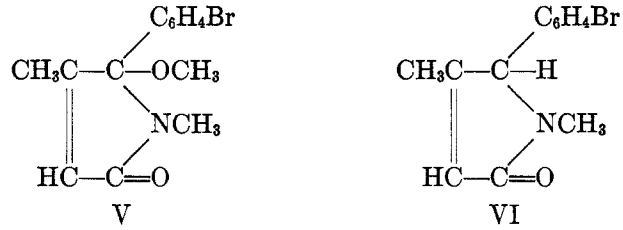
Aqueous methylamine reacted with the acid chloride (I) of *cis*-3-bromobenzoyl-3-methylacrylic acid to give an amide which exhibited all of the characteristics of an unsaturated lactamol or hydroxypyrrolinone and has therefore been assigned the structure II rather than the alternatives III or IV.

The compound is soluble in cold dilute aqueous sodium hydroxide and is precipitated unchanged by acids. It is stable towards boiling concentrated acetic and hydrochloric acid mixture in contrast to the ammonia analog which is quickly attacked under these conditions.



I II III IV

Methylation with methanol and hydrochloric acid gives a methyl ether (V) which is readily hydrolyzed by hydrochloric and acetic acids. However, extended treatment with the methanol-hydrochloric acid reagent is without action on the compound in contrast with the inversion and methanolysis which results when the ammonia analog is subjected to these more drastic conditions. Evidently, the N-methyl group makes for greater stability in this respect.



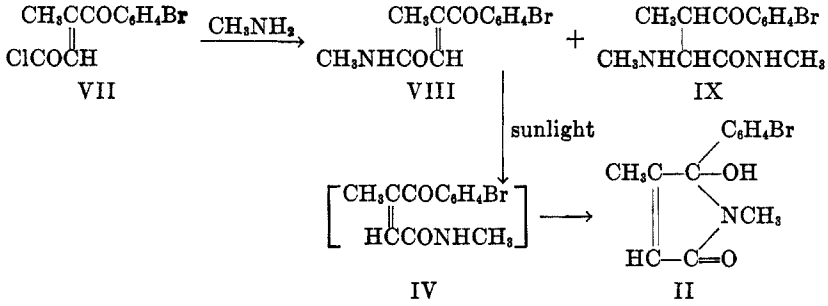
V VI

Stannous chloride reduction of the N-methylamide (II) in a mixture of conc'd acetic and hydrochloric acids gave a typical unsaturated lactam or α-pyrrolinone (VI) which showed the characteristic positive test with Tollens' reagent.

An unsuccessful attempt was made to isomerize the amide (II) into the *trans* isomer (VIII) by the action of sunlight on a chloroform solution containing iodine.

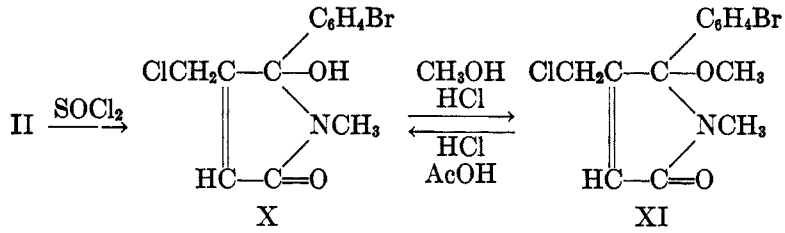
The *trans* amide (VIII) was made from the *trans* acid chloride (VII) by the action of aqueous methylamine; but the amide was not the sole product, the reaction differing in this respect from the analogous reaction with ammonia. Two other compounds were obtained besides the amide,

one of which appeared from analyses and chemical character to be the methylamine addition-compound, IX; these two compounds will be investigated further.



The *trans* amide (VIII), when subjected to the action of sunlight, was transformed into the hydroxypyrrolinone (II), presumably through the primary formation of an unstable open-chain *cis* form (IV), followed by cyclization.

Chlorination of the *cis* compound (II) with thionyl chloride produced a chloro derivative (X) which is analogous to that derived similarly from the ammonia analog, with chlorine replacing a hydrogen of the methyl group. This compound was soluble in dilute sodium hydroxide and was readily converted into the easily hydrolyzable methyl ether (XI).



Further work is being done in both this and the ammonia series in an effort to obtain the aminofuranone forms (III) which, it is believed, should be capable of independent existence.

EXPERIMENTAL[5]

5-(p-Bromophenyl)-1,4-dimethyl-5-hydroxypyrrolinone-2 (the lactamol of *cis*-3-(bromobenzoyl)-3-methylacrylic acid) (II). A solution of 10 g. of the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (I) in 100 cc. of dry dioxane was cooled in an ice-bath and treated with 30 cc. of 33% aqueous methylamine, added gradually with constant stirring. The solution was allowed to stand for 16 hours and was then heated on a water-bath for 3 hours. It was cooled, diluted with water to the point of crystallization, and concentrated by evaporation with an air blast. When precipitation appeared to be complete, the white crystals were filtered and washed

with water; yield 9.4 g. (93%) melting at 190–193°. Repeated crystallization from 50% methanol raised the melting point to 192.5–193.5°.

Anal. Calc'd for $C_{12}H_{12}BrNO_2$: C, 51.1; H, 4.3.
Found: C, 51.2; H, 4.3. (A quantitative estimation showed no methoxyl.)

The compound dissolved in 10% sodium hydroxide and was precipitated unchanged by hydrochloric acid. It was recovered unchanged after treatment with 30:1 conc'd acetic-hydrochloric acid (refluxing for 1 hour). It was recovered to the extent of 90% when allowed to stand for 15 hours at room temperature in methanol saturated with hydrogen chloride. Zinc dust and conc'd acetic acid for 1 hour at room temperature was without action. Attempts to benzoylate with benzoyl chloride and pyridine (standing 20 hours) and with benzoyl chloride and the sodium salt, were without success, the starting material being recovered almost quantitatively. Only starting material was obtained after treatment with phosphorus pentachloride in dry dioxane, followed by methanolysis. The compound was recovered in quantitative yield after treatment with acetic anhydride and a small amount of conc'd sulfuric acid (room temperature). At 60° for 10 min. only resinous products were obtained. Similarly, unchanged material was obtained when acetyl chloride and pyridine was used. No change was observed when a sample in chloroform containing a visible trace of iodine was subjected to the action of bright sunlight for 5 hours.

5-(p-Bromophenyl)-1,4-dimethyl-5-methoxypyrrolinone-2 (V). A solution of 0.75 g. of the hydroxypyrrolinone (II) in 30 cc. of methanol and 1 cc. of conc'd hydrochloric acid was allowed to stand for 12 hours and then refluxed for 10 hours. Upon cooling, neutralizing with sodium carbonate, and diluting with water (while mechanically stirred), flaky crystals were obtained. The product was filtered and washed with water; yield 0.54 g. (72%) melting at 69–71°. It was purified by vacuum evaporation onto a cold-finger condenser and melted at 71–72°.

Anal. Calc'd for $C_{13}H_{14}BrNO_2$: OCH_3, 10.5. Found: OCH_3, 10.7, 10.4.

Hydrolysis of 0.3 g. upon standing for 24 hours in 10 cc. of conc'd acetic and 1 cc. of conc'd hydrochloric acids at room temperature gave 0.21 g. (70%) of the hydroxypyrrolinone (II).

5-(p-Bromophenyl)-1,4-dimethyl-2,5-dihydropyrrolone-2 (VI). A solution of 0.5 g. of the hydroxypyrrolinone (II) in 10 cc. of conc'd acetic acid was added slowly to a suspension of 4 g. of finely powdered stannous chloride in a mixture of 5 cc. of conc'd hydrochloric and 20 cc. of conc'd acetic acids. The mixture was stirred for 1 hour at room temperature and then was diluted with water and concentrated by an air stream. The partially crystalline precipitate was separated by decanting the mother liquors and was dissolved in a small amount of alcohol. Crystallization was induced by adding a few drops of water; yield 0.28 g. (56%), melting point 99–100°. Recrystallization from 50% methanol raised the melting point to 100–101°.

Anal. Calc'd for $C_{12}H_{12}BrNO$: C, 54.1; H, 4.6.
Found: C, 53.8; H, 4.6.

The compound gave an immediate black precipitate when an ethanol solution was treated with ammoniacal silver nitrate solution.

trans-*3-(p-Bromobenzoyl)-3-methylacrylic N-methylamide* (VIII). In a number of preparations under varied conditions a mixture of three compounds invariably was obtained. A typical experiment follows.

One gram each of finely powdered phosphorus pentachloride and *trans*-3-bromobenzoyl-3-methylacrylic acid was mixed, and after the reaction subsided the phosphorus oxychloride was evaporated under reduced pressure. The residual oil was dissolved in 15 cc. of dry dioxane and decanted from unchanged phosphorus penta-

chloride (rinsing with 10 cc. more dioxane). The cooled solution was treated with 4 cc. of 33% aqueous methylamine with vigorous stirring, the solution then being allowed to warm to room temperature. It was poured into 100 cc. of water and after standing 0.5 hours was partially evaporated in an air stream until precipitation appeared to be complete. The solution was decanted from the partly crystalline mass and the residue was leached with several portions of boiling benzene. The insoluble residue (0.2 g.) was crystallized repeatedly from 10% ethanol, and melted at 211–224° (decomp.). The material was not the amide and gave the *anal.*, calc'd for $C_{12}H_{12}BrNO_2$: N, 5.0. Found: N, 5.35. It has not yet been investigated.

The benzene extracts, on cooling, deposited fine white crystals (0.2 g.), which on recrystallization from this solvent melted at 169.5–170.5°. This compound gave the *anal.*, calc'd for $C_{12}H_{17}BrN_2O_2$: N, 9.3; found: N, 9.15. It was formulated as IX and has as yet not been studied.

The benzene filtrate from the above on concentrating and standing deposited a more soluble compound (0.2 g.) which was purified by repeated crystallization from 1:1 benzene-ligroin, and melted at 112–113°.

Anal. Calc'd for $C_{12}H_{12}BrNO_2$: C, 51.1; H, 4.3; N, 5.0.
Found: C, 51.3; H, 4.6; N, 4.9.

Inversion was brought about in 50% yield by exposure in methanol solution to the action of bright sunlight for 5 hours. The product was the hydroxypyrrolinone (II).

5-(p-Bromophenyl)-4-chloromethyl-5-hydroxy-1-methyl-pyrrolinone-2 (X). Ten cubic centimeters of thionyl chloride was added to 1 g. of the hydroxypyrrolinone (II) and the mixture was heated on a water-bath for 10 minutes. On cooling and hydrolyzing in ice and water, a white crystalline powder was obtained; 0.55 g. (54%). It was purified by repeated crystallizations from 75% acetic acid and melted at 198–200° (decomp.).

Anal. Calc'd for $C_{12}H_{11}BrClNO_2$: C, 45.5; H, 3.5; N, 4.4; ClBr, 36.5.
Found: C, 45.1; H, 3.7; N, 4.3; ClBr, 35.7.

The compound dissolved slowly in cold and rapidly in warm (60–70°) 10% sodium hydroxide and was precipitated unchanged upon acidification with hydrochloric acid.

5-(p-Bromophenyl)-4-chloromethyl-5-methoxy-1-methyl-pyrrolinone-2 (XI). A solution of 0.5 g. of the hydroxypyrrolinone (II) in 5 cc. of thionyl chloride was allowed to stand at room temperature for 15 minutes and evaporated in a stream of dry air. Ten cubic centimeters of methanol was added, and the mixture heated at 60° for 1 hour. One cubic centimeter of water was then added, and on cooling and concentrating by an air stream, crystallization occurred; yield 0.5 g. (80%) melting at 100–105°. Repeated crystallization from methanol and vacuum evaporation onto a cold finger gave a pure product melting at 110–110.5°.

Anal. Calc'd for $C_{13}H_{13}BrClNO_2$: C, 47.25; H, 4.0; OCH_3, 9.4.
Found: C, 47.4; H, 4.3; OCH_3, 9.4.

This compound was obtained also in good yield by treating 0.25 g. of the chloro derivative (X) with 7 cc. of methanol and 0.1 cc. of conc'd hydrochloric acid, refluxing for 1.5 hours and standing at room temperature for 24 hours.

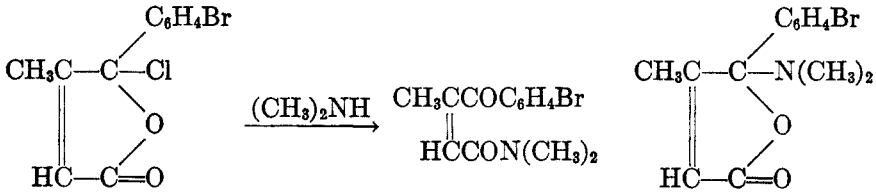
Hydrolysis of 0.5 g. in 10 cc. of conc'd acetic and 1 cc. of conc'd hydrochloric acids (24 hours at room temperature) gave 0.45 g. (95%) of the chloro derivative (X).

III. THE COMPOUNDS DERIVED FROM DIMETHYLAMINE

The N-dimethylamide is of particular interest because it cannot exist in the hydroxypyrrolinone form. Although the investigation of the com-

pounds in this series is incomplete, a preliminary report is being made at this time in order to supplement the discussion of the N-methylanilino series (4c), where all of the theoretically possible isomers have been obtained.

The compound made by the action of aqueous dimethylamine on the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (I), as would be expected, is unlike the compounds made similarly with ammonia or methylamine (9). Of the two possible formulations of the product, as the open-chain amide (II) or the N-dimethylaminofuranone (III), the former has been assigned, although the evidence is not as strong or as complete as could be desired.



I II III

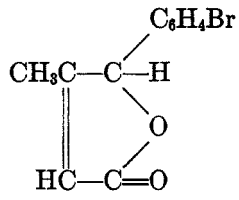
The structure of the amide does not follow from the synthesis because various mechanisms are possible, involving 1,2 or 1,4[6]-reactions as well as interchanges between II and III in either direction through addition and elimination of dimethylamine which was present in excess. The 1,4-reaction mechanism, however, is improbable since both aniline and methylaniline appear to react exclusively 1,2 (4c).

The amide is resistant towards acid hydrolysis, a property hardly to be expected of an aminofuranone such as III. It is reduced, with some difficulty, giving a non-crystalline nitrogen-containing product which has not yet been obtained pure and characterized. No evidence was observed of the formation of the nitrogen-free unsaturated lactone (IV) or the saturated ketonic acid which would be formed from it by hydrolysis, a result which would have been expected if the aminofuranone formulation were correct.[7] In this connection it should be noted that the unsaturated lactone or furanone (IV) has now been synthesized by dehydration of β-bromobenzoyl-β-methylpropionic acid, and if it had been formed in the reduction under discussion, it would have been isolated as such, or as

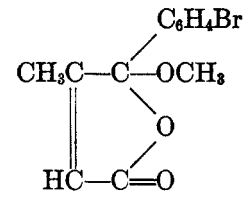
[6] *Cf.* the discussion of this type of reaction, Ref. 2.

[7] *Cf.* the reductions of the ammonia and methylamine compounds to the corresponding unsaturated lactams (9) and the reduction of *cis*-2,3-dimethyl-3-xenoylacrylic acid to the unsaturated lactone (2).

the saturated ketonic acid. The foregoing results, while favoring formula II over III, obviously are inconclusive.



IV



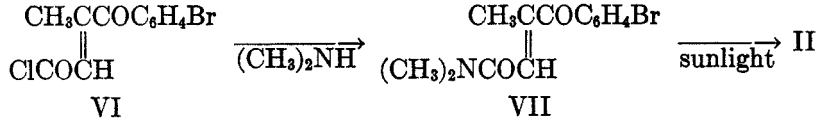
V

Alkaline hydrolysis proceeds very slowly, with cleavage of the molecule and production of *p*-bromopropiophenone, a type of reaction already observed with the *cis* acid itself (1a).

Methanolysis with methanol and hydrochloric acid eliminated the nitrogen and produced the cyclic or pseudo methyl ester (V), a result which would be expected on the basis of either formula II or III; stereochemical inversion did not occur as happens in the methanolysis of the ammonia anolog (4c).

Unsuccessful attempts were made to isomerize the dimethylamide by the action of sunlight on a chloroform solution with iodine as a catalyst, a common procedure for the *cis* to *trans* inversion. This evidence might be regarded as negative and favoring the cyclic structure (III), but little significance can be attached to the point because of the uncertainty in this type of reaction.

Positive evidence in favor of the open-chain formulation (II) is found in the study of the *trans* amide (VII) which was made from the *trans* acid chloride (VI) by the action of aqueous dimethylamine. Unfortunately,



VI VII

this product was not obtained in crystalline form, but its existence was demonstrated by subjecting the best sample, in methanol solution, to the action of bright sunlight; the result was conversion in good yield into the same amide obtained directly from the *cis* acid chloride (I) by the action of dimethylamine. This synthesis constitutes strong evidence in favor of formula II rather than III, since it is very unlikely (although not excluded) that the N-dimethylamino group of the primary open-chain product (II) would migrate under these conditions to give a cyclic compound such as

III [the analogous N-methylanilino group actually does not so migrate under these conditions as has now been shown (4c)].

Further studies are being undertaken in this series, particularly in an effort to obtain the isomeric amide of structure III.

EXPERIMENTAL

cis-*3*-(p-*Bromobenzoyl*)-*3*-*methylacrylic N-dimethylamide* (II). A solution of 70 g. of the *cis* acid chloride (I) in 150 cc. of dry dioxane was treated with a solution of 22 g. of dimethylamine hydrochloride in 50 cc. of 20% sodium hydroxide, added slowly with mechanical stirring. The temperature was maintained at 50° with continued stirring for 1 hour. The solution was then poured into ice. A current of air was used to evaporate some of the dioxane, and the oil which separated was washed by decantation with 10% sodium carbonate. The oil by that time had crystallized; this material was filtered, pulverized, and again leached with sodium carbonate solution. The crude yield was 38.3 g. (54%). Repeated crystallization from 50% methanol gave slender needles melting at 116–117°.

Anal. Calc'd for $C_{13}H_{14}BrNO_2$: C, 52.7; H, 4.8.
Found: C, 52.55; H, 4.8.

The sodium carbonate extracts (above) on acidification gave 31 g. (45%) of *cis*-β-bromobenzoyl-β-methylacrylic acid, thus accounting for practically all of the material.

When II was boiled with 10% sodium hydroxide, dimethylamine was expelled and an oily product remained. This was removed by extraction with ether, and on steam distillation, it gave a small amount of *p*-bromopropiophenone which was identified by mixture melting point with an authentic sample.

The *cis* amide (II) was recovered unchanged after treatment with 20:1 conc'd acetic and hydrochloric acids (refluxing 1 hour). Methanolysis with 30:1.5 methanol-conc'd hydrochloric acid (refluxing 10 hours) gave a small amount of the *cis* pseudo ester (V).

Chlorination by thionyl chloride gave a non-crystalline product.

Reduction. The *cis* amide (II) was reduced in three ways: (a) by stannous chloride in 5:1 conc'd acetic-hydrochloric acid mixtures, refluxing for 1.45 hours (at room temperature no reduction took place); (b) by sodium hydrosulfite in 70% ethanol, refluxing for 3, 10, or 37 hours (three experiments); and (c) by zinc dust in conc'd acetic acid (1 hour at room temperature). The products in all cases were oils and these separately were evaporated in the vacuum oven at temperatures of 180–200° at 10 mm. [the sample from (c) distilled at a lower temperature, 131–136°, but at a lower and unknown pressure]. The products were collected dropwise on a cold-finger condenser, the refractive index being determined on successive drops. The data obtained for the main fractions which showed constant refractive indices follow:

(a) n_D^{27} 1.5690–1.5700. *Anal.* N, 2.5, 2.4.
(b) n_D^{27} 1.5693–1.5699. *Anal.* N, 2.5, 2.4.
(c) n_D^{27} 1.5439. *Anal.* N, 3.9, 4.0.

These oils gave no reaction with Tollens' reagent and attempts to isolate the unsaturated lactone (IV) failed.

trans-*3*-(p-*Bromobenzoyl*)-*3*-*methylacrylic N-dimethylamide* (VII). One gram of *trans*-β-bromobenzoyl-β-methylacrylic acid and 1 g. of phosphorus pentachloride were intimately mixed. Rapid reaction occurred without evolution of much heat. The phosphorus oxychloride was evaporated under reduced pressure and the residual

oil [the *trans* acid chloride (VI)] was taken up in 7 cc. of dry dioxane. A solution of 2 g. of dimethylamine hydrochloride in 9.5 cc. of 9.5% sodium hydroxide was added, the mixture being allowed to stand at room temperature for 16 hours. Dilution with water and partial evaporation in a current of air gave a yellow oil which could not be induced to crystallize. Repetition of the reaction in benzene, using a 5% solution of dimethylamine in benzene, produced the same result.

A solution of 0.55 g. of the oily product in 40 cc. of methanol was exposed to bright sunlight for 8 hours. On concentrating by a current of air, a white crystalline precipitate appeared; 0.37 g. (67%). It was purified by crystallization from benzene-ligroin mixtures and was identified by mixture melting point as the *cis* amide (II).

5-(p-Bromophenyl)-4-methyl-2,5-dihydrofuranone-[8]*2* (IV). A suspension of 2 g. of β-bromobenzoyl-β-methylpropionic acid (1a) in 10 cc. of acetyl chloride was refluxed for 1.5 hours. The resulting solution was evaporated and the solid residue washed with water; yield, 1.87 g. (96%) melting at 76–81°. After repeated crystallization it melted at 88.5–89.5°. It decomposed upon standing for several months.

Anal. Calc'd for $C_{11}H_9BrO_2$: C, 52.2; H, 3.6.

Found: C, 52.5; H, 3.7.

It was insoluble in sodium carbonate and gave a black precipitate when treated in the usual way with Tollens' reagent.

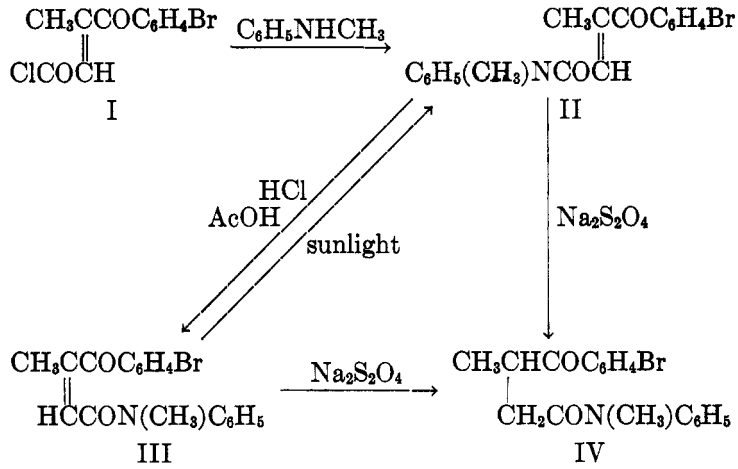
IV. THE COMPOUNDS DERIVED FROM METHYLANILINE

The amides made from methylaniline, a typical secondary amine, have been studied because it was expected that the two possible types in this series would be stable and would both be obtained by the methods which were only partially successful in the analogous N-dimethylamine series. Attention was turned to this series now, rather than to the completion of the investigation of the N-dimethylamino compounds, because here the products proved to be much more amenable to study and because there was immediate prospect of success in obtaining the complete series of derivatives in crystalline condition.

The *cis* (open-chain) N-methylanilide (III) was made from the *trans* isomer (II), which is necessarily open-chain, through inversion by sunlight. The *trans* N-methylanilide was made in good yield and without side reactions from the *trans* acid chloride (I). Both the *cis* and *trans* isomers were reduced easily and in excellent yields to the same compound, 3-bromobenzoyl-3-methylpropionic N-methylanilide (IV). Both isomers proved to be very resistant towards acid hydrolysis, and the action of refluxing conc'd hydrochloric and acetic acids served only to cause partial stereochemical inversion of the *cis* into the more stable *trans* form. In connection with the latter transformation, however, it should be noted that the action of sunlight on a chloroform solution of the *cis* isomer, with iodine as catalyst, was without effect, but of course little significance can be

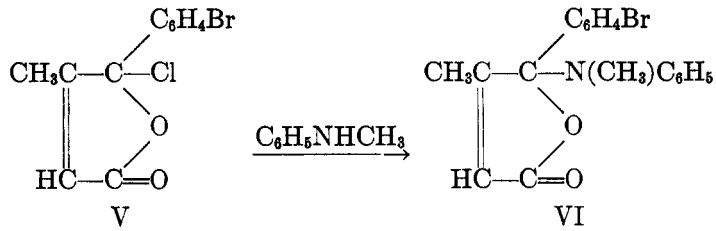
[8] Here the expanded and more proper term is used (rather than the commonly used abbreviation "furanone")in order to distinguish between this form and the isomeric enol lactone (*cf.* 9).

attached to this negative evidence in view of the uncertainty in this particular type of reaction.



The formulation of these compounds and reactions as given in the above diagram is supported by the mode of formation of the compounds involved, particularly (a) the formation of the *cis* amide (III) under conditions which would hardly be expected to permit rearrangement by actual migration of the N-methylanilino group (to give VI); (b) the reverse transformation from the labile *cis* to the stable *trans* form (which indicates the absence of a restrictive cyclic structure); and (c) the ease of reduction of both the *cis* and *trans* isomers by sodium hydrosulfite, a reaction which is characteristic and indicative of the unsaturated 1,4-dicarbonyl system.

An isomeric *cis* N-methylanilide was obtained by the interaction of the *cis* (pseudo) acid chloride of 3-bromobenzoyl-3-methylacrylic acid (V) and methylaniline. Since it is different from the open-chain *cis* methylanilide (III), it must be given the only alternative formulation as the methylanilinofuranone (VI). In turn, the existence of this isomer leaves no room for doubt concerning the structure of the open-chain isomer (III).



As would be expected from this formulation, the product (VI) is not easily reduced and is not affected by sodium hydrosulfite under the condi-

tions which are effective in reduction of the open-chain *cis* isomer and the *trans* isomer. The action of boiling conc'd acetic and hydrochloric acids converted this compound in excellent yield into a new nitrogen-containing substance which has not yet been identified and which is now under investigation.

In the methylanilides, then, we have been able to obtain all of the three possible types of compounds, the *cis* and *trans* isomers and the methylanilinofuranone form of the *cis* compound; furthermore, the modes of formation and reactions leave no doubt as to the structures which have been assigned.

EXPERIMENTAL[5]

trans-*3*-(p-*Bromobenzoyl*)-*3*-*methylacrylic N-methylanilide* (II). A sample of the non-crystalline *trans* acid chloride (I) was made in the usual way from 6 g. of the acid and phosphorus pentachloride, the phosphorus oxychloride being removed by evaporation under reduced pressure. This was taken up in 60 cc. of dry dioxane and treated with 6 cc. of methylaniline at 60° for 0.5 hours. Upon cooling and diluting with water, followed by partial evaporation in an air stream, 8.4 g. of II, m.p. 73–78° was obtained. Repeated crystallization from 9:1 ligroin-benzene mixtures raised the melting point to 96–97.5°.

Anal. Calc'd for $C_{18}H_{16}BrNO_2$: C, 60.4; H, 4.5.
Found: C, 60.6; H, 4.76.

cis-*3*-(p-*Bromobenzoyl*)-*3*-*methylacrylic N-methylanilide* (III). A solution of 0.5 g. of the *trans* isomer (II) in 50 cc. of methanol was exposed to bright sunlight for 12 hours. Addition of water dropwise, with scratching, induced crystallization. The yield was 0.46 g. (92%) of nearly pure product melting at 124–125°. Repeated crystallization from 4:1 ligroin-benzene mixture raised the melting point to 125.5–126.5°.

Anal. Calc'd for $C_{18}H_{16}BrNO_2$: C, 60.4; H, 4.5.
Found: C, 60.3; H, 4.3.

A sample was recovered quantitatively after exposure to the action of bright sunlight for 12 hours in chloroform solution containing a visible amount of iodine.

Reduction with zinc dust and conc'd acetic acid (1 hour at room temperature) gave a non-crystalline product.

Inversion. A solution of 0.2 g. of the *cis* compound (III) in 12 cc. of conc'd acetic acid and 5 drops of conc'd hydrochloric acid was refluxed for 1 hour, giving 0.12 g. (60%) of crude *trans* methylanilide (II) which was recrystallized and identified by mixture melting point.

3-(p-*Bromobenzoyl*)*butyric N-methylanilide* (3-bromobenzoyl-3-methylpropionic N-methylanilide) (IV). A mixture of 1 g. of sodium hydrosulfite, 20 cc. of 20% ethanol, and 0.3 g. of either the *cis* or the *trans* N-methylanilides (II or III) was refluxed for 1 hour. It was then diluted with water and partially concentrated by a current of air. When precipitation appeared to be complete, the white crystalline product was filtered. The yields of material (melting at 100–102°) were identical in both cases (0.28 g. or 93%). Repeated crystallization from ligroin raised the melting point to 103–104°.

Anal. Calc'd for $C_{18}H_{18}BrNO_2$; C, 60.0; H, 5.0.
Found: C, 59.9; H, 5.1.

5-(p-*Bromophenyl*)-*4*-*methyl*-*5*-(*N-methylanilino*)*furanone-2* (VI). A solution of

25 g. of the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (V) in 20 cc. of dry dioxane was treated with 20 cc. of methylaniline and the mixture maintained at 50–55° for 0.5 hours and then for 12 hours at room temperature. The crude product precipitated as a resin upon diluting with water; it was digested with 10% sodium carbonate solution and washed with water (by decantation). It was then crystallized from methanol; yield 11.85 g. (34%) melting at 138–144°. Repeated crystallization from 9:1 ligroin-benzene mixtures raised the melting point to 146–148°.

Anal. Calc'd for $C_{18}H_{16}BrNO_2$: C, 60.36; H, 4.5.
Found: C, 60.05; H, 4.2.

Reduction. Sodium hydrosulfite in 70% ethanol (refluxing for 2 hours with further additions of reducing agent) was without effect, 90% of the material being recovered unchanged. Reduction with zinc dust and conc'd acetic acid (1 hour at room temperature) gave an intractable oil.

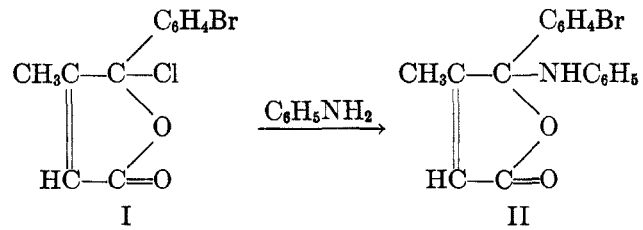
Acid hydrolysis or *methanolysis*, by refluxing for 1 hour in a mixture of 0.2 g. in 12 cc. of conc'd acetic acid and 5 drops of conc'd hydrochloric acid (or in methanol and hydrochloric acid with 7 hours refluxing) gave the same product, in practically quantitative yield in the first case and 80% in the second. Upon repeated crystallization from a 9:1 mixture of ligroin and benzene, it melted at 137–138°.

Anal. Calc'd for $C_{18}H_{16}BrNO$: C, 60.4; H, 5.1; N, 4.4.
Found: C, 60.1; 60.2; H, 5.0; 4.7; N, 4.6; 4.5.

V. THE COMPOUNDS DERIVED FROM ANILINE

Since no series of amides would be completely representative without the anilides, this type has also been investigated. It was expected that the N-phenyl group would tend to stabilize the compounds in some degree and it was hoped that all of the possible isomers might be obtained. This hope was realized in part.

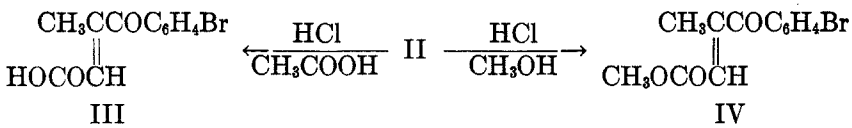
The action of aniline on the pseudo acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (I) produced in good yield a compound in which the anilino group had replaced the chlorine. From analogy to the reactions with ammonia and methylamine (9) and the reaction between aniline and the pseudo acid chloride of *o*-benzoylbenzoic acid (3h), one might have expected this product to be the hydroxy-N-phenylpyrrolinone (X). But upon investigation, it quickly became evident from the properties, and from the isolation of the isomer [the true hydroxypyrrolinone (X) described below], that this compound is the anilinofuranone (II), the reaction being analogous to that with methylaniline and to that between aniline and opianic acid (3f).



I II

This anilinofuranone (II) was slightly acidic. It reacted with aqueous sodium hydroxide to give an oil which evidently was the sodium salt since it dissolved when the mother liquor containing the excess of sodium hydroxide was decanted and water was added. The original compound was precipitated unaltered from the solutions upon acidification.

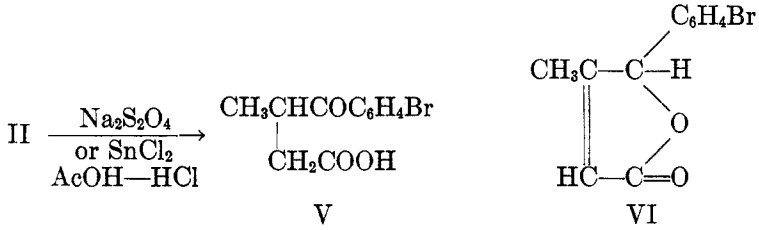
The anilinofuranone was easily hydrolyzed by hydrochloric acid in conc'd acetic acid at room temperature, but curiously the product was the *trans* acid (III), inversion of the configuration having taken place also. This reaction is in sharp contrast with the resistance towards hydrolysis by this reagent at refluxing temperature of the hydroxypyrrolinones, including the N-phenyl derivative (X), described below. The ease of hydrolysis in this case supports the anilinofuranone formulation (II).



The action of methanol and hydrochloric acid on the anilinofuranone (II) produced the *trans* ester (IV), involving both methanolysis and inversion of the configuration. This reaction is analogous to the hydrolysis and inversion described above, and is in striking contrast to the conversion under comparable conditions of the true hydroxypyrrolinones [including the anilino derivative (X) described below] into the corresponding methyl ethers. This reaction also is consistent with and supports formula II.

The two reactions, hydrolysis and methanolysis, as described above, present an interesting problem of mechanism, in that the inversion apparently cannot involve the *cis* acid, the open-chain or pseudo *cis* esters, or the *trans* anilide. Further work on this problem is in progress.

The reduction of the anilinofuranone (II) was accomplished by either stannous chloride or sodium hydrosulfite, the product being 3-bromobenzoyl-3-methylpropionic acid (V).

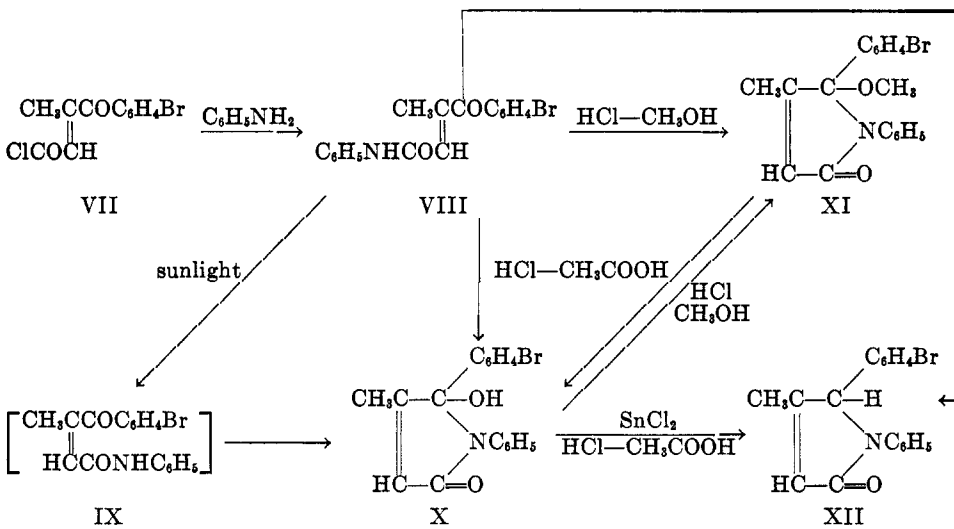


The elimination of nitrogen in both reductions is significant. The acid conditions involved in the stannous chloride reduction are sufficient to cause hydrolysis and inversion, and the *trans* acid (III) is therefore very

probably an intermediate. In the sodium hydrosulfite reduction, however, it seems likely that another mechanism may be involved, perhaps reductive elimination first of the nitrogen to give an unsaturated lactone (VI), followed by hydrolysis to the acid V. The results of these reductions are to be contrasted with the course of the reductions of the hydroxypyrrolinones, including the N-phenyl derivative (X) described below. The formula II explains the results satisfactorily.

From the foregoing facts the anilinofuranone structure (II) seems established. The compound is analogous to the methylanilino derivative, but is quite different in character from the dimethylamino compound. It is to be presumed that in the preparation of all three types from the *cis* pseudo acid chloride (I) the reactions are initially direct (9, 3h) but that with the more reactive dimethylamine a secondary reaction occurs, with rearrangement taking place through addition and elimination of dimethylamine, which is present in excess.

An isomeric anilide, which proved to be the hydroxypyrrolinone (X) has been prepared from the *trans* acid chloride (VII) through the *trans* anilide (VIII). The last step of the transformation, which involved inversion, was accomplished in two ways, by sunlight, and with hydrochloric acid. The intermediate and primary product of the sunlight reaction, of course, must be the true *cis* anilide (IX) but the properties of the compound obtained indicated that immediate cyclization to the hydroxy-N-phenylpyrrolinone (X) had followed.



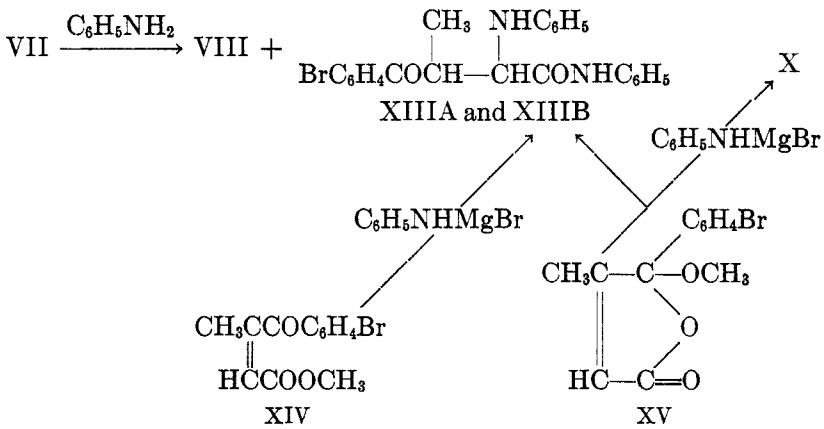
The compound is soluble in dilute sodium hydroxide and is precipitated unchanged upon acidification, as would be expected from the structure X.

The isomerization of the compound by hydrochloric acid, in the direction *trans* to *cis*, is explicable only on the basis of the cyclic formulation (X). The tendency to form the stable ring evidently constitutes the driving force overbalancing the natural tendency of the hypothetical open-chain *cis* form to undergo rearrangement to the thermodynamically more stable *trans* isomer. In contrast to this, as already shown, the *trans methyl*anilide is not affected by hydrochloric acid, presumably because the *cis* form can not cyclize directly, whereas the *cis* isomer, which must be open-chain, will undergo rearrangement to the *trans* in the normal way under these conditions. These differences between the anilide and the methylanilide constitute evidence for the cyclic formulation of the former (X).

Methanol and hydrochloric acid convert the hydroxypyrrolinone (X) into a methyl ether (XI); this reaction is characteristic of the type. The *trans* anilide (VIII) also is converted into this same methyl ether (XI), cyclization evidently being the driving force which is responsible for rearrangement in this direction. This latter reaction is in contrast with the transformation in the opposite direction under these conditions of the *cis* to the *trans* methylanilide. The methyl ether (XI) is easily hydrolyzed by hydrochloric acid in concentrated acetic acid. The hydroxypyrrolinone itself, however, is very resistant towards acid hydrolysis, and thus far attempts to eliminate the nitrogen have been unsuccessful.

Reduction of the hydroxypyrrolinone (X) with stannous chloride in concentrated acetic and hydrochloric acids gives a typical unsaturated lactam, the pyrrolinone (XII). This type of reduction, involving loss of an oxygen, but retention of the nitrogen, is characteristic of this class of compounds and lends further support to the formulation X. Incidentally, the *trans* anilide (VIII) also is converted into the pyrrolinone (XII) under the same conditions, but this reaction must involve first rearrangement to the hydroxypyrrolinone (X) since this change is known to occur readily under the general reaction conditions.

It is perhaps significant that the anilinofuranone (II) is produced in good yield from the *cis* acid chloride (I) by the reaction with aniline without the noticeable formation of secondary aniline addition compounds. The *trans* anilide (VIII), when first obtained by the action of aniline on the *trans* acid chloride (VII), was accompanied by three secondary products, although the yield of the true anilide (VIII) could be made almost quantitative under controlled conditions. Of the three secondary products, two contained two nitrogens each and evidently were stereoisomers of XIII, aniline having added to the α,β-unsaturated ketone system present [a similar addition compound is formed in the reaction with methylamine (9)]. The third compound contained three nitrogens. These compounds have not yet been investigated.



An obvious and probable explanation for the failure of secondary addition of aniline to occur in the reaction with the *cis* pseudo acid chloride (I) is that no reactive α,β-unsaturated ketone system is present in the compounds involved or in the final product (II).

In this connection some experiments should be described dealing with an attempt to prepare the anilides through the action of anilinomagnesium bromide on the open-chain and cyclic *cis* esters (XIV and XV). With the open-chain ester (XIV) only a small amount of one of the anilide addition compounds (XIIIB) was obtained, but when the pseudo ester XV was used, the yield of this same secondary product (XIIIB) was almost 60% and in addition a yield of approximately 40% of the hydroxypyrrolinone (X) was isolated, no other product being obtained.

In summary of the foregoing results, it may be stated that three of the four possible anilides have been made, namely, the *trans* isomer (IV), and the two cyclic forms in the *cis* series, the anilinofuranone (II) and the hydroxypyrrolinone (X). It has not been possible to obtain the true open-chain *cis* amide, and it seems very unlikely that this compound would be stable enough to exist under ordinary conditions.

EXPERIMENTAL[5]

5-Anilino-5-(p-*bromophenyl*)*-4-methylfuranone-2* (II). A solution of 88.6 g. of the pseudo acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (I) in 125 cc. of dry dioxane was treated with 70 cc. of aniline diluted with 25 cc. of dioxane. The mixture was maintained at 50–60° with continual stirring for 1.5 hours. The solution was poured into a large volume of water containing 100 cc. of conc'd hydrochloric acid. The resinous product was allowed to coagulate, separated by decantation, and digested with boiling methanol. The product solidified and was filtered; crude yield 117.5 g. (95%). Repeated crystallization from methanol, or benzene (in which it is more soluble), gave an analytical sample melting at 169.5–170.5°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: C, 59.3; H, 4.1; N, 4.1; Br, 23.2.
Found: C, 58.8, 58.8; H, 4.1, 4.05; N, 4.2, 4.0; Br. 23.55.

The compound reacts with 10% sodium hydroxide, giving an oil which was separated by decantation; it then dissolved readily in water. Acidification regenerated the anilinofuranone.

Hydrolysis of 0.2 g. in 12 cc. of conc'd acetic acid and 5 drops of conc'd hydrochloric acid (at room temperature or refluxed for 1 hour) gave 0.13 g. (92%) of nearly pure *trans* acid (III) which was purified and identified. When run on a larger scale as a method of preparing the *trans* acid (III), the yields were not as good, and when run at room temperature there usually was recovered some unchanged material, which could easily be separated by taking advantage of its insolubility in sodium bicarbonate.

Methanolysis of 0.5 g. in 30 cc. of methanol and 2 cc. of conc'd hydrochloric acid (refluxing for 7 hours and standing for 12 hours at room temperature) gave 0.22 g. (57%) of nearly pure *trans* ester (IV). The product was isolated by concentrating the solution and cooling.

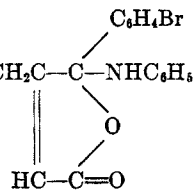
Reduction. A solution of 0.5 g. in 10 cc. of conc'd acetic acid and 10 cc. of ethyl acetate was added to a suspension of 4 g. of stannous chloride in 5 cc. of conc'd hydrochloric acid and 20 cc. of conc'd acetic acid, with vigorous stirring for 1 hour at room temperature. Dilution with water gave 0.31 g. of crude solid (81% yield) from which a pure sample of β-bromobenzoyl-β-methylpropionic acid was obtained upon crystallization; m.p. 94–94.5°; identified by mixture melting point with an authentic sample (1a). A similar result was obtained when sodium hydrosulfite in 80% ethanol was used (refluxing 3 hours).

Reduction with zinc dust, added to a well-stirred solution of the anilinofuranone (II) in conc'd acetic acid and with continued stirring for 1 hour at room temperature, gave a viscous, non-acidic oil which was evaporated in the vacuum oven and collected dropwise on the cold finger. The middle fraction, coming over at an oven temperature of 205–215°, was pale yellow and gave a microanalysis for nitrogen of 3.35%.

Reaction with thionyl chloride gave an amorphous solid product which was purified by repeated precipitation from methanol by addition of water. It melted at 178–179.5° (decomp.).

Anal. Calc'd for $C_{17}H_{13}BrClNO_2$: N, 3.7. Found: N, 3.7.

Evidently simple chlorination had occurred. The following formula is suggested for this product:



Phosphorus pentachloride converted a sample of the anilinofuranone in good yield into the *trans* acid.

Attempts to methylate the salts failed, only unchanged material being recovered in the following experiments: (a) Dimethyl sulfate was added dropwise to II in 2.5% sodium hydroxide, and (b) methyl iodide was added dropwise with stirring to a 1% sodium methoxide solution, followed by refluxing for 2 hours.

When methyl iodide was added to a carefully prepared sample of the silver salt in methanol with shaking for 2 hours, an intractable oil was obtained. The silver salt was made by adding silver nitrate to an aqueous solution of the sodium salt, filtering, and washing with water and methanol.

A new method of synthesis of trans-*3*-(p-*bromobenzoyl*)-*3*-*methylacrylic acid* (III).

The above described hydrolysis and inversion of the anilinofuranone (II) to the *trans* acid (III) has proved to be very useful in preparing quantities of the *trans* acid. The earlier method of synthesis started with citraconic anhydride and in seven steps through citraconic acid, mesaconic acid, the diester, the monoester, the monoester monoacid chloride, and the *trans*-3-bromobenzoyl-3-methylacrylic ester (IV), followed by hydrolysis, gave over-all yields of less than 10% (1a). The new synthesis starting from citraconic anhydride proceeds directly to *cis*-3-bromobenzoyl-3-methylacrylic acid, and then through the acid chloride (I) and the anilinofuranone (II), and involves only four steps with an over-all yield of approximately 50%.

trans-*3*-(p-*Bromobenzoyl*)-*3*-*methylacrylic anilide* (VIII). The oily acid chloride (VII) obtained in the usual way by the action of phosphorus pentachloride on 1 g. of the acid (III), with evaporation of the phosphorus oxychloride, was dissolved in 25 cc. of dry dioxane and cooled to 0–5°. One cubic centimeter of aniline was added dropwise and the temperature maintained at 5° for 1 hour. The mixture was then allowed to come to room temperature over a period of 0.5 hour. When poured into water and ice a precipitate formed, and 1.4 g. of material melting at 135–141° was obtained. Repeated crystallization from methanol brought the melting point to 143–144.5°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: C, 59.3; H, 4.1; N, 4.1.
Found: C, 59.4, 59.55; H, 4.1, 4.1; N, 4.2.

Reduction with zinc dust and conc'd acetic acid (1 hour at room temperature) gave a non-crystalline product. Sodium hydrosulfite in 80% ethanol (refluxing for 3 hours) gave a mixture of solid products which have not been identified.

Secondary products. When the acid chloride from 1 g. of the acid (III) was treated with an excess of aniline in dioxane and the mixture was allowed to stand for 18 hours at room temperature, 1.16 g. of crystalline material was obtained. It melted at 46–92°. Leaching with hot ethyl acetate gave a residue which melted at 151–161° (decomp.) and which was repeatedly crystallized from ethanol. This compound then melted at 163–165° and is probably a stereoisomer of XIII. It will be designated as isomer-A.

Anal. Calc'd for $C_{23}H_{21}BrN_2O_2$; N, 6.4. Found: N, 6.5.

The ethyl acetate filtrate (above) was evaporated to a gum which was taken up in ethanol; crystallization followed giving 0.2 g. of product melting at 213–215° (decomp.). Repeated crystallization from ethanol gave short white needles melting at 221–222° (decomp.). This is designated as isomer-B (it is presumably the stereoisomer of XIIIA).

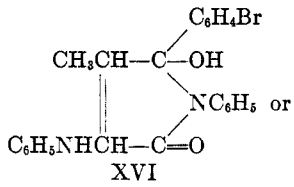
Anal. Calc'd for $C_{23}H_{21}BrN_2O_2$: N, 6.4. Found: N, 6.3.

In a second run on this reaction (with the time of standing reduced to 1 hour) the products were worked up as above. Ethyl acetate, however, dissolved all of the material. Recrystallization from benzene and a little ligroin gave a new compound which crystallized from ethanol as short white needles and melted at 193–197° (decomp.).

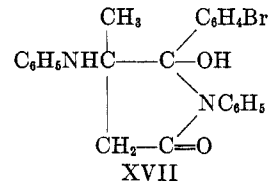
Anal. Calc'd for $C_{29}H_{28}BrN_3O_2$: N, 7.9. Found: N, 8.04.

The filtrate from this was concentrated and gave a sample of the *trans* anilide (VIII).

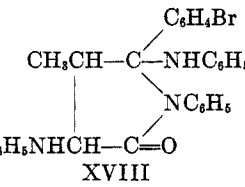
Alternative structural possibilities for one or both of the dianilino derivatives XIIIA and XIIIB are the following (XVI and XVII), and possibilities for the compound containing three nitrogens would be these structures with anilino replacing the hydroxyl, for example, XVIII.



XVI



XVII



XVIII

5-(p-Bromophenyl)-5-hydroxy-4-methyl-N-phenylpyrrolinone-2 (X). This compound was prepared in three ways as follows. (a) *By inversion of the* trans *anilide under acid conditions.* A solution of 0.1 g. of the *trans* anilide (VIII) in 10 cc. of conc'd acetic acid and 6 drops of conc'd hydrochloric acid was refluxed for 1 hour and diluted with ice and water. A quantitative yield of nearly pure hydroxypyrrolinone (X) precipitated.

(b) *By sunlight inversion of the* trans *anilide.* A solution of 0.1 g. of the *trans* anilide (VIII) in 15 cc. of methanol was exposed to bright sunlight for 6 hours. Upon evaporation and washing the residue with 10% methanol a quantitative yield of the *cis* compound (X) was obtained (m.p. 206-207°). Repeated crystallization from 65% ethanol raised the melting point slightly to 207-207.5°. The reaction worked equally well on a larger scale using 1 g. to 100 cc. of methanol.

Anal. Calc'd. for $C_{17}H_{14}BrNO_2$: C, 59.3; H, 4.1; N, 4.1.
Found: C, 59.1; H, 4.1; N, 4.2.

(c) *By the action of aniline magnesium bromide on the pseudo methyl ester of* cis-*3-bromobenzoyl-3-methylacrylic acid.* An ethereal solution containing approximately 4 g. of phenylmagnesium bromide was added to 20 cc. of dry benzene in a three-necked flask, mechanically stirred and maintained under an atmosphere of dry nitrogen. A solution of 5 cc. of aniline in 10 cc. of dry benzene was added dropwise with stirring, followed by stirring for 0.5 hour. A solution of 2 g. of the pseudo *cis* methyl ester of 3-bromobenzoyl-3-methylacrylic acid (XV) in 20 cc. of dry benzene was then added dropwise with stirring and the mixture finally heated at 50-60° for 1 hour. The solution was treated with ice-water, washed with dilute hydrochloric acid, 5% sodium hydroxide and then water. Evaporation gave a solid residue which was digested with ethanol and filtered; yield 2.1 g. (81%) melting at 161-165°. Extraction with boiling methanol gave a residue (1.26 g., 60%) of nearly pure aniline addition product, XIIIB, melting at 207-216° (identified by mixture melting point). From the methanol filtrate, on cooling, 0.8 g. (40%) of the hydroxypyrrolinone (X) was obtained and identified.

When the open-chain *cis* ester (XIV) of 3-bromobenzoyl-3-methylacrylic acid was used in a comparable experiment, only a 15% yield of the addition compound (XIIIB) was obtained, and no other crystalline product was isolated.

The hydroxypyrrolinone (X) is soluble in an excess of sodium hydroxide and is precipitated unchanged by acid. It is stable towards conc'd acetic acid and added conc'd hydrochloric acid (refluxed for 1 hour). Zinc dust and conc'd acetic acid (1 hour at room temperature) were without any action, the compound being recovered quantitatively. Exposure of a solution in chloroform with a visible amount of iodine to strong sunlight for 6 hours was without effect.

5-(p-Bromophenyl)-5-methoxy-4-methyl-N-phenylpyrrolinone-2 (XI). A solution of the hydroxypyrrolinone (X) in 20 cc. of methanol and 1 cc. of conc'd hydrochloric acid was refluxed for 7 hours. Then, after standing overnight, a few drops of water were added and the solution concentrated by an air stream. A partly crystalline mass appeared and was crystallized from isopropanol by adding a few drops of water

and allowing the solution to evaporate slowly. A yield of 0.13 g. (65%) of material melting at 92–95° was thus obtained. It was difficult to crystallize, usually coming down as an oil. It crystallized best from isopropanol or isopropanol-ethanol mixtures; melting point 92–95°.

Anal. Calc'd for $C_{18}H_{16}BrNO_2$: C, 60.4; H, 4.5; OCH_3, 8.6.
Found: C, 60.6; H, 4.6; OCH_3, 8.2, 7.9.

Similar results were obtained when the above reaction was carried out on the *trans* anilide (VIII).

Hydrolysis of 0.1 g. with 6 cc. of conc'd acetic acid and 12 drops of conc'd hydrochloric acid (standing for 18 hours at room temperature) gave 0.1 g. of nearly pure product which was purified and identified by mixture melting point as the hydroxypyrrolinone (X).

5-(p-Bromophenyl)-4-methyl-N-phenyl-2,5-dihydropyrrolone-2 (XII). A solution of 0.2 g. of the hydroxypyrrolinone (X) in 10 cc. of conc'd acetic acid was added slowly to a suspension of 2 g. of powdered stannous chloride in a mixture of 10 cc. of conc'd acetic and 2 cc. of conc'd hydrochloric acids. The mixture was stirred mechanically for 1 hour at room temperature, and was then diluted with water and extracted with ether. Evaporation of the ether and neutralization of the acetic acid with sodium bicarbonate was followed by leaching with two portions of boiling methanol. The methanol solution, on concentration, gave 0.2 g. of product which on repeated crystallization from 80% ethanol melted at 172–173.5°.

Anal. Calc'd for $C_{17}H_{14}BrNO$: C, 62.2; H, 4.3.
Found: C, 62.3; H, 4.2.

A similar result was obtained when the *trans* anilide (VIII) was substituted in the above reaction.

This compound gave a black precipitate when an alcohol solution of it was treated with Tollens' reagent. The hydroxypyrrolinone (X) in a similar test did not react.

SUMMARIES

I

The same amide was obtained from both the open-chain and pseudo esters and the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid. It has been assigned the unsaturated lactamol or hydroxypyrrolinone structure on the basis of alkali solubility, resistance towards reduction, elimination of the oxygen by the action of stannous chloride, conversion by methanolic hydrogen chloride into the easily hydrolyzable methyl ether, stability towards hydrolysis, and failure to undergo inversion into the *trans* isomer.

The action of sulfuric and nitrous acids caused elimination of the nitrogen and gave the *cis* acid. Extended treatment with methanol and hydrochloric acid gave the *trans* methyl ester by inversion of the configuration and elimination of the nitrogen. Ozonization gave *p*-bromobenzoic acid and *p*-bromophenyl and methyl diketone.

The amide of *trans*-3-bromobenzoyl-3-methylacrylic acid was made by the action of ammonia on the acid chloride. It underwent methanolysis

to the *trans* ester with elimination of the nitrogen. The action of sunlight converted it by inversion and cyclization into the same hydroxypyrrolinone as was obtained from the *cis* acid.

The action of thionyl chloride on the hydroxypyrrolinone brought about substitution of chlorine in the methyl group. The location of the chlorine was demonstrated by degradations. The hydroxypyrrolinone structure was shown by the reactions which paralleled those of the parent amide. The easily hydrolyzable methyl ether was made by the action of methanolic hydrogen chloride.

II

The amide obtained by the action of methylamine on the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid evidently has the lactamol or hydroxypyrrolinone structure. It gives an easily hydrolyzable methyl ether and is reduced by stannous chloride to the simple pyrrolinone or unsaturated lactam.

The *trans* amide was made from the corresponding *trans* acid chloride. It was converted by the action of sunlight into the hydroxypyrrolinone through inversion and cyclization.

Thionyl chloride converted the hydroxypyrrolinone into a chloro derivative, the chlorine entering the methyl group. The easily hydrolyzable methyl ether of this compound was made.

III

The action of dimethylamine on the pseudo acid chloride of *cis*-3-(*p*-bromobenzoyl)-3-methylacrylic acid gives apparently the true open-chain *cis* dimethylamide. The evidence for the open-chain formulation of the product is the synthesis of this same compound by sunlight inversion of the *trans* dimethylamide which was obtained from the *trans* acid chloride by the action of dimethylamine.

IV

The *trans* N-methylanilide was made through the *trans* acid chloride. It was converted into the *cis* isomer by the action of sunlight. The reverse transformation from *cis* to *trans* was brought about by hydrochloric acid. Both the *cis* and *trans* isomers were reduced to the same N-methylanilide of 3-bromobenzoyl-3-methylpropionic acid. The structure follows from the reactions involved.

The isomeric N-methylanilinofuranone form of the *cis* methylanilide was made from the pseudo acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid.

V

The action of aniline on the pseudo acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid produced the anilinofuranone, the structure of which was shown by the ease of hydrolysis and methanolysis with inversion of configuration to give, respectively, the *trans*-3-bromobenzyol-3-methylacrylic acid and its ester. Reduction eliminated nitrogen giving 3-bromobenzoyl-3-methylpropionic acid.

The above hydrolytic inversion made possible a greatly improved synthesis of the *trans* acid.

The *trans* anilide was made by the action of aniline on the acid chloride, the reaction proceeding in quantitative yield under controlled conditions, but otherwise giving three secondary products, two containing two nitrogens each, and the other, three. The action of hydrochloric acid converted the *trans* anilide into the hydroxypyrrolinone by inversion and cyclization.

The isomeric cyclic anilide (the hydroxy-N-phenylpyrrolinone) was made through the *trans* anilide by isomerization by sunlight or hydrochloric acid. The evidence for the cyclic structure is the formation of the compound through rearrangement of the *trans* isomer by hydrochloric acid, methylation to an easily hydrolyzable methyl ether, and reduction to the unsaturated N-phenyllactam or pyrrolinone.

The true open-chain *cis* anilide was not obtained and is evidently incapable of existence.

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[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, U. S. DEPARTMENT OF AGRICULTURE]

ALLENES. IV. THE REACTION OF SOME ALLENES WITH LEAD TETRAACETATE

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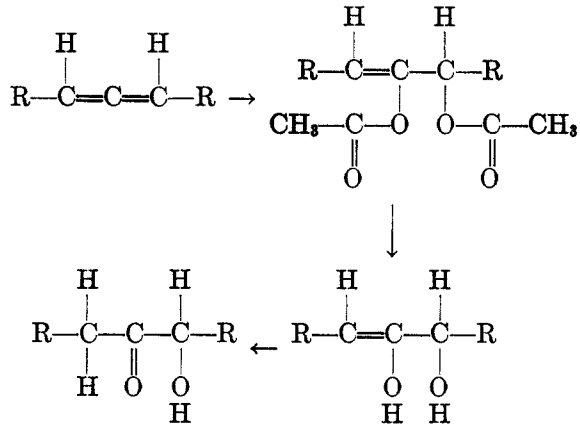
The action of lead tetraacetate upon ethylene compounds has been extensively investigated. From the results reported, especially by Dimroth and Schweizer (1) and by Criegee, Kraft, and Rank (2), it is evident that the reaction generally proceeds in several directions but in many instances consists mainly in the addition of a pair of acetoxy radicals to the double bonds. Saponification of the diacetyl derivatives furnishes the corresponding glycols. There is in the literature no report of the reaction of lead tetraacetate with a compound containing the cumulated system of double bonds.

In connection with our investigations on the relation of these compounds to pyrethrone, it was of interest to apply to them the reaction with lead tetraacetate as a method for identifying the cumulated system. It is evident that if one of a pair of adjacent double bonds in a compound were saturated by addition of two acetoxy groups, saponification of the diacetyl derivative would result in the formation of an *alpha*-hydroxy enol, which would rearrange to an *alpha*-hydroxy ketone.



This series of reactions was applied to 1-phenyl-1,2-butadiene (3), 1-cyclohexyl-2,3-pentadiene (4), and 2,3-pentadiene (5). The method

employed consisted in agitating an acetic acid solution of the hydrocarbon with the calculated quantity of lead tetraacetate until the reagent had been used up. The temperature was kept at 40° or slightly higher, depending on which hydrocarbon was being treated. Two methods of isolation recommended by Criegee and co-workers (2) were employed. If no water-soluble products were anticipated, part of the acetic acid was removed under reduced pressure, water was added, and the reaction-products were extracted with ether (method A); if water-soluble products were expected, the acetic acid solution was diluted with absolute ether and the lead acetate removed by filtration, after which the solvents were removed, the residue again dissolved in ether, and the remaining acid and lead acetate removed with the minimum of water and bicarbonate solution (method B).

When 1-phenyl-1,2-butadiene was treated with lead tetraacetate, the reaction-product isolated by method A was a sirup which in a short time crystallized to a large extent. This crystalline reaction-product on analysis proved to be a diacetoxy compound corresponding to the empirical formula $C_{14}H_{16}O_4$, which may be either 1-phenyl-2,3-acetoxy-1-butene, $C_6H_5CH{=}C(CH_3CO_2)CH(CH_3CO_2)CH_3$ (I), or 1-phenyl-1,2-acetoxy-2-butene, $C_6H_5CH(CH_3CO_2)C(CH_3CO_2){=}CHCH_3$ (II), the former being more probable, since it has been shown that halogens add to 1-phenyl-1,2-butadiene in the 2,3 position (6). Furthermore, the crystalline diacetoxy derivative may be either the cis or the trans form, and its geometric isomer may be present in the noncrystalline part of the reaction-product, as will be referred to later. The crystalline compound still contained one double bond, since hydrogenation resulted in a dihydro derivative. The original diacetoxy compound was unstable in the presence of alkalies, but complete saponification could be accomplished smoothly by boiling in ethanolic potassium acetate solution.

The reaction-product, however, proved to be a ketone of formula $C_{10}H_{10}O$, instead of the expected hydroxy ketone of formula $C_{10}H_{12}O_2$. The empirical formula was established by analysis of the ketone itself, its semicarbazone, and its *p*-nitro- and 2,4 dinitro- phenylhydrazones. The formula $C_{10}H_{10}O$ corresponds to that of a phenylbutenone. Two compounds of this category are well known—1-phenyl-2-butene-1-one, $C_6H_5COCH{=}CHCH_3$ (III), and 1-phenyl-1-butene-3-one, $C_6H_5CH{=}CHCOCH_3$ (IV)—both of which are unlikely to result from I or II, for either of those compounds should furnish a ketone with the carbonyl in position 2. Moreover, both III and IV are definitely excluded by the properties of their derivatives. There still remained the possibility of the ketone being the unknown 1-phenyl-3-butene-2-one, $C_6H_5CH_2COCH{=}CH_2$ (V), but this is also excluded because vinylalkyl ketones form characteristic semicarbazide-semicarbazones and they are easily hydrogenated to ethyl-

alkyl ketones. The ketone resulting from the saponification of the diacetoxy derivative I or II does not hydrogenate like an unsaturated compound. The hydrogenation proceeds slowly, and when the required volume of hydrogen is absorbed the product is a mixture consisting of the unchanged ketone, which may be isolated as the semicarbazone, and products of deep-seated hydrogenation. It may be concluded, therefore, that the ketone does not contain an unsaturated linkage but probably a cyclic structure in the side chain. Oxidation would be expected to settle the question whether there were one or two points of attachment to the benzene ring. In the first case benzoic acid would result; in the second, phthalic acid. Permanganate oxidation furnished benzoic acid in nearly quantitative yield, thus excluding a double attachment to the benzene ring, and acetic acid was the only other oxidation-product. Hence the ketone of formula $C_{10}H_{10}O$ contains a methyl as well as a phenyl group, and formula V is again excluded.

There is now only one possible structural formula remaining which corresponds to all the facts, namely, 1-phenyl-3-methyl-cyclopropane-2-one, $C_6H_5CH\text{—}CO$ (VI). A compound of this formula would result by ring
$\diagdown\!\diagup$
$HCCH_3$
closure with elimination of water from the hydroxy ketone formed as the intermediate compound on saponification of either I or II. It seems most probable that formula I would best lend itself to dehydration after saponification, owing to the presence of the methylene group adjacent to the phenyl group. Subsequent experience showed that this ring closure does not occur when other allenes are subjected to the series of reactions just described.

The noncrystalline products of the reaction of lead tetraacetate on 1-phenyl-1,2-butadiene probably contain some of the geometric isomer of the crystalline diacetoxy compound, I or II, for on saponification they furnish considerable amounts of the ketone VI. Before saponification a small quantity of the ketone itself is also present, and it was obtained in the lowest-boiling fraction when the noncrystalline products were distilled.

When 1-cyclohexyl-2,3-pentadiene was treated with lead tetraacetate and the products were isolated by method B, no primary crystalline compounds were obtained. A considerable quantity of unchanged hydrocarbon was recovered on distillation of the reaction-product. Acetyl determinations indicated that the higher-boiling constituents of the reaction-product were mixtures. A fraction could be obtained, however, with the acetyl content of a diacetoxycyclohexylpentene, and saponification of this fraction yielded a material with the properties of a hydroxy ketone. On treatment with *p*-nitrophenylhydrazine in boiling ethanol solution, it

yielded a crystalline compound, which on analysis proved to be the osazone that would result from a cyclohexylhydroxypentanone. Therefore, no ring formation had occurred during saponification of the diacetyl derivative, as in the case of 1-phenyldiacetoxybutene.

The reaction between 2,3-pentadiene and lead tetraacetate proceeded in a manner analogous to the one just described. The reaction-products were treated according to method B, but on removal of the solvents considerable quantities of volatile products distilled with them, giving a yellow distillate from which nothing could be isolated. The residue was distilled at low pressure, yielding a fraction with the acetyl content corresponding to a diacetoxypentene. Saponification could be accomplished by boiling with potassium acetate in ethanol solution, but better results were obtained by boiling with ethanolic hydrochloric acid. The yellow solution was then distilled at atmospheric pressure. An aliquot of the yellow distillate, when treated with *p*-nitrophenylhydrazine, yielded a crystalline derivative which from analysis was shown to be the *p*-nitrophenylosazone corresponding to a hydroxypentanone.

Another aliquot of the distillate was treated with semicarbazide hydrochloride and furnished the disemicarbazone of a pentandione.

The volatile saponification-product of the diacetoxy derivative therefore consists of a mixture of hydroxy ketone and its oxidation-product, the diketone.

When pyrethrone was treated with lead tetraacetate, the reaction was very rapid. The product was isolated by method B, and from it nearly half of the pyrethrone employed was recovered unchanged on distillation. The remaining portion was a high-boiling viscous resin, which on saponification yielded no ketonic product. Its cyclopentenone component seems to be more susceptible to the action of lead tetraacetate than is the side chain and undergoes deep-seated decomposition.

EXPERIMENTAL

1-Phenyldiacetoxybutene (I or II). A solution of 5.9 g. of 1-phenyl-1,2-butadiene (3) in 40 cc. of glacial acetic acid was treated with 23 g. of lead tetraacetate, which was added in several portions. The temperature was maintained at 50–55°, and the suspension was agitated until the reaction was complete. The solution was concentrated under reduced pressure and then diluted with water, and the reaction-product was extracted with ether (method A). The ethereal solution was washed with water and then with sodium bicarbonate solution, dried, and the solvent removed, leaving a sirupy residue which promptly crystallized in part.

The crystalline reaction-product, consisting of heavy colorless prisms, was separated from the mother liquor by filtration on silk and washed with petroleum ether. The yield was 4.3 g. It was recrystallized from ligroin and melted at 73–74°.

Anal. Calc'd for $C_{14}H_{16}O_4$: C, 67.74; H, 6.48; 2 CH_3CO, 34.6.
Found: C, 67.99; H, 6.41; CH_3CO, 36.0.

The liquid portion of the reaction-products (4.6 g.) was distilled at 10 mm. pressure, yielding 0.45 g., b.p. 75–100°; 1.1 g., b.p. 125–135°, and 2.25 g., b.p. 140–160°. The highest-boiling fraction yielded a small quantity of the crystalline reaction-product melting at 73°, which was isolated by filtration and washing with petroleum ether. The remaining liquid product was analyzed for acetyl.

Anal. Calc'd for $C_{14}H_{16}O_4$: 2 CH_3CO, 34.6. Found: CH_3CO, 28.7.

Hydrogenation of 1-phenyldiacetoxybutene. Two grams of substance in about 15 cc. of glacial acetic acid was hydrogenated with platinum oxide catalyst, and absorbed 350 cc. of hydrogen in 35 minutes (calc'd for H_2, 366 cc.). The reaction-product was isolated by dilution of the acetic acid solution with water and extraction with ether. The ether residue was a mixture, which, when distilled at 9 mm., separated into two fractions, a small quantity of material of low but indefinite boiling point and a higher-boiling fraction. The latter was redistilled, yielding 1.5 g. of liquid boiling at 145–146° (9 mm.). Analysis indicated it to be *1*-phenyldiacetoxybutane.

Anal. Calc'd for $C_{14}H_{18}O_4$: C, 67.20; H, 7.21.
Found: C, 67.68; H, 7.53.

The low-boiling fraction appears from analysis to consist of more completely hydrogenated products.

Anal. Found: C, 82.64; H, 12.00.

Saponification of 1-phenyldiacetoxybutene (I or II). One gram of 1-phenyldiacetoxybutene was dissolved in 10 cc. of 90% ethanol containing 1.2 g. of potassium acetate, and the solution was boiled under reflux for 5 hours. The solution was then diluted with water and extracted with ether. The ethereal solution was washed with water to remove the ethanol, and dried. The solvent was removed, and the residue (0.7 g.), on standing, deposited a small quantity of crystals, which were separated by dissolving the liquid portion in petroleum ether. The crystalline material (0.15 g.) was identified as starting material. The liquid portion, after removal of the solvent, yielded on distillation 0.35 g. of product boiling at about 80° (0.7 mm.).

The semicarbazone was prepared in the usual manner in pyridine aqueous ethanol solution. The crystalline material that separated in a short time was recrystallized from methanol; it melted at 202–203°.

Anal. Calc'd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.44; N, 20.68.
Found: C, 65.10; H, 6.45; N, 20.47.

The *p*-nitrophenylhydrazone was prepared by adding 0.1 g. of distillate in 1 cc. of alcohol to 0.1 g. of *p*-nitrophenylhydrazine hydrochloride in 1 cc. of water. Crystallization began at once, and the crystals, after standing for some time, were removed by filtration and washed with 50% ethanol. The substance, when recrystallized from about 4 cc. of ethanol, melted at 175–176°; yield, 0.16 g.

Anal. Calc'd for $C_{16}H_{15}N_3O_2$: C, 68.32; H, 5.38; N, 14.94.
Found: C, 68.35; H, 5.23; N, 15.39.

In a second experiment the saponification of the 1-phenyldiacetoxybutene was accomplished completely by increasing the boiling time, and the reaction-product was converted directly into the semicarbazone. Two and five-tenths grams of the diacetoxy compound in 25 cc. of 90% ethanol containing 3 g. of potassium acetate was boiled for 10 hours under reflux. Two grams of pyridine and 2.5 g. of semicarbazide hydrochloride in 3 cc. of water were added to the solution. The separated potassium chloride was not removed, but the reaction-mixture was allowed to stand overnight, after which time the crystallization was complete. The solid material was removed by filtration and washed with a little ethanol. The salts were removed by washing with water, leaving the insoluble semicarbazone. The ethanolic mother liquor

furnished a small quantity of crystalline material on dilution with water, and this was combined with the main portion, and the whole washed with ether. The ether washings, on evaporation, yielded only a trace of residue, which crystallized on seeding with the starting material. The crude semicarbazone, when recrystallized from methanol, melted at 202–203°. The yield was 1.7 g.

The fractions (b.p. 100–110° and 140–160°) obtained on distillation of the non-crystalline products of the reaction of lead tetraacetate with 1-phenyl-1,2-butadiene also yielded the semicarbazone just described.

One and one-tenth grams of the distillate (b.p. 100–110°) was boiled for 7 hours with 1.2 g. of potassium acetate in 10 cc. of 90% ethanol, and the reaction-mixture, when treated as just described for the preparation of the semicarbazone, yielded 0.22 g., m.p. 203–205°.

Two grams of the fraction boiling at 140–160° treated in the same manner yielded 0.4 g. of the same semicarbazone.

Hydrolysis of ketone semicarbazone to 1-phenyl-3-methylcyclopropane-2-one (VI). Six-tenths gram of the semicarbazone was suspended in 10 cc. of water containing 1.2 g. of oxalic acid in a flask equipped for steam distillation, and a rapid current of steam was passed through the suspension. When the reaction was complete, as shown by the disappearance of the solid material, the combined distillates from three reactions were extracted with ether, the solution was dried, and the solvent removed. The residue on distillation yielded 1.0 g. of yellow liquid, b.p. 110–111° (10 mm.).

Anal. Calc'd for $C_{10}H_{10}O$: C, 82.14; H, 6.85.
Found: C, 80.67; H, 6.73.

The 2,4-dinitrophenylhydrazone was prepared by dissolving 0.1 g. of the compound in 10 cc. of ethanol containing 0.12 g. of 2,4-dinitrophenylhydrazine and adding a few drops of concentrated hydrochloric acid in a little ethanol to the boiling solution. The hydrazone separated at once and was removed by filtration. It melted at 201–202°; yield, 0.16 g.

Anal. Calc'd for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.29.
Found: C, 58.52; H, 4.16.

Hydrogenation of the ketone. When the ketone was shaken in the presence of platinum oxide catalyst in a hydrogen atmosphere in the usual manner, the reaction was very slow. After 1.5 hours, 0.45 g. absorbed 80 cc., or about 1 equivalent, of hydrogen. The reaction-product, which was isolated by dilution of the ethanol solution with water and extraction with ether, weighed 0.5 g. The material, however, was a mixture containing about 50% of unchanged ketone. Two-tenths gram of the reaction-product yielded 0.11 g. of semicarbazone by the usual procedure, which after recrystallization from ethanol melted at 205–206°, and was identified by the mixture melting point (204–205°) as the semicarbazone of the original ketone.

Two-tenths gram of the material yielded 0.15 g. of 2,4-dinitrophenylhydrazone, which after one recrystallization from ethanol melted at 198–200° and was identified by the mixture melting point (201–202°) as the 2,4-dinitrophenylhydrazone of the original ketone.

Permanganate oxidation of the ketone. One and three-tenths grams of the ketone was suspended in 130 cc. of water, and 4.5 g. of potassium permanganate was added in several portions to the rapidly stirred suspension at room temperature. Finally, the reaction-mixture was boiled for a few minutes and the manganese dioxide was removed by filtration. A slight excess of permanganate in the filtrate was decomposed with a little oxalic acid and the alkaline solution filtered clear. It was then concentrated to 15–20 cc. under reduced pressure. On addition of dilute sulfuric

acid, a voluminous precipitate was obtained, which was removed and recrystallized from water. The yield was 0.8 g. The product melted at 122–123°, and a mixture of it with benzoic acid also melted at the same temperature.

Anal. Calc'd for $C_7H_6O_2$: Mol. wt., 122.

Found: Equiv. wt. (titration), 128.

The filtrate from the benzoic acid was distilled with steam, and the 150 cc. of distillate was neutralized with potassium hydroxide and evaporated to dryness. The dry salt weighed 0.9 g. Four-tenths gram of the salt, when boiled with 1.2 g. of *p*-toluidine and 0.4 g. of concentrated hydrochloric acid, furnished 0.2 g. of a product that was identified as acetyl-*p*-toluidide by the mixture melting point with authentic material (148°).

Reaction of lead tetraacetate with 1-cyclohexyl-2,3-pentadiene. Seven and five-tenths grams of 1-cyclohexyl-2,3-pentadiene (4) in 25 cc. of glacial acetic acid was warmed with 23 g. of lead tetraacetate for four hours with constant stirring, after which time the reagent was consumed. The acetic acid solution was treated according to method B by mixing with 150 cc. of absolute ether, filtering after the lead acetate had crystallized, and removing the solvents under reduced pressure. The residue was dissolved in ether, which was extracted with a small quantity of water, and then with dilute sodium bicarbonate solution. The dried solution was evaporated, leaving 10.4 g. of liquid residue. On distillation at 0.7 mm., 3.5 g. of the unchanged 1-cyclohexylpentadiene was recovered, b.p. 78–82°. This was followed by an intermediate fraction of 2.3 g. boiling at 82–90° and a third fraction of 2.0 g. boiling at 90–150°.

According to its acetyl content, the third fraction consisted largely of the diacetoxy addition-product.

Anal. Calc'd for $C_{15}H_{24}O_4$: 2 CH_3CO, 32.1. Found: CH_3CO, 29.9.

Saponification of the fraction boiling at 90–150°. The distillate was boiled for 4 hours with 15 cc. of 90% ethanol and 2 g. of potassium acetate. The reaction-product was isolated by dilution with water, extraction with ether, and washing the ethereal solution with water to remove the ethanol. On evaporation of the dried solution an oily residue was obtained, which reduced Fehling's solution strongly. On distillation it yielded 1.3 g. of material boiling at 80–120° (0.7 mm.).

p-*Nitrophenylosazone.* Two-tenths gram of the distillate in 5 cc. of ethanol was boiled for a few minutes with 0.3 g. of *p*-nitrophenylhydrazine hydrochloride, yielding 0.1 g. of red crystals, which were almost insoluble in the usual solvents. When recrystallized from nitrobenzene, this material melted at 278° after shrinking at 270°. The analysis indicates that it is the osazone derived from cyclohexylhydroxypentanone.

Anal. Calc'd for $C_{23}H_{28}N_6O_4$: C, 61.06; H, 6.20.

Found: C, 60.92; H, 6.01.

No crystalline semicarbazone was obtained from another portion of the product.

Reaction of lead tetraacetate with 2,3-pentadiene. A solution of 6 g. of 2,3-pentadiene (5) in 40 cc. of acetic acid was placed in a closed flask equipped with stirring mechanism and reflux condenser, 40 g. of lead tetraacetate added, and the suspension agitated at 35–40° for 4 hours or until the reagent had been used up. The reaction-product was isolated by method B. The distilled acetic acid was bright yellow and contained volatile reaction-products which were not isolated. The residue was freed from traces of lead acetate and acetic acid by the process already described, and then distilled and divided into 0.75 g. of fraction I, b.p. 55–80° (7 mm.), and 1.58 g. of fraction II, b.p. 80–105° (7 mm.).

Anal. Calc'd for $C_9H_{14}O_4$: 2 CH_3CO, 46.2.

Found: CH_3CO, fraction I, 36.7; fraction II, 44.3.

The higher-boiling fraction was boiled for 4 hours in 15 cc. of 90% ethanol containing 1.8 g. of potassium acetate. Three cubic centimeters of the resulting solution was boiled with about the same volume of a saturated ethanol solution of 2,4-dinitrophenylhydrazine containing a little hydrochloric acid. The separated crystalline product, when recrystallized from a large volume of acetic acid, melted at 283°. The analysis indicated it to be the 2,4-dinitrophenylosazone derived from a hydroxypentanone.

Anal. Calc'd for $C_{17}H_{16}N_8O_8$: C, 44.33; H, 3.48.
Found: C, 44.57; H, 3.56.

The remainder of the solution, when treated with semicarbazide hydrochloride and pyridine, yielded a small quantity of crystalline product of melting point 258–260°, which was identical with the disemicarbazone obtained in the following experiment.

The reaction of lead tetraacetate with 2,3-pentadiene was repeated, and 1.3 g. of the fraction of the reaction-product corresponding to the above fraction II was saponified by boiling for 2 hours with 10 cc. of ethanol containing 1 cc. of concentrated hydrochloric acid and 1 cc. of water. The yellow solution was distilled at atmospheric pressure and 9 cc. of distillate collected. Three cubic centimeters of the distillate, when mixed with an aqueous solution of 0.35 g. of *p*-nitrophenylhydrazine, gave an orange crystalline reaction-product, which was removed by filtration and washed with ethanol. It was almost insoluble in the usual reagents, but when recrystallized from nitrobenzene it melted at 285° after softening at 270°. The analysis indicates that it is probably the osazone derived from a hydroxypentanone.

Anal. Calc'd for $C_{17}H_{18}N_6O_4$: C, 55.13; H, 4.86.
Found: C, 57.64; H, 5.16.

Another aliquot of 3 cc. of the distillate, on treatment with semicarbazide hydrochloride, furnished a crystalline derivative, almost insoluble in the usual solvents, and melting at 257–258°. The analysis agreed for the disemicarbazone of a pentandione.

Anal. Calc'd for $C_7H_{14}N_6O_2$: C, 39.25; H, 6.54.
Found: C, 39.74; H, 6.59.

The compound was identical with the disemicarbazone obtained by potassium acetate hydrolysis as shown by the mixture melting point (256–257°).

It seems likely, from the results obtained, that saponification of the diacetoxy compound by either method results in a mixture of *alpha*-hydroxy ketone and the *alpha*-diketone formed from it by oxidation. Both compounds would furnish an osazone and the latter a disemicarbazone.

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[CONTRIBUTION NO. 31 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

THE ACTION OF FORMALDEHYDE ON *meta*-NITROPHENOL

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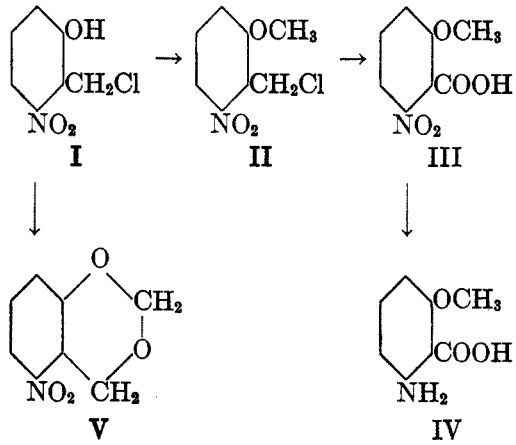
Although the literature contains many references to the reaction of formaldehyde with *o*- and *p*-nitrophenols, a study of the *m*-isomer has received little attention. A German patent (1) describes the preparation of 2,2′-dinitro-4,4′-dihydroxydiphenylmethane from *m*-nitrophenol, although we were unable to duplicate this claim. More recently, Mehta and Ayyar (2) obtained 5-nitro-1,3-benzodioxane from the *m*-substituted phenol.

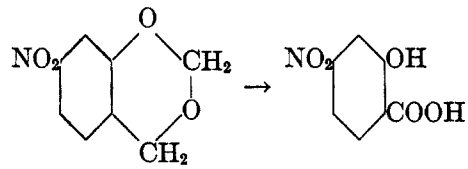
Under mild conditions the first product of the phenol-formaldehyde condensation is often a hydroxybenzyl alcohol or, if the reaction is carried out in hydrochloric acid medium, a hydroxybenzyl chloride. In some cases, such as *p*-nitrophenol (3) or salicylic acid (4), the benzyl chloride may be isolated in substantial yield. It was of interest not only to repeat these experiments using *m*-nitrophenol, but also to add to our limited knowledge of the position taken by a third substituent in this *m*-isomer, since the two substituents present oppose each other in their directing ability.



In our studies two products were obtained from *m*-nitrophenol. The first, 2-hydroxy-6-nitrobenzyl chloride, I, resulted from the action of

methylal and hydrochloric acid at 37–38°. Since this compound resinifies very easily, it was stabilized by methylation with diazomethane to give 2-methoxy-6-nitrobenzyl chloride, II, which on oxidation with potassium permanganate gave 2-methoxy-6-nitrobenzoic acid, III. Reduction of the latter produced 2-methoxy-6-aminobenzoic acid, IV. As a further method of structural proof, I was converted into 5-nitro-1,3-benzodioxane, V, by a method similar to that employed by Mehta and Ayyar (2) in producing the same compound from *m*-nitrophenol.

The second product obtained from *m*-nitrophenol, by the action of formaldehyde and sulfuric acid at 40°, was 7-nitro-1,3-benzodioxane, VI. This compound, on oxidation with potassium permanganate in acetic acid solution, gave the known 2-hydroxy-4-nitrobenzoic acid, VII. As an additional proof of structure, VII was converted into the ethyl ester which agreed in melting point with that of ethyl 2-hydroxy-4-nitrobenzoate.



VI VII

EXPERIMENTAL

Preparation of 2-hydroxy-6-nitrobenzyl chloride. A mixture of 50 g. of *m*-nitrophenol, 400 cc. of concentrated hydrochloric acid and 150 g. of methylal (b.p. 42–46°) in a three-necked, round-bottomed flask was heated under reflux with stirring at 37–38° while hydrogen chloride gas was continually passed through the reaction-mixture. After 24 hours some solid began to separate and the amount increased up to 120 hours, at which point the reaction was stopped. The reddish-yellow solid was separated by decantation or by filtration through sharkskin filter paper. After washing several times with water and then stirring in several portions of benzene, there remained 17–25 g. of the crude, yellow benzyl chloride, m.p. 130–140° with decomposition. For additional purification, this solid was taken up in a large quantity of benzene heated to not over 38°, and recrystallized by evaporation of the solvent with an electric fan. The yield of this purer, light yellow product, m.p. 142–143° with decomposition, was from 3 to 10 g. (5 to 15%).

Anal. Calc'd for $C_7H_6ClNO_3$: Cl, 18.93; mol. wt., 187.5.

Found: Cl, 18.93, 18.75; mol. wt. (cryoscopic, acetic acid), 194, 201, 198.

2-Methoxy-6-nitrobenzyl chloride. Diazomethane, 6.6 g., was generated from nitrosomethylurea (5) and dissolved in about 200 cc. of ether at 0°. This ethereal solution, kept at 0°, was mixed with another ethereal solution, about 100 cc. at 0°, containing 20 g. of the crude benzyl chloride. After 15 minutes the temperature was allowed to rise to that of the room, under which conditions the reaction-mixture was kept for 2 hours. The solid which had formed was then filtered off, and crude 2-methoxy-6-nitrobenzyl chloride was recovered as oily crystals upon evaporating the filtrate to dryness. After being washed with four or five 15-cc. portions of 95%

ethanol, the crystals were almost white. Recrystallization from a water-ethanol mixture gave 5.8 g. of white crystals melting at 65–66°.

Anal. Calc'd for $C_8H_8ClNO_3$: Cl, 17.61; mol. wt., 201.5.

Found: Cl, 17.53, 17.41; mol. wt. (cryoscopic, acetic acid), 207, 204.

2-Methoxy-6-nitrobenzoic acid. The methoxy chloride, 2 g., and 6 g. of potassium hydroxide were dissolved in 60 cc. of water. This solution was heated on a steam-bath while 6–10 g. of potassium permanganate was added gradually over a period of 30 minutes. After an additional hour of heating, the manganese hydroxide was filtered off and the filtrate was acidified with hydrochloric acid. Upon cooling, a white solid separated. After one crystallization from water, 0.9 g. of an almost white product, melting at 180–181°, was obtained [Roberts, Wiles, and Kent (6) give 180°].

Anal. Calc'd for $C_8H_7NO_5$: N, 7.11; neut. equiv., 197.

Found: N, 6.91, 7.00; neut. equiv., 202, 207.

2-Methoxy-6-aminobenzoic acid.[1] Reduction of the nitro acid was accomplished catalytically in absolute alcohol using Raney catalyst and hydrogen at 35 lbs. (2.4 atmos.) pressure. From 1 g., there was obtained about 1 g. of a crude product which after crystallization from water four times melted at 85° [Roberts and co-workers (6) give 87°].

Anal. Calc'd for $C_8H_9NO_3$: N, 8.38. Found: N, 8.37, 8.46.

5-Nitro-1,3-benzodioxane.[1] A solution of 1 g. of 2-hydroxy-6-nitrobenzyl chloride in 3 cc. of U. S. P. 40% formaldehyde and 15 cc. of concentrated hydrochloric acid was heated under reflux slowly to 100° for about 1 hour. The temperature was then raised to 140° where it was held for another hour. After cooling, the supernatant liquid was decanted from the reddish-brown viscous mass. This product was washed with a little water, and then extracted with ether. Upon evaporation, about 0.04 g. of a yellow solid was obtained. Crystallization from an ethanol-water mixture gave colorless needles, m.p. 77°.

Anal. Calc'd for $C_8H_7NO_4$: N, 7.73. Found: N, 7.70, 7.65.

A mixed melting point with a sample of 5-nitro-1,3-benzodioxane prepared by Mehta and Ayyar's method (2) gave no appreciable depression.

Preparation of 7-nitro-1,3-benzodioxane. A solution of 20 g. of *m*-nitrophenol in 25 cc. of 40% formaldehyde, prepared by gentle warming, was cooled to 10°. In a round-bottomed flask equipped with a stirrer, 60 cc. of a 3:1 sulfuric acid-water mixture was cooled to 10°. The formaldehyde solution was then added gradually over a period of 5 minutes to the stirred sulfuric acid so that the temperature did not rise above 42°. Some solid, which formed during this period, remained during three hours more agitation at 38–42°. The reaction-mixture was then poured into water, and an oil separated. This oil was washed with a saturated solution of sodium carbonate until the aqueous solution no longer became red in color. After remaining in the carbonate solution overnight, the oil became semi-solid. This product was washed with a small amount of water, and then crystallized from water in the form of long, white, glistening needles, melting at 90.5°; yield, 2.3 g. (9%).

Anal. Calc'd for $C_8H_7NO_4$: C, 53.03; H, 3.87; N, 7.73; mol. wt., 181.

Found: C, 53.26, 52.88; H, 3.98, 4.03; N, 7.61, 7.57, 7.63; mol. wt. (cryoscopic, benzene), 183, 182, 181.

2-Hydroxy-4-nitrobenzoic acid. 7-Nitro-1,3-benzodioxane, 1 g., was dissolved in 35 cc. of glacial acetic acid, and 5 g. of potassium permanganate and 55 cc. of water

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[1] We are indebted to Mr. Geo. W. Parker for this synthesis.

were added. This mixture was refluxed for about 4 hours, at the end of which time clarification was accomplished by bubbling sulfur dioxide through the mixture. The solution thus obtained was evaporated almost to dryness in a current of air, diluted with about 100 cc. of water, and 7 cc. of concentrated hydrochloric acid was added. The solid, which now completely precipitated, was filtered off, dissolved in hot water and treated with boneblack to remove the color. After filtration, the acid was again precipitated with hydrochloric acid and finally recrystallized from water as fine, slightly yellow needles; yield, 0.2 g. The pure product darkened at 225° and melted at 235° with decomposition [Borsche (7) gives 235° with decomposition].

Anal. Calc'd for $C_7H_6NO_4$: N, 7.65; neut. equiv., 183.
Found: N, 7.73, 7.84; neut. equiv., 185, 184.

The acid, 0.7 g., was esterified as recommended by Borsche (7) to give 0.5 g. of the ethyl ester, m.p. 86–87° (Borsche gives 87°).

SUMMARY

On condensing *m*-nitrophenol with methylal and with formaldehyde, each in acid medium, the directing influence of the hydroxyl group predominates, since moderate yields of 2-hydroxy-6-nitrobenzyl chloride and 7-nitro-1,3-benzodioxane, respectively, were obtained.

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[CONTRIBUTIONS NO. 60 AND 61 FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

A SYSTEM CORRELATING MOLECULAR STRUCTURE OF ORGANIC COMPOUNDS WITH THEIR BOILING POINTS

CORLISS R. KINNEY

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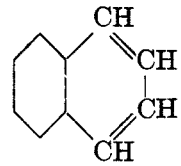
IV. FUSED POLYCYCLIC AROMATIC HYDROCARBONS

The boiling points of the polycyclic aromatic hydrocarbons, including their aliphatic derivatives, may be calculated using the boiling point equation (1), the boiling point numbers given in Parts II (2) and III (3), and two or three additional boiling point numbers characteristic of the various combinations of these rings. Using these b.p.n's. it is possible to calculate the boiling points of 84.7% of the known hydrocarbons in these classes to within ±10°, the average deviation being +0.34°.

The additional b.p.n. characteristic of an aliphatic ring, either saturated or unsaturated, fused to an aromatic ring is 1.5. The boiling point of naphthalene may now be calculated very satisfactorily using the following structure.



Phenylene radical	18.0
Carbon in the alicyclic portion	3.2
Hydrogen in the alicyclic portion	4.0
Double bonds, 2 of the type RCH=CHR	3.8
Conjugation of the double bonds	0.8
Phenyl attached to double bonds (2 × 1.0)	2.0
Six membered alicyclic ring	2.7
Alicyclic ring fused to benzene	1.5
Calculated B.P.N.	36.0
Calculated B.P.	216.9°
Observed B.P.	218.0°

In calculating the boiling point of derivatives of naphthalene the B.P.N. of naphthalene (36.0) is lowered one unit for each hydrogen displaced and the b.p.n. of the group introduced added in. From the B.P.N. thus obtained for the molecule the boiling point is calculated by use of the

boiling point equation or more easily from the data in Table II in Part II (2).

The position taken by the substituent in naphthalene should, in general, make only a small difference in the boiling point and the β-substitution-products would be expected to have the higher boiling point. This is borne out by a comparison of the known boiling points of seven pairs of α,β-substitution-products. In four of the seven cases the β-isomer is higher-boiling, although one of these is only half a degree higher, in two cases the α is higher-boiling and in one case the two isomers have the same recorded boiling point. In view of the latter irregularities it would appear that the boiling points of these isomers should be redetermined carefully, especially the ethyl and isoamyl derivatives, the β-isomers of which have unusually low observed boiling points.

The calculation of the boiling points of α- and β-phenylnaphthalene involves the exaltation of the boiling point caused by attachment of two aryl groups, for which in diphenyl a b.p.n. of 2.5 gave satisfactory results. With the phenylnaphthalenes this value gives a calculated boiling point midway between the observed boiling points of the α- and β-isomers, which may be considered satisfactory for the present.

Naphthyl	35.0
Phenyl	19.0
Attachment of two aryl groups by a single bond	2.5
Calculated B.P.N.	56.5
Calculated B.P.	340.1°
Observed B.P.	
α-isomer	334.0°
β-isomer	345.5°

The boiling point of β,β′-binaphthyl of 452° requires a b.p.n. of 10.0 for the union of two naphthyl groups in the β-position. This is an unusually high exaltation but is of the same order of size as that for *p*-terphenyl which required a b.p.n. of 9.0.

The boiling points of other aromatic polycyclic hydrocarbons containing aliphatic rings may be calculated using the b.p.n. of 1.5 for the fusing of the alicyclic ring to the aromatic. These calculations are given in Table I. For those hydrocarbons in which rings are formed by linking aryl groups by single bonds or unsubstituted carbon chains the appropriate b.p.n. must be included for those factors [see Part III (3)]. Fluorene, 9,10-dihydroanthracene, and 9,10-dihydrophenanthrene are examples of this class.

A comparison of the boiling points of the polycyclic aromatic hydrocarbons containing only aromatic nuclei shows a marked difference between naphthalene and the higher members. This is shown by the difference in B.P.N's. for these hydrocarbons. The B.P.N. of naphthalene

has been calculated to be 36.0 of which 18.0 units were due to the introduction of the second ring. To account satisfactorily for the boiling points of the higher members of this series containing three or more aromatic rings, a b.p.n. of 23.0 must be added for each additional ring introduced beginning with naphthalene. Since B.P.N's. may be compared directly this indicates a marked alteration in the difference between the B.P.N's. of benzene and naphthalene as compared with the difference between the B.P.N's. of the higher members of the series. These differ-

TABLE I

THE CALCULATED AND OBSERVED BOILING POINTS OF THE FUSED POLYCYCLIC AROMATIC HYDROCARBONS

HYDROCARBON	B.P.N. (CALC'D)							B.P. (CALC'D)	B.P. (OBS'D)	DEVIATION, °C.
Indane	18 +	2.5 +	6 +	2.5 +			1.5 = 30.5	175.3	176.5	+1.2
Indene	18 +	2.5 +	4 +	2.5 +	1.9 +	1.0 +	1.5 31.3	182.3	182.4	+0.1
Tetralin	18 +	3.2 +	8 +	2.7 +			1.5 33.4	198.1	206.4	+8.4
Tetrahydroacenaphthene	17 +	4.8 +	11 +	5.2 +			3.0 41.0	250.6	254.0	+3.4
Acenaphthene	34 +	1.6 +	4 +	2.5 +			1.5 43.6	267.0	277.5	+10.5
Acenaphthylene	34 +	1.6 +	2 +	2.5 +	1.9 +	2.0 +	1.5 45.5	278.6	270.0	−8.6
Fluorene	36 +	0.8 +	2 +	2.5 +	2.5 +	1.8 +	1.5 47.1	288.1	295.0	+6.9
9,10-Dihydroanthracene	36 +	1.6 +	4 +	2.7 +	1.8 +	1.8 +	1.5 49.4	301.4	305.0	+3.6
9,10-Dihydrophenanthrene	36 +	1.6 +	4 +	2.7 +	2.5 +	1.8 +	1.5 50.1	305.4	313.0	+7.6
Anthracene	34 + 23						57.0	342.7	342.3	−0.4
Phenanthrene	34 + 23						57.0	342.7	340.0	−2.7
Chrysene	32 + 23	+ 23					78.0	440.3	448.0	+7.7
Picene	32 + 23	+ 23 + 23					99.0	521.7	520.0	−1.7

ences indicate a marked change in the structure of the higher aromatic hydrocarbons as compared with that of naphthalene. In calculating the boiling points of the higher members, the B.P.N. of naphthalene may be considered to be the fundamental unit which is altered by the introduction of additional aromatic rings, the amount of change being represented by 23.0 units instead of 18.0. In calculating the B.P.N's. of the higher members, the B.P.N. of the naphthalene nucleus is lowered two units for the two hydrogen atoms displaced by each additional aromatic ring introduced. Calculations of the boiling points of the four hydrocarbons whose boiling points have been determined (anthracene, phenanthrene, chrysene, and picene) appear in Table I.

The B.P.N's. of the alkyl derivatives of the parent hydrocarbons given in Table I may be calculated from the B.P.N's. of the parent hydrocarbon by lowering the B.P.N. one unit for each hydrogen atom displaced and adding the normal b.p.n. of the group introduced. The boiling point is then obtained in the usual way from the B.P.N. of the molecule. The boiling point of retene, 1-methyl-7-isopropyl phenanthrene, may be calculated as an example.

Phenanthrene, less two hydrogen atoms	55.0
Methyl	3.8
Isopropyl	8.65
Calculated B.P.N.	67.45
Calculated B.P.	393.8°
Observed B.P.	394.0°

The hydrocarbons of the types included in this paper whose boiling points differ from the calculated by more than ±10° are given in Table II.

TABLE II

THE CALCULATED AND OBSERVED BOILING POINTS OF THOSE HYDROCARBONS WHOSE OBSERVED BOILING POINTS DEVIATE FROM THE CALCULATED BY ± 10°

HYDROCARBON	B.P.N. (CALC'D)					B.P. (CALC'D)	B.P. (OBS'D)	DEVIATION, °C.
1,4-Dimethyl-6-ethyl-naphthalene	33 + 7.6 + 6.6				= 47.2	288.7	300.0	+11.3
2-(3-Methylbutyl)-naphthalene	35 + 11.2 +	3.05			49.25	300.6	290.0	−10.6
1-Methylindane	18 + 9.9 + 3.8 +		1.5		33.2	196.6	182.5	−14.1
2-Methylindane	18 + 9.9 + 3.8 +		1.5		33.2	196.6	184.0	−12.6
2-Methylindene	18 + 7.9 + 3.8 +	3.3	+ 1.5		34.5	206.2	184.5	−21.7
1,4-Dihydronaphthalene	18 + 11.9 +	1.9	+ 1.5		33.3	197.4	212.0	+14.6
Acenaphthene	34 + 8.1 +		1.5		43.6	267.0	277.5	+10.5
Hexahydrofluorene	18 + 22.3 +		3.0		41.8	255.7	245.0	−10.7
9-Methylfluorene	36 + 4.3 + 3.8 +		5.0		49.1	299.7	320.0	+20.3

Many of these boiling points appear to be incorrect when compared with the boiling points of similarly constituted hydrocarbons and should be redetermined. On the other hand, it is possible that some of these hydrocarbons need additional b.p.n's. to account for the boiling point given by a particular structure. Acenaphthene is one of these. The recorded boiling point is 10.5° higher than the calculated, and if this boiling point is correct an additional b.p.n. should be included to account for the higher boiling point given by the acenaphthene structure. However, the observed boiling point of the similarly constituted acenaphthylene is 8.6° lower than the calculated, but possibly is low because the substance decomposes slowly at the boiling point.

V. ALIPHATIC POLYCYCLIC HYDROCARBONS

The calculation of the boiling points of the aliphatic polycyclic hydrocarbons may be made using the b.p.n's. obtained for the simple alicyclic hydrocarbons (2) and the following additional b.p.n's. which account for the various combinations of the rings. The effect upon the boiling point is, in many cases, similar to that of the analogously constituted aromatic polycyclic hydrocarbons, Part IV, and emphasizes the important effect of molecular configuration on the boiling point of compounds.

When two alicyclic rings are attached by a single bond or to the ends of an unsubstituted carbon chain a b.p.n. of 1.5 should be added in obtaining the B.P.N. for the molecule. The presence of alkyl groups on the chain between the rings destroys the effect and the b.p.n. should not be used for these derivatives. This difference is shown by the boiling points of the following related hydrocarbons.

	1,3-DICYCLOHEXYLPROPANE	1,3-DICYCLOHEXYL-2-METHYLPROPANE
Cyclohexyl groups	37.0	37.0
Carbon in the aliphatic chain	2.4	2.4
Hydrogen in the aliphatic chain	6.0	5.0
Methyl group		3.05
Two rings at the end of an unsubstituted chain	1.5	
Calculated B.P.N.	46.9	47.45
Calculated B.P.	286.9°	290.1°
Observed B.P.	289.5°	291.0°

The boiling points of only two spirobicyclic hydrocarbons were found in the literature. They were spiro-4,5-decane and *s*-spirohendecane. By using a b.p.n. of 0.5 for the spiro configuration the calculated boiling points fall within a few tenths of a degree of the observed.

The boiling points of the various fused bi- and tri-cyclic hydrocarbons are calculated in the same general way as those of the monocyclic hydrocarbons described in Part II (2) with the additional rules that all alkyl radicals attached to the rings be assigned the branched chain b.p.n's. and that a b.p.n. of 0.5 be added to the B.P.N. of those derivatives in which there are no carbon atoms between the points of attachment of the rings and 0.5 subtracted from the B.P.N. of those in which there are carbon atoms between the points of attachment. The difference is probably due to the greater symmetry of the former class of compound. By way of example, carene, 3,7,7-trimethylbicyclo [4,1,0]hept-3-ene, which does not have a carbon atom between the points of attachment, has a higher boiling point by 13.7° than the isomeric pinene, 2,7,7-trimethylbicyclo[3,1,1]hept-2-ene. The addition of 0.5 to the B.P.N. of the former compound and the substraction of 0.5 from the latter accounts for the difference fairly well. These boiling points are calculated as follows.

CARENE		PINENE	
7 Carbons in rings	5.6		5.6
7 Hydrogens attached to rings	7.0		7.0
3 Methyl radicals	9.15		9.15
1 3-membered ring	2.1		
1 4-membered ring			2.3
1 6-membered ring	2.7		2.7
1 Double bond, type $R_2C = CHR$,	2.3		2.3
No carbon atom between the points of attachment of the rings	+0.5	A carbon atom between the points of attachment of the rings	−0.5
Calculated B.P.N.	29.35		28.55
Calculated B.P.	166.9°		160.4°
Observed B.P.	168.5°		154.8°

TABLE I

THE CALCULATED AND OBSERVED BOILING POINTS OF THE FUSED ALIPHATIC TRICYCLIC HYDROCARBONS

HYDROCARBON	B.P.N. (CALC'D)		B.P. (CALC'D)	B.P. (OBS'D)	DEVIATION, °C.
Tricyclo-[4,3,0,$1^{6,9}$]-deca-2,7-diene (dicyclopentadiene)	8.0 + 12 + 2.5 + 2.5 + 2.5 + 3.8 − 0.5 =	30.8	178.4	170.0	−8.4
Tricyclo-[4,3,0,$4^{3,4}$]-tridecane (dodecahydrofluorene)	10.4 + 22 + 2.7 + 2.5 + 2.7 + 1.0 =	41.3	252.5	253.0	+0.5
Decahydrofluorene	10.4 + 20 + 2.7 + 2.5 + 2.7 + 2.8 + 1.0 =	42.1	257.6	258.0	+0.4
Octahydrofluorene	10.4 + 18 + 2.7 + 2.5 + 2.7 + 6.4 + 1.0 =	43.7	267.6	273.5	+5.9
Tricyclo-[4,4,0,$4^{3,4}$]-tetradecane (tetradecahydrophenanthrene)	11.2 + 24 + 2.7 + 2.7 + 2.7 + 1.0 =	44.3	271.3	272.5	+0.8
Tricyclo-[4,4,0,$4^{3,4}$]-tedradecene-(−?) (dodecahydrophenanthrene	11.2 + 22 + 2.7 + 2.7 + 2.7 + 1.9 + 1.0 =	44.2	270.7	268.5	−2.2
Tricyclo-[4,4,0,$4^{3,4}$]-tetradecadiene(?) (decahydrophenanthrene)	11.2 + 20 + 2.7 + 2.7 + 2.7 + 5.5 + 1.0 =	41.3	252.5	253.0	+0.5

The fused tricyclic hydrocarbons (so-called) may be divided into two classes, those which are actually tricyclic and those which are tetracyclic. The latter hydrocarbons contain a bicyclic ring system with an additional bridge or bond from the outside of one ring to the outside of the other. Apocyclene, tricyclene, and adamantane are examples.

The calculation of the boiling points of the true tricyclic hydrocarbons (excluding the spiro derivatives) may be accomplished using the same b.p.n's. as for bicyclic derivatives. The boiling points of seven hydrocarbons were obtained from the literature and all were well within ±10° of the calculated boiling point. Calculations for these hydrocarbons are given in Table I.

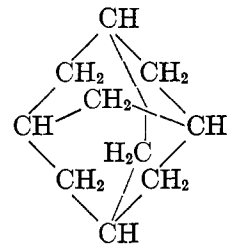
TABLE II

THE CALCULATED AND OBSERVED BOILING POINTS OF THE FUSED ALIPHATIC TRICYCLIC HYDROCARBONS CONTAINING FOUR RINGS

HYDROCARBON	B.P.N. (CALC'D)		B.P. (CALC'D)	B.P. (OBS'D)	DEVIATION, °C.
7,7-Dimethyltricyclo-[2,2,1,$0^{2,6}$]-heptane (apocyclene).....	5.6 + 8 + 6.1 + 2.5 + 2.5 + 2.5 − 1.5 =	25.7	136.2	138.5	+0.6
1,7,7-Trimethyltricyclo[2,2,1,$0^{2,6}$] heptane (tricyclene).....	5.6 + 7 + 9.15 + 2.5 + 2.5 + 2.5 − 1.5	27.75	153.7	153.0	−0.7
4,7,7-Trimethyltricyclo[2,2,1,$0^{2,6}$] heptane.....	5.6 + 7 + 9.15 + 2.5 + 2.5 + 2.5 − 1.5	27.75	153.7	150.5	−3.2

The boiling points of the tricyclic hydrocarbons which actually contain four rings are calculated on the basis of the three largest rings in the molecule using the same b.p.n's. as for the true tricyclic hydrocarbons. The boiling points of only three hydrocarbons were obtained from the literature, but all of these are close to the calculated. The calculations for these compounds appear in Table II.

A very interesting hydrocarbon, adamantane, has been obtained from a petroleum fraction boiling from 190° to 195°. This substance has a melting point in a sealed tube of 268°, but apparently has a vapor pressure equal to 760 mm. at a much lower temperature. Because of the high melting point and other properties the substance was given the highly symmetrical structure



If the boiling point of this structure is calculated on the basis of three rings as before we obtain a value which is too low, but on the basis of four rings the boiling point obtained coincides with the boiling point of the petroleum fraction from which the compound was taken.

10 Carbon atoms	8.0		8.0
16 Hydrogen atoms	16.0		16.0
3 6-membered rings	8.1	4 6-membered rings	10.8
3 Rings containing carbon atoms between the points of attachment	−1.5	4 Rings containing carbon atoms between the points of attachment	−2.0
Calculated B.P.N.	30.6		32.8
Calculated B.P.	176.9°		193.7°
Boiling point of petroleum fraction from which compound was taken			190°–195.0°

In view of the high symmetry of the molecule it may be desirable to calculate the boiling points of such molecules using b.p.n's. for all four rings in the molecule or even possibly an additional b.p.n. as it is possible that the temperature at which the vapor pressure of the molecule reaches 760 mm. is higher than that indicated by the boiling range of the petroleum fraction. The question can best be settled by the synthesis of this hydrocarbon and the determination of its boiling point.

The boiling point of one spiro tricyclic hydrocarbon appears in the literature, that of 6,6-tetramethylenebicyclo[3,1,0]hexane. The boiling point may be calculated using the boiling point number of 0.5 for the spiro configuration.

10 Carbon atoms	8.0
16 Hydrogen atoms	16.0
2 5-membered rings	5.0
1 3-membered ring	2.1
Two rings containing carbon atoms between the points of attachment.	0.5
Spiro configuration of the third ring	0.5
Calculated B.P.N.	32.1
Calculated B.P.	188.4°
Observed B.P.	189.5°

SUMMARIES

IV

B.p.n's. have been obtained to account for the boiling points of the polycyclic aromatic hydrocarbons. For 84.7%, the observed boiling points deviate from the calculated by less than ±10°. The average deviation is +0.34°.

V

The boiling points of the polycyclic aliphatic hydrocarbons may be calculated using the b.p.n's. of the simple alicyclic hydrocarbons together with additional b.p.n's. characteristic of the various combinations of rings.

The boiling points of a total of 78 aliphatic polycyclic hydrocarbons have been calculated and compared with the observed values. The deviation of 91.1% is less than ±10°. The average deviation is −0.34°.

SALT LAKE CITY, UTAH.

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(1) KINNEY, *J. Am. Chem. Soc.*, **60**, 3032 (1938).
(2) KINNEY, *Ind. Eng. Chem.*, **32**, 559 (1940).
(3) KINNEY, *Ind. Eng. Chem.*, in press.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE CHEMISTRY OF VITAMIN E. XXVI.[1] 5-HYDROXY-4,6,7-TRIMETHYLCOUMARAN, 5-HYDROXY-2,2,4,6,7-PENTAMETHYLCOUMARAN, 6-HYDROXY-2,2,5-TRIMETHYL-7,8-BENZOCHROMAN, AND 5-HYDROXY-2,4-DIMETHYL-6,7-BENZOCOUMARON.

LEE IRVIN SMITH, STANLEY WAWZONEK, AND HENRY C. MILLER

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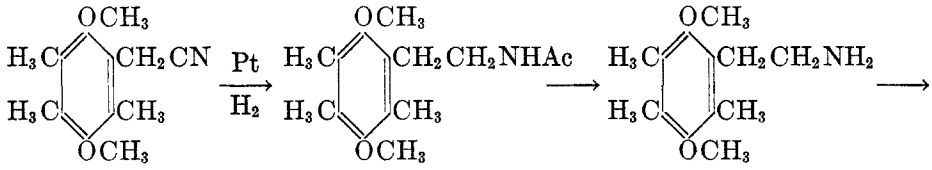
In connection with an investigation of the behavior at the dropping mercury electrode of substances related in structure to the tocopherols, a wide variety of *p*-hydroxy-coumarans and -chromans was needed. Several of these substances, obtained in connection with previous work in the field, were already available, but these did not include enough different types for a general study of the kind contemplated. In particular, the only *p*-hydroxycoumarans available were those which carried only one substituent in the 2-position, and for purposes of comparison it was desired to include in the study coumarans of this type unsubstituted in the 2-position, as well as those carrying two substituents in this position. This paper reports the synthesis of one *p*-hydroxycoumaran, 5-hydroxy-4,6,7-trimethylcoumaran (VI), unsubstituted in the 2-position, and another, 5-hydroxy-2,2,4,6,7-pentamethylcoumaran (XIII), carrying two substituents in the 2-position, as well as a new benzochroman, 6-hydroxy-2,2,5-trimethyl-7,8-benzochroman (XX) and a benzocoumaron, 5-hydroxy-2,4-dimethyl-6,7-benzocoumaron (XXI). The syntheses were planned with a view to using readily available starting materials, and known reaction steps, so that in the final cyclization there could be little doubt as to the size of the resulting heterocyclic ring. Most of the reactions proceeded smoothly and gave good yields, and the methods used appear to be of quite general applicability.

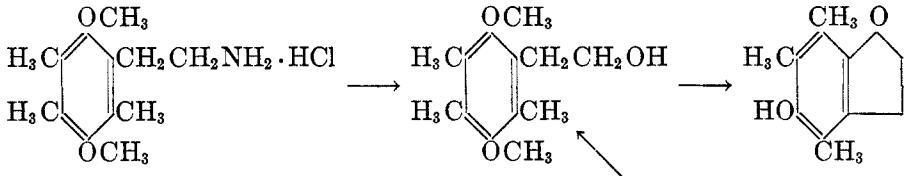
5-Hydroxy-4,6,7-trimethylcoumaran (VI) was prepared by demethylation and cyclization of the carbinol V, which in turn was obtained by two methods, as shown in the chart. In one of these methods the carbinol V was obtained by action of nitrous acid upon the corresponding amine (IV); in this case, although a small amount of the pure carbinol was obtained, the entire crude product of the reaction—a yellow oil—was cyclized to the coumaran VI. In the second method, the carbinol V was obtained

[1] Paper XXV, *Chem. Rev.*, **27**, 287 (1940); XXIV, *J. Am. Chem. Soc.*, **62**, 1869 (1940).

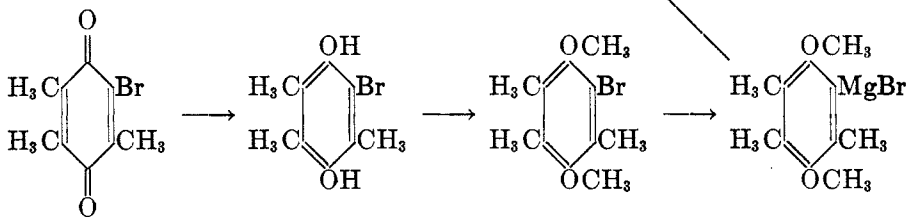
by action of the Grignard reagent X upon ethylene oxide, and from the product of this reaction a good yield of the pure carbinol was easily obtained.



I II III

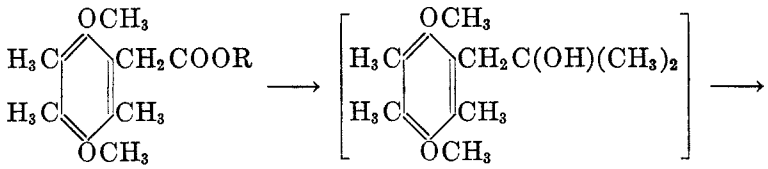


IV V VI



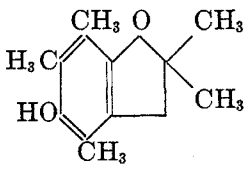
VII VIII IX X

5-Hydroxy-2,2,4,6,7-pentamethylcoumaran (XIII) was synthesized from ethyl 2,5-dimethoxy-3,4,6-trimethylphenylacetate (XII) (1) *via* the carbinol XIIa. The carbinol was obtained as an oil from which no solid could be crystallized. Consequently the crude product was demethylated and cyclized directly to the coumaran XIII.



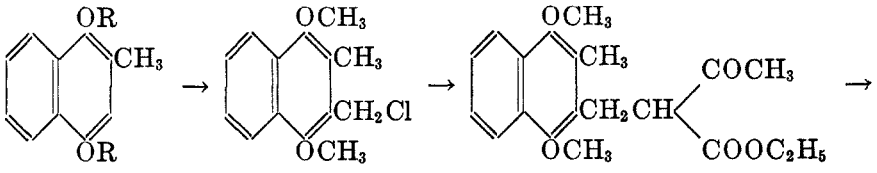
XI, R = H
XII, R = C_2H_5

XIIa



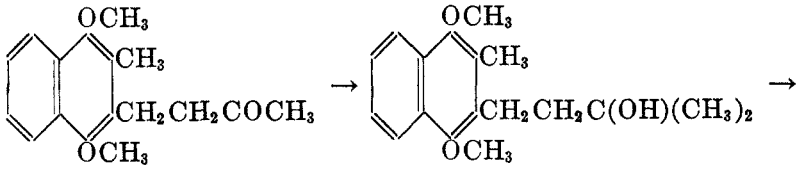
XIII

6-Hydroxy-2,2,5-trimethyl-7,8-benzochroman (XX) was synthesized from 2-methyl-1,4-naphthohydroquinone (XIV) by a series of reactions similar to that employed in previous work (2) for the synthesis of 6-hydroxy-2,2,5,7,8-pentamethylchroman. The steps in the synthesis are shown below.

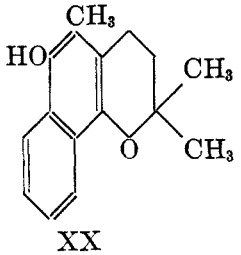


XIV, R = H
XV, R = CH_3

XVI XVII

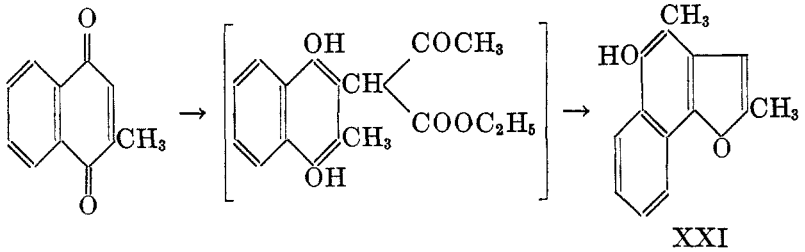


XVIII XIX



XX

5-Hydroxy-2,4-dimethyl-6,7-benzocoumaron (XXI) was synthesized from 2-methyl-1,4-naphthoquinone and acetoacetic ester, using a variant of the method of Smith and MacMullen (1) for the preparation of *p*-hydroxycoumarons.



XXI

EXPERIMENTAL[2]

β-Acetaminoethylpseudocumohydroquinone dimethyl ether (II). 3,6-Dimethoxy-2,4,5-trimethylbenzylcyanide (1) (9.7 g.) was dissolved in acetic anhydride (90 cc.) and the solution was shaken with platinum oxide catalyst (0.25 g.) under forty pounds (2.7 atoms.) of hydrogen for twenty-four hours. Acetic acid was added to dissolve the solid formed in the reaction. The catalyst was filtered off and the filtrate was poured into water. The white precipitate (9.1 g., m.p. 160°) was removed and crystallized from benzene. It formed silky needles which melted at 160–161°.

Anal. Calc'd for $C_{15}H_{23}NO_3$: C, 67.93; H, 8.68.
Found: C, 67.57; H, 8.89.

β-Aminoethylpseudocumohydroquinone dimethyl ether (III). β-Acetaminoethylpseudocumohydroquinone dimethyl ether (II) (9.1 g.) was refluxed with potassium hydroxide (25.0 g.) in methanol (125 cc.) for nine hours. Water (25 cc.) and potassium hydroxide (25 g.) were added and the solution was refluxed for three hours longer. After standing overnight the mixture was poured into water and acidified. Extraction with ether removed 1.53 g. of the starting material (II). Addition of alkali followed by extraction with ether gave a light yellow oil (5.45 g.) which was distilled. The amine was obtained as a colorless liquid which boiled at 170–175° under 20 mm.

Anal. Calc'd for $C_{13}H_{21}NO_2$: C, 69.95; H, 9.42.
Found: C, 69.17; H, 9.50.

Hydrochloride (IV). Passing dry hydrogen chloride through a carbon tetrachloride solution of the above amine (III) precipitated a white hydrochloride, which after one crystallization from a mixture of absolute ethanol and absolute ether melted at 263–265° (decomp.).

Anal. Calc'd for $C_{13}H_{22}ClNO_2$: C, 60.11; H, 8.48.
Found: C, 60.24; H, 8.65.

5-Hydroxy-4,6,7-trimethylcoumaran (VI). To the above amine hydrochloride (IV) (2.65 g.) in 50 cc. of water was added sodium nitrite (1.50 g.), and the resulting solution was heated at 100° until all gas evolution had ceased. The cooled mixture was extracted with ether. Removal of the solvent gave an oily product (2.47 g.) from which only a small amount of the carbinol (V), m.p. 65–70°, could be isolated. When mixed with the carbinol (m.p. 69.5–72°) prepared by the Grignard reaction (see below), the substance melted at 65–70°. The oil was not purified further but was dissolved in acetic acid (10 cc.) containing hydrobromic acid (3 cc., 40%) and the solution was refluxed for four hours. Water was added and the mixture was steam distilled. From the distillate was obtained coumaran VI (0.55 g.), which after one crystallization from petroleum ether (b.p. 60–68°) melted at 144–146°, alone or when mixed with the coumaran prepared from the pure carbinol.

Bromopseudocumoquinone (VII). To a solution of pseudocumoquinone (5.0 g.) in ether (15 cc.) was added slowly liquid bromine (1.8 cc.). Removal of the solvent followed by crystallization of the residue from ethanol gave the bromoquinone (6.07 g.) in bright yellow needles melting at 77–80°. Smith and Johnson (3) report 79–80° as the melting point.

Bromopseudocumohydroquinone (VIII). A solution of pseudocumohydroquinone (24 g.) in ether (600 cc.) was placed in a three-necked flask equipped with a stirrer and condenser. Bromine (9 cc.) was slowly added from a dropping-funnel. After the reaction was complete the solvent was removed under a vacuum. The black crystals were dissolved in ethanol (200 cc.), sodium hydrosulfite (10 g.) was added,

[2] Microanalyses by E. E. Renfrew.

and the mixture was refluxed for forty-five minutes and filtered while hot. The cooled filtrate deposited 27 g. of the hydroquinone, which melted at 172–173° (decomp.). A further 6 g. could be obtained by evaporating the filtrate to 100 cc. Smith and Johnson (3), by reducing bromopseudocumoquinone with stannous chloride and hydrochloric acid, obtained a product which melted at 185° (decomp.). However, the hydroquinone prepared as described above was sufficiently pure for use in the next step.

Bromopseudocumohydroquinone dimethyl ether (IX). This substance was prepared from the hydroquinone using the procedure of Smith and Johnson (3).

3,6-Dimethoxy-2,4,5-trimethylphenylmagnesium bromide (X). To 2.0 g. of magnesium was slowly added (45 minutes) a solution of bromopseudocumohydroquinone dimethyl ether (IX) (10 g.) and ethyl bromide (3.0 cc.) in absolute ether (40 cc.). The mixture was refluxed throughout the course of the reaction.

β-Hydroxyethylpseudocumohydroquinone dimethyl ether (V). The above Grignard reagent was cooled (salt-ice mixture and flask fitted with a reflux condenser containing water below 10°) and to it was added dry ethylene oxide (15 g.) over a period of twenty minutes. The cooling bath was removed and the mixture was allowed to reflux spontaneously for forty-five minutes, then heat was applied until the mixture set to a thick transparent gel. Iced sulfuric acid (25%) was added and unchanged bromopseudocumohydroquinone dimethyl ether (1.25 g.) was removed by steam distillation. The residue was extracted with ether and the solvent was evaporated. The residual yellow oil (5.27 g.) crystallized when its solution in petroleum ether was cooled. The carbinol weighed 2.70 g. and melted at 69.5–72°. After several crystallizations from a mixture of ether and petroleum ether it melted at 73.5–75°.

Anal. Calc'd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.93.
Found: C, 69.86; H, 8.51.

5-Hydroxy-4,6,7-trimethylcoumaran (VI). β-Hydroxyethylpseudocumohydroquinone dimethyl ether (V) (1.0 g.) was dissolved in acetic acid (10 cc.) containing hydrobromic acid (3.25 cc., 40%) and the solution was refluxed for three hours. Water was added and the coumaran was removed by steam distillation. The product weighed 0.5 g. and melted at 144–146°. After crystallization from petroleum ether (b.p. 60–68°) it formed white needles which melted at 145–146°.

Anal. Calc'd for $C_{11}H_{14}O_2$: C, 74.16; H, 7.86.
Found: C, 74.42; H, 8.26.

Ethyl 3,6-dimethoxy-2,4,5-trimethylphenylacetate (XII). 3,6-Dimethyoxy-2,4,5-trimethylphenylacetic acid (1) (XI) (1.74 g.) was dissolved in absolute ethanol (50 cc.) containing concentrated sulfuric acid (1 cc.). The solution was refluxed for eight hours, then was poured into water and the product filtered off. The ester was purified by steam distillation. It weighed 1.2 g. and melted at 79–80°.

Anal. Calc'd for $C_{15}H_{22}O_4$: C, 67.67; H, 8.27.
Found: C, 67.69; H, 8.28.

5-Hydroxy-2,2,4,6,7-pentamethylcoumaran (XIII). A solution of ethyl 3,6-dimethoxy-2,4,5-trimethylphenylacetate (XII) (1.2 g.) in absolute ether (10 cc.) and dry benzene (20 cc.) was refluxed with excess methylmagnesium iodide (0.02 moles in 40 cc. of ether) for ten hours. After decomposition in the usual way, removal of the ether left an oil which could not be crystallized. The oil was dissolved in acetic acid (10 cc.) and hydrobromic acid (10 cc., 40%) and the solution was refluxed for three hours. Addition of water precipitated the coumaran as a white solid (0.75 g.), which after crystallization from petroleum ether (b.p. 60–68°) melted at 125–126.5°.

Anal. Calc'd for $C_{13}H_{18}O_2$: C, 75.72; H, 8.74.
Found: C, 75.57; H, 8.63.

1,4-Dimethoxy-2-methylnaphthalene (XV). The following directions are a modification of those given by Ansbacher, Fernholz, and Dolliver (4). In a flask fitted with reflux condenser and stirrer were placed 1,4-dihydroxy-2-methylnaphthalene (5) (8.7 g.), absolute methanol (50 cc.), and dimethyl sulfate (63 g.). The mixture was heated to the boiling point, heating was then discontinued and a hot solution of potassium hydroxide (60 g.) in methanol (300 cc.) was added in portions as rapidly as possible without causing the material to be thrown out through the condenser. After the addition of the alkali was complete the mixture was boiled for one-half hour and then steam distilled. Ether extraction of the distillate gave an oil which solidified upon cooling. After crystallization from petroleum ether (b.p. 60–68°) the product formed a white solid (6.38 g.) which melted at 35–36°. Ansbacher, Fernholz, and Dolliver report the melting point 48–49° for a product that had been distilled before crystallization.

1,4-Dimethoxy-2-methyl-3-chloromethylnaphthalene (XVI). 1,4-Dimethoxy-2-methylnaphthalene (XV) (32 g.), concentrated hydrochloric acid (120 g.), and formalin (24 g.) were stirred at 70° for seven hours while a stream of dry hydrogen chloride was passed through the mixture. The red product was poured into water and extracted with ether. Removal of the solvent left an oil which was distilled (b.p. 222° at 32 mm.). After two crystallizations from petroleum ether (b.p. 60–68°) and one vacuum sublimation at 28 mm., the compound melted at 71–72°.

Anal. Calc'd for $C_{14}H_{15}ClO_2$: C, 67.07; H, 5.99.
Found: C, 67.02; H, 6.16.

Ethyl β-(1,4-dimethoxy-2-methylnaphthyl)-α-acetylpropionate (XVII). To a stirred solution of sodium acetoacetic ester prepared from acetoacetic ester (9.75 g.) and sodium (1.725 g.) in absolute ethanol (100 cc.) was added a solution of 1,4-dimethoxy-2-methyl-3-chloromethylnaphthalene (18.8 g.) in absolute ethanol (100 cc.) and absolute ether (35 cc.). The resulting solution was stirred for three hours, refluxed for one hour, and then allowed to stand overnight. Acidification followed by removal of the solvent under a vacuum gave the product as a solid. A portion of this solid was crystallized twice from petroleum ether (b.p. 60–68°). It then melted at 75–76.5°.

Anal. Calc'd for $C_{20}H_{24}O_5$: C, 69.77; H, 6.98.
Found: C, 69.66; H, 7.23.

1-(1,4-Dimethoxy-2-methyl-3-naphthyl)butanone-3 (XVIII). The moist solid (XVII) obtained in the above experiment was stirred with aqueous sodium hydroxide (100 cc., 7%) for four hours and then allowed to stand overnight. After the addition of ethanol (50 cc.) the solution was refluxed for one hour and filtered. The cooled filtrate was made acid to Congo red with dilute sulfuric acid. The precipitate was removed and crystallized from ethanol. The product weighed 18.0 g., and melted at 85–87°. A second crystallization from ethanol gave white prisms melting at 87.5–88°.

Anal. Calc'd for $C_{17}H_{20}O_3$: C, 75.00; H, 7.35.
Found: C, 74.60; H, 7.70.

1-(1,4-Dimethoxy-2-methyl-3-naphthyl)-3-methylbutanol-3 (XIX). To a solution of methylmagnesium iodide (0.075 moles) in absolute ether (60 cc.) was added a solution of 1-(1,4-dimethoxy-2-methyl-3-naphthyl)butanone-3 (XVIII) (6.8 g.) in ether (70 cc.) and the mixture was refluxed for three hours. Decomposition with iced ammonium chloride solution followed by extraction with ether gave a white solid (6.6 g.) which after two crystallizations from petroleum ether (b.p. 60–68°) melted at 73–75°.

Anal. Calc'd for $C_{18}H_{24}O_3$: C, 75.00; H, 8.33.
Found: C, 74.71; H, 8.66.

6-Hydroxy-2,2,5-trimethyl-7,8-benzochroman (XX). 1-(1,4-Dimethoxy-2-methyl-3-naphthyl)-3-methylbutanol-3 (XIX) (6.0 g.) was dissolved in acetic acid (50 cc.) containing hydrobromic acid (15 cc., 40%). The mixture was refluxed for four hours under nitrogen. The resulting solution was poured into water and extracted with ether. Removal of the ether gave a red oil which was chromatographed on aluminum oxide into two fractions. The first of these, a pale yellow oil, insoluble in Claisen's alkali, was probably the methyl ether of the chroman. The second fraction was a brownish oil (1.57 g.) which solidified upon the addition of petroleum ether (b.p. 60-68°). After three crystallizations from petroleum ether (b.p. 60-68°) and one vacuum sublimation at 22 mm. the chroman melted at 117-118°.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.34; H, 7.44.
Found: C, 79.68; H, 7.66.

5-Hydroxy-2,4-dimethyl-6,7-benzocoumaron (XXI). A solution of 2-methyl-1,4-naphthoquinone (8 g.) in a mixture of absolute ethanol (60 cc.), benzene (20 cc.), and dry ether (20 cc.) was dropped slowly and with stirring into a solution of sodium acetoacetic ester [prepared by adding acetoacetic ester (7.5 cc.) in dry alcohol (15 cc.) to a solution of sodium (1.15 g.) in dry ethanol (50 cc.)]. After standing at room temperature for sixteen hours, the resulting purple solution was poured into iced hydrochloric acid and extracted with ether. Removal of the ether left a solid from which the coumaron was separated by steam distillation. Extraction of the distillate with ether gave 1.05 g. of coumaron melting at 115°; after two crystallizations from aqueous ethanol, the substance melted at 118-119°. The residue from the steam distillation was a dark gummy material which was not investigated further.

Anal. Calc'd for $C_{14}H_{12}O_2$: C, 79.25; H, 5.66.
Found: C, 78.62; H, 6.35.

SUMMARY

1. Four methods, of general applicability, have been outlined for the synthesis of *p*-hydroxy-chromans and -coumarans. In these syntheses, the cyclization was the final step, and the substances cyclized were such that there could be little doubt concerning the size of the heterocyclic ring formed. By these methods the following new compounds were prepared: 5-hydroxy-4,6,7-trimethylcoumaran, 5-hydroxy-2,2,4,6,7-pentamethylcoumaran, 6-hydroxy-2,2,5-trimethyl-7,8-benzochroman, and 5-hydroxy-2,4-dimethyl-6,7-benzocoumaron.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE CHEMISTRY OF VITAMIN E. XXVII.[1] OXIDATION OF HYDROQUINONES, *p*-HYDROXYCHROMANS AND *p*-HYDROXYCOUMARANS TO QUINONES WITH CERIC SULFATE

LEE IRVIN SMITH, P. M. RUOFF, AND STANLEY WAWZONEK

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The excellent results obtained by Furman and Wallace (1) in the potentiometric titration of hydroquinone with ceric sulfate in aqueous solutions suggested a further investigation of this reaction, not only as a volumetric method for determination of hydroquinones generally, but also of *p*-hydroxychromans and *p*-hydroxycoumarans related in structure to vitamin E. In addition, it was hoped that the reagent would not oxidize the chromans and coumarans beyond the yellow *p*-quinone stage, and so would become useful as a method of converting these *p*-hydroxy-chromans and -coumarans into *p*-quinones which were hydroxylated in the side chain.

It has been found that not only is ceric sulfate an excellent reagent for the volumetric estimation of these types of compounds, but also it is of considerable value for preparative purposes in converting these compounds into the corresponding quinones. Using barium diphenylaminesulfonate and phenanthroline-ferrous sulfate (2) as indicators, excellent results were obtained in titrating 0.002 M. solutions of hydroquinone, *p*-xylohydroquinone, 2,2,5,7,8-pentamethyl-6-hydroxychroman, and 2,4,6,7-tetramethyl-5-hydroxycoumaran in 50% ethanol-*N* sulfuric acid, using either 0.1 *N* or 0.01 *N* ceric sulfate. At these concentrations the reactions were complete in one minute, and all of the components of the system were soluble even after twenty-four hours. There was, however, a slight precipitation of the inorganic salts when more concentrated solutions were used. In every case two equivalents of the reagent were required per mole of substance oxidized. Table I summarizes the analytical results obtained, and the data are representative of a large number of analyses carried out by this method.

By extracting a titrated solution of a 6-hydroxychroman or a 5-hydroxycoumaran with ether, it was possible to isolate the *p*-quinones in fairly good yields. These *p*-quinones are themselves sensitive substances; they

[1] Paper XXVI, *J. Org. Chem.*, 6, 229 (1941).

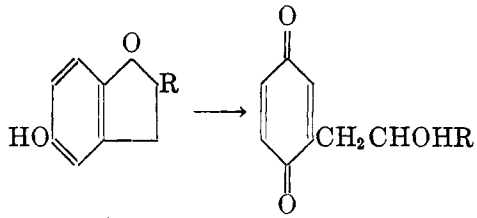
carry the hydroxyl group in the side chain, either in the β- or γ-position, and it is usually a matter of some difficulty to oxidize the chromans and coumarans to these quinones without at the same time oxidizing the quinones further, so that the isolation and purification of the low-melting, yellow *p*-quinones is frequently very troublesome. By the procedure

TABLE I

SUMMARY OF ANALYTICAL RESULTS

	HYDROQUINONE		*p*-XYLOHYDROQUINONE	6-HYDROXY-2,2,5,7,8-PENTAMETHYLCHROMAN		5-HYDROXY-2,4,6,7-TETRAMETHYLCOUMARAN
Material, g.	0.0220	0.0055	0.0411	0.050	0.00553	0.0105
Solvent, cc.	100	110	100	40	35	35
0.111 *N* $Ce(SO_4)_2$, cc.	3.61		5.38	4.15		
0.0139 *N* $Ce(SO_4)_2$, cc.		7.23*			3.63	7.99
Time, min.	1	2	1–2	2–3	1	1–2
Error, %	0.1	0.1	0.1	1	0.1	2

* Corrected Indicator blank 0.07 cc.



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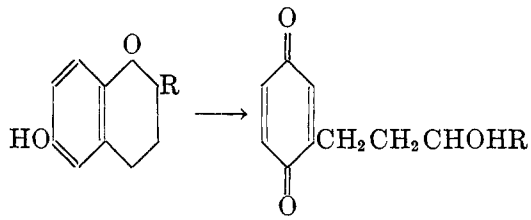


(B)

outlined above, however, these quinones were usually obtained as solids merely by evaporating the solvent, and even when the quinones were oily, the products were so nearly pure that reduction of the ethereal solutions with sodium hydrosulfite gave the pure hydroquinones in good yields. That the quinones had the structures assigned to them was shown by reduction to the hydroquinone and cyclization of the latter to the original chroman or coumaran. In one case—that of 5-hydroxy-2-methylcou-

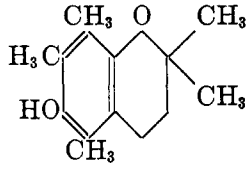
maran (3),—the method gave a very poor yield of the quinone. This quinone (A, R = CH_3) is an extremely sensitive substance, and it was not possible to complete the oxidation of the coumaran without at the same time destroying a great deal of the quinone.

TABLE II

PREPARATION OF *p*-QUINONES FROM HYDROXYCHROMANS AND HYDROXYCOUMARANS

COMPOUND	WEIGHT, G.	CC. OF 50% ETHANOL	WT. OF PRODUCT, G.	
			Quinone	Hydroquinone
6-Hydroxy-2,2,5,7,8-pentamethylchroman (I) (4)	0.22	200		0.10
6-Hydroxy-2,5,7,8-tetramethylchroman (II) (5)	1.03	500	0.67	
5-Hydroxy-2,4,7,8-tetramethylcoumaran (III) (6)	0.60	400	.25	
5-Hydroxy-2,2,4,7,8-pentamethylcoumaran (IV) (7)	.18	200		.09
5-Hydroxy-2-ethyl-4,7,8-trimethylcoumaran (V) (8)	.206	200		.11

Table II summarizes the results obtained, and the formulas for the various compounds involved are given in the chart.



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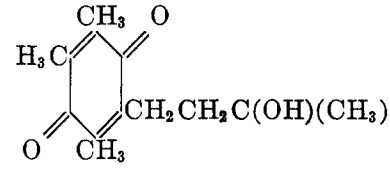

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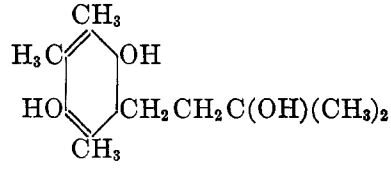

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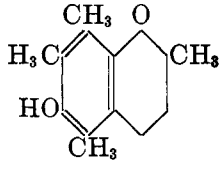

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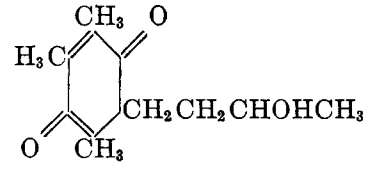

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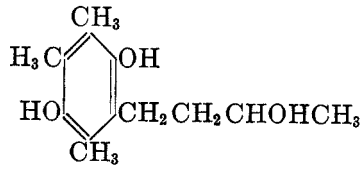

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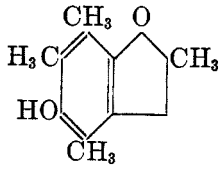

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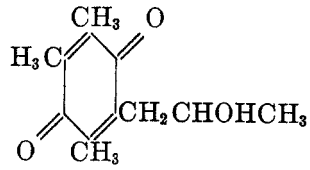

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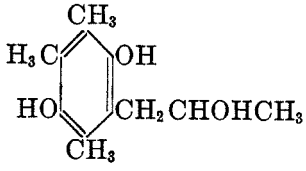

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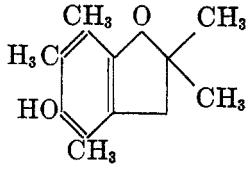

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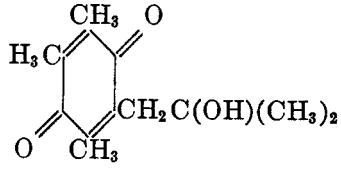
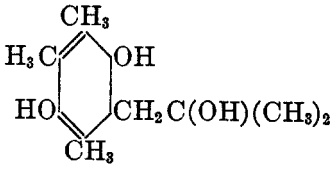


IVa



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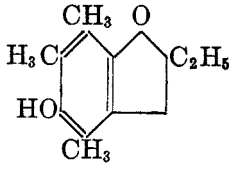

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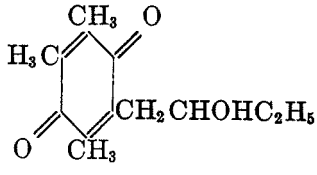
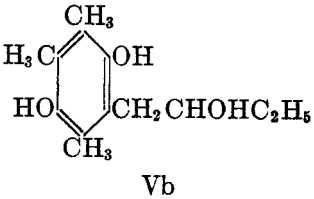


Va



Vb

EXPERIMENTAL[2]

Volumetric titration. The solutions of the organic substances were generally made up by dissolving a weighed amount of the material in 50 or 100 cc. of the solvent. A few cc. of this solution was then pipetted into 100 cc. of 50% ethanol-*N* sulfuric acid. A few drops of the indicator was added and then the ceric sulfate was added rapidly from a microburette until a permanent color change occurred. Since the violet oxidation-product of barium diphenylaminesulfonate is slowly decomposed on standing, the phenanthroline-ferrous sulfate indicator is preferred, although the color change (red to colorless) is not as contrasting as that of the diphenylamine indicator (colorless to violet).

Preparation of quinones. The procedure used in all cases consisted in dissolving the 6-hydroxychroman or 5-hydroxycoumaran in 50% ethanol, adding the theoretical amount of 0.1167 *N* ceric sulfate, allowing to stand for two minutes, and then extracting with ether. After washing the ether extract with water and sodium bicarbonate solution, the solvent was removed, and the residual red oil was crystallized from petroleum ether (b.p. 60–68°). If the quinone could not be made to crystallize, it was taken up in ether, and after shaking the solution with aqueous sodium hydrosulfite, the hydroquinone was readily isolated.

2,3,5-Trimethyl-6-(3'-methyl-3'-hydroxybutyl)benzoquinone (Ia). The quinone prepared from 6-hydroxy-2,2,5,7,8-pentamethylchroman was difficult to crystallize. Several crystallizations from petroleum ether (b.p. 60–68°) after a sublimation at 10^{-6} mm. gave a solid melting at 45–46°, which soon liquefied upon standing at room temperature. John (9) reports the melting point 62°.

Anal. Calc'd for $C_{14}H_{20}O_3$: C, 71.19; H, 8.47.
Found: C, 71.44; H, 8.60.

1-(3,6-Dihydroxy-2,4,5-trimethylphenyl)-3-methylbutanol-3 (Ib). The quinone Ia (0.64 g.) was refluxed in 10 cc. of glacial acetic acid with excess zinc dust until colorless. The mixture was filtered and the filtrate was diluted with water and extracted with ether. Removal of the ether left a white solid (0.37 g.) which after two crystallizations from ether-benzene and one from ethyl acetate melted at 154.5–156°. Sodium hydrosulfite can also be used for the reduction.

Anal. Calc'd for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24.
Found: C, 70.67; H, 9.26.

Triacetate. The hydroquinone Ib (0.1 g.) and anhydrous sodium acetate (0.05 g.) were dissolved in acetic anhydride (5 cc.) and the solution was refluxed for 25 minutes. After dilution with water, ether extraction removed a white solid which after one crystallization from petroleum ether (b.p. 60–68°) melted at 106–109°. Even though the melting point was low, the substance did not depress the melting point (113–114°) of a sample prepared by the reductive acetylation of the quinone (9, 10).

Cyclization. The hydroquinone Ib (0.119 g.) in absolute ethanol (5 cc.) was treated with a drop of concentrated sulfuric acid and allowed to stand overnight. Pouring the solution into water, followed by extraction with ether, gave a white solid (.08 g.) melting at 94–95°, alone or when mixed with an authentic specimen of 2,2,5,7,8-pentamethyl-6-hydroxychroman (I).

2,3,5-Trimethyl-6-(3'-hydroxybutyl)benzoquinone (IIa). The quinone prepared from 6-hydroxy-2,5,7,8-tetramethylchroman melted at 77–78°. Reduction with sodium hydrosulfite gave the hydroquinone IIb, which melted at 137–138°. John and Schmeil (11) report melting points of 79° and 138°, respectively.

[2] Microanalyses by E. E. Renfrew.

2,3,5-Trimethyl-6-(2'-hydroxypropyl)benzoquinone (IIIa). The quinone prepared from 5-hydroxy-2,4,6,7-tetramethylcoumaran melted at 57.5–58.5°. Reduction with sodium hydrosulfite gave the hydroquinone IIIb melting at 136–138°. Karrer and co-workers (12) give the melting point of the quinone as 56.5°, and that of the hydroquinone as 137°.

1-(3,6-Dihydroxy-2,4,5-trimethylphenyl)-2-methylpropanol-2 (IVb). The hydroquinone prepared from 5-hydroxy-2,2,4,6,7-pentamethylcoumaran after two crystallizations from benzene melted at 177–180°.

Anal. Calc'd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.93.
Found: C, 69.41; H, 9.31.

1-(3,6-Dihydroxy-2,4,5-trimethylphenyl)butanol-2 (Vb). This hydroquinone, prepared from 5-hydroxy-2-ethyl-4,6,7-trimethylcoumaran, melted at 104–105° after two crystallizations from benzene.

Anal. Calc'd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.93.
Found: C, 69.62; H, 8.95.

Cyclization. The hydroquinone Vb (0.05 g.) was allowed to stand overnight in acetic acid (5 cc.) containing a drop of concentrated sulfuric acid. Dilution with water produced a white solid (0.03 g.) which melted at 118–120°, alone or when mixed with 5-hydroxy-2-ethyl-4,6,7-trimethylcoumaran (V).

SUMMARY

1. Accurate volumetric analysis of hydroquinones, 6-hydroxychromans, and 5-hydroxycoumarans has been accomplished with ceric sulfate in 50% ethanol.

2. The preparation of quinones and hydroquinones from 6-hydroxychromans and 5-hydroxycoumarans by means of ceric sulfate is reported.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY]

REACTION OF HEXAHYDROAROMATICS WITH OLEFINS IN THE PRESENCE OF ALUMINUM CHLORIDE

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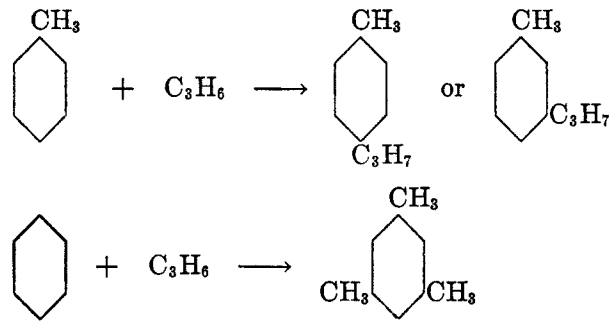
Received November 20, 1940

The reaction of naphthenes with olefins other than ethylene has heretofore not been reported in the literature. This paper deals with the reaction of cyclohexane and methylcyclohexane with propene, *n*-butenes, and isobutene.

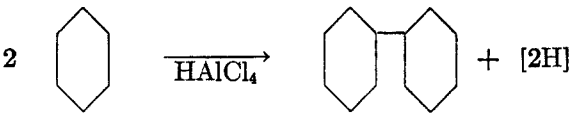
It is interesting to note that whereas the addition of methylcyclohexane to olefins yields alkylated methylcyclohexane, the reaction of cyclohexane with olefins is accompanied by isomerization and the products resulting from such reaction consists of polymethylated cyclohexane.



The reaction between olefins and naphthenes is accompanied by side-reactions which are due mainly to the intermolecular hydrogenation-dehydrogenation of the reactants. Part of the olefins used are converted to paraffins. This is especially true when the reaction is carried out at relatively high temperatures.

Two molecules of cyclohexane react to yield dicyclohexyl and hydrogen, the latter hydrogenates the olefins to paraffins as represented by reaction [A]. The hydrogen necessary for the hydrogenation of olefins to paraffins is also derived from the dehydrogenation of naphthenes to cycloolefins. The latter are combined with the aluminum chloride and form "catalyst layer"; the highly unsaturated cycloolefins are liberated by treating the "catalyst layer" with water. Cyclohexene undergoes polymerization and further dehydrogenation.

This type of intermolecular hydrogenation reaction is not new and was observed to take place also during the polymerization of olefins with phosphoric acid (1), sulfuric acid (2), aluminum chloride (3), and in many hydrocarbon reactions catalyzed by aluminum chloride (4, 5). In order for

[A] 

$$CH_3—CH=CH_2 + 2H \rightarrow CH_3—CH_2—CH_3$$

[B] 

$$CH_3—CH=CH_2 + 2H \rightarrow CH_3—CH_2—CH_3$$

intermolecular hydrogenation-dehydrogenation to proceed, it is necessary to have conditions favorable to the dehydrogenation of an organic compound as well as an acceptor which can combine with the liberated hydrogen. From the numerous reactions made, it was found that hexahydroaromatics are donors of hydrogen, while open-chain olefins are acceptors. Molecular hydrogen does not cause the hydrogenation of olefins to paraffins under the conditions described.

Cyclohexane and Olefins

The reaction of cyclohexane with propene and isobutene in the presence of aluminum chloride-hydrogen chloride catalyst was studied at a temperature of 10–45°, with the exception of one experiment which was made at superatmospheric pressure and at a temperature of 100°. At 10° the alkylation of cyclohexane with olefins does not proceed nearly as completely as at 45°. Of the olefins studied, propene alkylates cyclohexane more easily than does isobutene; the latter undergoes mostly polymerization.

The product obtained from the reaction between cyclohexane and olefins was a complex mixture composed of alkylated cyclohexane, dicyclohexyl, alkylated dicyclohexyl, etc. The alkylated cyclohexane consisted of polymethylated cyclohexane, owing to the isomerization of alkylcyclohexane to polymethylcyclohexane. In the reaction-product of propene with cyclohexane, 1,3,5-trimethylcyclohexane was identified. The structure of the alkylated cyclohexane was established by dehydrogenating the naphthenes to the corresponding aromatic hydrocarbons, and identifying the latter by their bromo and nitro derivatives.

When the reaction between propene and cyclohexane was carried out at a temperature of 100° and at superatmospheric pressure, intermolecular hydrogenation-dehydrogenation occurred to a great extent.

Methylcyclohexane and Olefins

The alkylation of methylcyclohexane with *n*-butenes and isobutene was studied at temperatures ranging from −25° to +25°; the alkylation with propene was made at −25° to +50°. Methylcyclohexane reacts with olefins more easily than cyclohexane; as with the latter, the reaction is complicated, and intermolecular hydrogenation-dehydrogenation takes place, coupled with isomerization.

The main products formed by reacting methylcyclohexane with propene were 1,3- and 1,4-methylpropylcyclohexane; polymethylated cyclohexane was not found. This is significant, in view of the fact that cyclohexane on reacting with propene formed trimethylcyclohexane; it seems that a

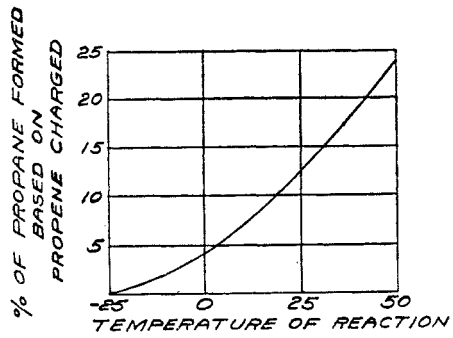


FIG. 1

methyl group attached to a cyclohexyl group stabilizes the molecule and prevents the isomerization of methylpropylcyclohexane to tetramethylcyclohexane.

The product boiling at 220–240° probably consists of methyldipropylcyclohexane, as determined by carbon and hydrogen analysis and molecular weight determination. The dehydrogenation of this compound yielded a hydrocarbon corresponding to methyldipropylbenzene (b.p. 233–241°). On oxidation, however, isophthalic and terephthalic acid were formed and not tricarboxybenzene as expected. This indicates either that one of the alkyl groups split off during oxidation, or that propene underwent polymerization to hexene and the latter reacted with methylcyclohexane to yield 1,3- and 1,4-methylhexylbenzene. We favor the first interpretation, although further work would need to be done in order to settle this point.

The gaseous hydrocarbons formed during the reaction are composed

mainly of propane, the amount of which increases as the temperature of the reaction is raised (Fig. I).

The catalyst layer consists of highly unsaturated hydrocarbons, which were formed as indicated already by the disproportionation of hydrogen between naphthenes and olefins which occurs under the influence of aluminum chloride.

n-Butene on reacting with methylcyclohexane formed as a main product 1,3- and 1,4-methylbutylcyclohexane; the yield of these compounds decreased as the temperature of reaction was raised. The catalyst layer after hydrolysis yielded high-boiling unsaturated hydrocarbons. The gaseous hydrocarbons contain *n*-butane.

Isobutene, owing to the ease with which it undergoes polymerization, reacted with difficulty with methylcyclohexane. At −25° and 0° only polymerization had taken place; at +25° some of the isobutene alkylated methylcyclohexane; 1,3-methylbutylcyclohexane and dimethylpropylcyclohexane were formed during the reaction.

EXPERIMENTAL PART

Apparatus and Procedure

The sketch of the apparatus is self-explanatory. In a reaction-flask of 1000 cc. capacity were placed aluminum chloride and cyclohexane or methylcyclohexane.

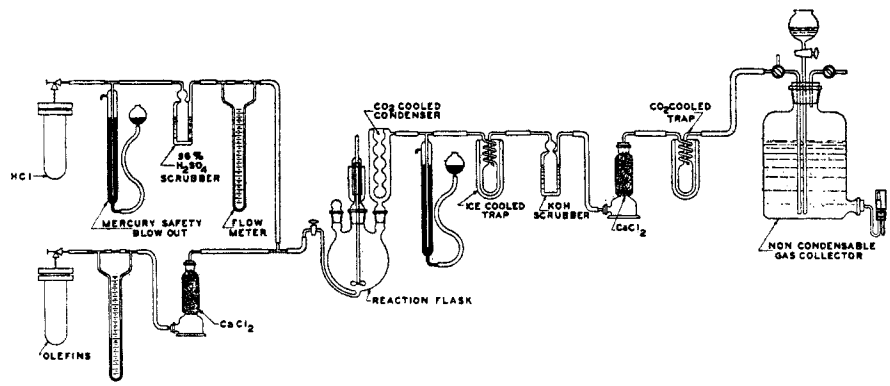


FIG. 2

Hydrogen chloride and the gaseous olefinic hydrocarbons were charged from tared Duralumin bombs.

When the reaction was carried out at −25°, the catalyst layer was separated from the hydrocarbon layer and the latter heated to room temperature in order to recover the gaseous hydrocarbons. When the alkylation was carried out at higher temperature, after the reaction was considered finished, the carbon dioxide-cooled condenser was replaced by an air condenser and the gaseous hydrocarbons collected as shown in the figure. The hydrocarbon layer was washed, neutralized, dried and distilled. The catalyst layer was decomposed with ice; the hydrocarbons which separated were washed and distilled. The gaseous hydrocarbons were identified by low-temperature Podbielniak distillation and regular gas analysis.

Proof of Structure

The structure of the alkylated cyclohexanes was determined by dehydrogenating the product to the corresponding aromatic hydrocarbons. The latter were identified by bromination, nitration, or oxidation. The dehydrogenation was carried out by passing the product under investigation over 30 g. of platinized alumina at 250° and at a rate of 7 cc. per hour, according to the procedure described by us (5, 6).

The bromination was carried out by heating 1 cc. of the aromatic hydrocarbons with 4 cc. of bromine containing 1% of iodine.

The oxidation was accomplished by heating one gram of the dehydrogenated alkycyclohexane with 15 cc. of concentrated nitric acid and 25 cc. of water in a sealed tube, according to the procedure we have described (5).

TABLE I

REACTION OF CYCLOHEXANE WITH OLEFINS

EXPERIMENT NO.	9-54[a]	9-56	9-64	9-58	9-66
Reagents used:					
Cyclohexane, g.	250 (3m)	168 (2m)	168 (2m)	168 (2m)	169 (2m)
Olefins, kind	Propene	Propene	Propene	*i*-Butene	*i*-Butene
Olefins, g.	100 (2.4m)	54 (1.3m)	65 (1.5m)	63 (1.5m)	89 (2m)
$AlCl_3$, g.	25	20	20	20	20
Temp. of reaction, °C.	40	15	45	10	43
Products obtained:					
Hydrocarbon layer, g.	258	213	203	221	228
Catalyst layer, g.	74	27	35	34	50
Condensable gases, g.	37	0	13[b]	0	5
Cyclohexane recovered,[c] % (Based on amount charged)	60	86	56	92	81

[a] The experiment was made under 10 atmospheres pressure.

[b] Analysis: Propene 16.6 mole per cent, propane 62.5, isobutane 10.9, pentane 10.

[c] "Cyclohexane recovered" includes a mixture of cyclohexane and methylcyclopentane. The latter was formed by the isomerization of cyclohexane.

The nitration was carried out by treating 1 cc. of the product under investigation with 4 cc. of a nitrating mixture consisting of 1 volume of concentrated nitric acid and 2 volumes of 96% sulfuric acid.

Cyclohexane and propene (Expt. 9-64). The following liquid main products were isolated:

A. Boiling point 142–159°. *Anal.* Calc'd for C_9H_{18}: C, 85.63; H, 14.37; Mol. Wt. 126.

Found: C, 85.08; H, 14.93; n_D^{20} 1.4303; d_4^{20} 0.7788; Mol. Wt. 134.

The product after dehydrogenation followed by bromination yielded:

(a) White crystals m.p. 112–113° crystallized from hot 75% ethanol.

Anal. Calc'd for $C_{10}H_{10}Br_4$: Br, 71.11. Found: Br, 71.43.

(b) White crystals m.p. 225–226°, difficultly soluble in hot alcohol, crystallized from benzene; corresponds to tribromomesitylene, no depression in melting point with a synthetic product.

Anal. Calc'd for $C_9H_9Br_3$: Br, 67.23; Found: Br, 67.36.

On nitration, the dehydrogenated product yielded trinitromesitylene melting at 232-234°.

TABLE II

REACTION OF METHYLCYCLOHEXANE WITH PROPENE

EXPERIMENT NO.	11-31	11-21[a]	11-29	11-35	11-35a
Reagents used:					
Methylcyclohexane, g.	98.2 (1m)	588.1 (6m)	196 (2m)	161 (1.6m)	196 (2m)
Propene, g.	34 (0.75m)	193.5 (4.6m)	65 (1.5m)	53 (1.3m)	64 (1.5m)
Hydrogen chloride, g.	2.1	12.8	2.6	1.2	1.6
Aluminum chloride, g.	12.0	60.0	20.0	14.8	20.2
Temperature, °C.	−25	+7	+30	+50	+50
Product recovered					
Hydrocarbon layer, g.	121.0	735.2	239.0	181.4	22.8
Catalyst layer, g.	23.8	105.5	35.7	29.8	37.1
Condensable gases, g.	None	17.6	8.8	19.0	18.8
Methylcyclohexane, %	58	54.3	49.4	52	46
Moles of monopropylmethylcyclohexane formed based on 1 mole of $C_6H_{11}CH_3$ reacted	0.52	0.38	0.57	0.40	0.51
Molal ratio of methylcyclohexane to olefins reacted with	1:1.2	1:1.2	1:1	1:0.87	1:0.97

EXPERIMENT NO.	ANALYSIS OF CONDENSABLE GASES, MOLE %			
	C_3H_8	i-C_4H_{10}	n-C_4H_{10}	C_5H_{12}+
11-21	84.2	7.1	—	7.9
11-29	83.4	9.8	—	6.1
11-35A	81.1	8.1	3.3	7.5

[a] Products of three experiments were combined.

Anal. Calc'd for $C_9H_9N_3O_6$: N, 16.48; Found: N, 16.81.

From the derivatives obtained we can conclude that the original product contained *1,3,5-trimethylcyclohexane.*

B. Boiling point 200–217°. *Anal.* Calc'd for $C_{12}H_{24}$ (alkylated cyclohexanes): C, 85.63; H, 14.37; Mol. Wt. 168.

Found: C, 85.81; H, 14.13; d_4^{20} 0.8166; n_D^{20} 1.4491 Mol. Wt. 175.

C. Boiling point 279–309°. *Anal.* Calc'd for $C_{18}H_{34}$ (dipropyldicyclohexyl): C, 86.31; H, 13.69; Mol. Wt. 250.

Found: C, 85.92; H, 13.90; d_4^{20} 0.8497; n_D^{20} 1.4669 Mol. Wt. 250.

Cyclohexane and propene at 100° (Expt. 9–54). The following are some of the main fractions analyzed:

A. Boiling point 214–221°. *Anal.* Calc'd for $C_{12}H_{22}$ (dicyclic naphthene): C, 86.75; H, 13.25; Mol. Wt., 166.

Found: C, 86.24; H, 13.79; d_4^2 0.8468; n_D^{20} 1.4621, Mol. Wt. 174.

B. Boiling point 298–311. *Anal.* Calc'd for $C_{18}H_{34}$ (dipropyldicyclohexyl ?): C, 86.31; H, 13.69; Mol. Wt. 250.

Found: C, 86.50; H, 13.56; d_4^{20} 0.8774; Mol. Wt. 263.

Methylcyclohexane and propene (Expt. 11–21). The following main fractions were investigated:

A. Fraction boiling 168–171°. Represents 31% of the total alkylated methycyclohexane.

Anal. Calc'd for $C_{10}H_{20}$: C, 85.63; H, 14.37; Mol. Wt. 140.

Found: C, 85.51; H, 14.24; n_D^{20} 1.4387; d_4^{20} 0.7960; Mol. Wt. 146.

Seventy-three grams of the material was dehydrogenated; according to the hydrogen liberated, 68% of the naphthenes were converted to aromatic hydrocarbons. A fraction, boiling point 177–179°, was separated and investigated.

Anal. Calc'd for $C_{10}H_{14}$: C, 89.55; H, 10.45; Mol. Wt., 134.

Found: C, 88.81; H, 10.84; d_4^{20} 0.8553; n_D^{20} 1.4884; Mol. Wt. 135.

The aromatic hydrocarbons obtained were oxidized. A white crystalline compound was obtained which had a neutralization equivalent of 82; calculated for phthalic acid, 83.

By preparing the dimethyl ester of the product two compounds were separated by fractional crystallization from methyl alcohol.

1. M.p. 61–63° corresponding to dimethyl isophthalate.

2. M.p. 141.5–142° corresponding to dimethyl terephthalate.

Anal. Calc'd for $C_{10}H_{10}O_4$: C, 61.82; H, 5.19.

Found: C, 61.34; H, 5.15.

On the basis of the results obtained we can conclude that the original product consisted of 1,3- and 1,4-methylpropylcyclohexane.

B. Fractions boiling 218–238°. *Anal.* Calc'd for $C_{13}H_{26}$ (methyldiisopropylcyclohexane): C, 85.63; H, 14.37; Mol. Wt. 182.

Found: C, 85.37; H, 14.33; d_4^{20} 0.8142; Mol. Wt. 181.

On dehydrogenation a product was obtained boiling at 231–241°, n_D^{20} 1.4714. On oxidation it yielded phthalic acid, with a neutralization equivalent of 82. Two methyl esters were obtained, which were separated by their difference in solubility in methyl alcohol.

1. The less soluble compound had the m.p. 136–137°; it corresponded to dimethyl terephthalate and showed no depression in melting point with a synthetic sample. 2. The more soluble compound melted at 68°, which corresponds to dimethyl isophthalate.

Anal. Calc'd for $C_{10}H_{10}O_4$: C, 61.34; H, 5.15.

Found: C, 61.80; H, 5.08.

Catalyst layer. The aluminum chloride layer was decomposed with water, washed, and dried; it distilled between 60 and 220° at 10 mm., and the different fractions had

TABLE III

REACTION OF METHYLCYCLOHEXANE WITH *n*-BUTENE AND ISOBUTENE

	ISOBUTENE			N-BUTENES		
EXPERIMENT NO.	11-11	11-3	11-7	11-23	11-15	11-19
Reagents used:						
Methylcyclohexane, g.	98 (1m)	196 (2m)	196 (2m)	98 (1m)	196 (2m)	196 (2m)
Butene, g.	43.5 (0.75m)	87.5 (1.5m)	83.5 (1.5m)	42.0 (0.75m)	78.5 (1.4m)	78.0 (1.4m)
Aluminum chloride, g.	12.0	20.0	20.0	12.0	20.0	20.0
Hydrogen chloride, g.	2.7	5.0	5.0	5.0	4.2	3.2
Temperature, °C.	−25	0	25	−25	3	28
Product obtained:						
Hydrocarbon layer, g.	136.8	243.3	236.0	129.8	245.3	239.5
Catalyst layer, g.	16.8	52.5	57.5	13.0	36.5	46.0
Condensable gases, g.	1.8	4.2	10.5[b]	5.6[c]	18.2[d]	12.0
Methylcyclohexane, % recovered, based on methylcyclohexane charged	84.3	90.8	71.8	63.7	81.6	58.0
Molal ratio of methylcyclohexane to olefins reacted	1:4.6	1:5.5[a]	1:1.2[a]	1:2.0	1:2.2	1:0.8
Moles of monobutylmethylcyclohexane formed based on 1 mol methylcyclohexane reacted	0	0	0.44	0.70	0.60	0.46

[a] The hydrocarbon layer is unstable towards nitrating mixture; it contains isobutene polymers.

Analysis of the condensable gases:

[b] *i*-C_4H_8, 11.6%; *i*-C_4H_{10}, 73.5%; C_5H_{12}, 14.9%.

[c] *n*-C_4H_{10}, 99%; *i*-C_4H_{10}, 1%.

[d] *n*-C_4H_8, 74.0%; *i*-C_4H_8, 5.9%; *n*-C_4H_{10}, 16.2%; C_5H_{12}, 3.9%.

refractive indices ranging from n_D^{20} 1.4523 to n_D^{20} 1.5150. The product was highly unsaturated.

Methylcyclohexane and propene (at 50°) (Expt. 11-35 a). Physical constants of monopropylated methylcyclohexane were the same as in Experiment 11-21, described above. By the dehydrogenation and oxidation method it was shown that the products correspond to *1-methyl-3-propyl- and 1-methyl-4-propyl- cyclohexane.*

Methylcyclohexane and n-*butene (Expt. 11-19).* The following are the main fractions that were examined.

A. Fraction b.p. 190-195°. *Anal.* Calc'd for $C_{11}H_{22}$: C, 85.63; H, 14.37; Mol. Wt. 154.

Found: C, 85.51; H, 14.50; d_4^{20} 0.7996; n_D^{20} 1.4421; Mol. Wt. 150.

The compound on dehydrogenation yielded aromatic hydrocarbons, from which, on distillation, was separated a fraction boiling at 190-195°, n_D^{20} 1.4875. On oxidation, phthalic acids with a neutralization equivalent of 85 were obtained. The methyl esters of these acids were separated by fractional crystallization from methyl alcohol. 1. Melting point 138°, dimethyl terephthalate. 2. Melting point 62°, dimethyl isophthalate.

On the basis of the derivatives made we can conclude that the original product consisted of *1-methyl-3-butyl- and 1-methyl-4-butyl- cyclohexane.*

Methylcyclohexane and isobutene (Expt. 11-7). The product was distilled and the main fraction, boiling point 175-185°, n_D^{20} 1.4369, which was submitted to dehydrogenation, distilled at 187-198°, n_D^{20} 1.4687. This product was oxidized and methyl esters of the obtained acids were prepared. The following compounds were identified by melting points and mixed melting points.

1. M.p. 62-63°, corresponding to dimethyl isophthalate.

Anal. Calc'd for $C_{10}H_{10}O_4$: C, 61.34; H, 5.15.
Found: C, 61.79; H, 5.05.

2. M.p. 113-116°, corresponding to trimethyl ester mixed with some dimethyl ester of dicarboxybenzenes.

Anal. Calc'd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.76.
Found: C, 58.80; H, 4.91.

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We wish to express our thanks to Mr. John Grover for his valuable assistance in carrying out some of the experimental work.

SUMMARY

The reaction of hexahydroaromatics with olefins in the presence of aluminum chloride was studied at temperatures varying from −25 to 50°. The reaction is accompanied by intermolecular hydrogenation-dehydrogenation.

Cyclohexane reacts with propene to form among other products 1,3,5-trimethylcyclohexane and alkylated dicyclic naphthenes.

Methylcyclohexane reacts with propene and *n*-butenes to yield as main products of reaction of 1-methyl-3-propyl- and 1-methyl-4-propyl-cyclohexane and 1-methyl-3-butyl-, 1-methyl-4-butyl- cyclohexane, respectively.

Isobutene reacts with naphthenes with difficulty; both polymerization and alkylation takes place.

The "catalyst layer" yields on decomposition with water, highly unsaturated cyclic hydrocarbons.

During the alkylation part of the olefins are converted to the corresponding paraffins.

RIVERSIDE, ILL.

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[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE COLLEGE]

CONDENSATION OF DIMETHYLAMYL CARBINOLS WITH BENZENE IN THE PRESENCE OF ALUMINUM CHLORIDE

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In continuation and extension of previous work from this laboratory (1), the following tertiary dimethylamyl carbinols, *viz:* 2-methylheptanol-2 (2), 2,3-dimethylhexanol-2 (3), 2,4-dimethylhexanol-2 (4, 5), 2,5-dimethylhexanol-2 (6), 2-methyl-3-ethylpentanol-2 (7), 2,3,3-trimethylpentanol-2 (8), 2,3,4-trimethylpentanol-2 (9), and 2,4,4-trimethylpentanol-2 (10) were prepared and condensed with benzene.

The resulting alkyl benzenes were separated from the reaction-mixtures by repeated fractionation under reduced pressure. Physical constants were determined. In cases where sufficient quantity of the alkylated product was available, it was nitrated, reduced, diazotized, and hydrolyzed to the corresponding phenol (9). In some cases, the monoacetamino derivative (11), was prepared.

The alcohols were prepared as reported in a previous communication (9) with these exceptions. Some of the 2-methyl-3-ethylpentanol-2 was prepared by a modification of the Whitmore (12) procedure, by reacting the Grignard reagent of 3-bromopentane with acetyl chloride, treating the ketone with methylmagnesium bromide and finally hydrolyzing to give the tertiary alcohol; yield, 11%. A part of the 2,4,4-trimethylpentanol-2 was prepared by oxidation of di-isobutylene (13) to 2,2-dimethylpentanone-4 and subsequent reaction of this ketone with methylmagnesium bromide. This method gave a 22% yield of the carbinol based on di-isobutylene. The method of Butlerow (10) gave a 46% yield based on di-isobutylene. The physical constants of the alcohols were carefully determined and are included in summary in Table I.

CONDENSATIONS

In general, the following procedure with slight modifications was adopted. Two and one-half moles of benzene was placed in a 500 ml. three-necked round-bottom flask with a glycerine-sealed mechanical stirrer, a thermometer, calcium chloride tube, and dropping-funnel. To this was added one-quarter mole of anhydrous aluminum chloride (Baker's C. P.). The aluminum chloride was kept in suspension in the benzene by vigorous mechanical stirring while one-half mole of the carbinol

was added by dropping-funnel at the rate of approximately a drop a second. Temperature control was maintained when necessary by immersion of the reaction-flask in a suitable bath. To prevent freezing of the benzene at low temperatures, 125 ml. of petroleum ether per mole of benzene was added.

After addition of all the carbinol the reaction-mixture was stirred for at least four hours at the temperature used in the condensation and then allowed to stand overnight. It was then stirred for an hour and decomposed by ice and concentrated hydrochloric acid.

The organic layer was separated from the aqueous layer and the latter extracted three times with ether. The combined ether extracts were added to the organic layer and the whole was washed with dilute sodium carbonate and dried overnight with anhydrous sodium sulfate. The low-boiling solvents were removed by distillation on a water-bath and the remaining fraction was distilled under reduced pressure, using a twelve-inch Vigreux column.

Upon condensation several of the carbinols gave, in addition to the expected octylbenzenes, alkyl benzenes of lower molecular weight. Because this was apparently

TABLE I

PHYSICAL PROPERTIES OF ALCOHOLS

	B.P., °C. 748 MM. MICRO	B.P. °C.	d_4^{20}	n_D^{20}	γ^{20}
2-Methylheptanol-2	161.2	77–80 at 30 mm.	0.8142	1.4250	26.75
2,3-Dimethylhexanol-2	159.6	68–69 at 15 mm.	.8365	1.4335	27.65
2,4-Dimethylhexanol-2	150.2	66–69 at 10 mm.	.8099	1.4232	26.50
2,5-Dimethylhexanol-2	151.6	73–75 at 20 mm.	.8158	1.4210	25.48
2-Methyl-3-ethylpentanol-2	157.2	46–50 at 5 mm.	.8382	1.4325	27.43
2,4,4-Trimethylpentanol-2	145.8	42–44 at 7 mm.	.8225	1.4284	26.23
2,3,3-Trimethylpentanol-2	156.6	45–47 at 6 mm.	.8517	1.4393	28.77
2,3,4-Trimethylpentanol-2	157.2	43–48 at 5 mm.	.8080	1.4365	27.48

the result of fragmentation of the longer alkyl chains, methods to eliminate or decrease this splitting were sought. One modification already described was the lowering of reaction temperature. In the condensation of both 2,4,4-trimethylpentanol-2 and 2,3,3-trimethylpentanol-2, the result was a greater yield of octylbenzene.

The method used in condensation of phenol and tertiary alcohols (14), which was found to be less effective with benzene and secondary or tertiary alcohols of lower molecular weight, was reinvestigated in connection with these highly-branched tertiary alcohols and found to give condensation. An apparatus similar to the one already described was used except that a stopper replaced the dropping-funnel. The alcohol (one-half mole) and the benzene (two and one-half moles), with or without petroleum ether, depending on the temperature, was placed in the flask and anhydrous aluminum chloride was added to the mixture a little at a time (one-half gram per five minute interval) from an especially designed shaker. The shaker consisted of 10 cm. of a 14 mm. glass tube inserted in the cork of the aluminum chloride bottle. The whole shaker was kept sealed except when in use and then the powdered reagent was added to the flask through the shaker tube. The amount added was determined by weight difference.

Another method still under investigation and worthy of mention from a theoretical

standpoint is that in which aluminum chloride and benzene were heated together for several hours at the reflux temperature. The mixture was then cooled and the carbinol added. An extension of this procedure was the treatment of benzene with aluminum chloride and heat, and subsequent filtration of the yellow to orange, oily liquid to remove any solid aluminum chloride. When a carbinol was dropped into this filtrate, it was decolorized and a small volume of hydrochloric acid was liberated. Using 2,4,4-trimethylpentanol-2 as the carbinol, small yields of both tertiary butylbenzene and 2,4,4-trimethyl-2-phenylpentane were isolated.

TABLE II

CONDENSATION OF ALCOHOLS

ALCOHOL	TEMP. OF COND., °C.	PET. ETHER	NO. COND.	PRODUCTS	AV. YIELD, %
2-Methylheptanol-2	25	0	4	2-methyl-2-phenylheptane	24.4
2,3-Dimethylhexanol-2	10	0	4	2,3-dimethyl-2-phenyl-	19.5
	25	0	2	hexane	6.3
2,4-Dimethylhexanol-2	25	0	4	2,4-dimethyl-2-phenyl-hexane	24.5
2,5-Dimethylhexanol-2	25	0	5	2,5-dimethyl-2-phenyl-hexane	22.7
2-Methyl-3-ethylpentanol-2	10	0	3	2-methyl-3-ethyl-2-phenyl-	17.5
	−15	300 cc.	2	pentane	12.5
2,4,4-Trimethylpentanol-2	10	0	2	2,4,4-trimethyl-2-phenyl-pentane	9.4
				tertiary butylbenzene	42.0
	−10	300 cc.	2	2,4,4-trimethyl-2-phenylpentane	22.0
				tertiary butylbenzene	17.5
2,3,3-Trimethylpentanol-2	−15	300 cc.	3	2,3,3-trimethyl-2-phenyl-pentane	3.5
				tertiary butylbenzene	9.

A summary of condensations, conditions, and yields is included in Table II. This summary is limited to condensations carried out by addition of carbinol to a benzene aluminum chloride suspension with or without petroleum ether.

PHYSICAL CONSTANTS

The physical constants, *i.e.*, boiling point, refractive index, surface tension, molecular volume, molecular refraction, and parachors were determined by methods indicated in a previous paper (1). Molecular weights were determined by tne cryoscopic method, using benzene as the solvent.

DERIVATIVES

The *p*-nitro, *p*-amino, and *p*-hydroxy derivatives of six of the *tert*-octylbenzenes have been reported (9) along with their methods of preparation and analysis.

In the present investigation all but one of the possible amyldimethylphenylmethanes were converted into the *p*-hydroxy derivatives by nitration, reduction to the amine, and diazotization. These were proved, by mixed melting points of the α-naphthylurethane, to be identical with the products formed by direct alkylation of phenol (9).

The melting point recorded (9) for 2,3,3-trimethyl-2-*p*-hydroxyphenylpentane is in error and is corrected to 60–61°. Condensations in which larger quantities of reactants were used gave this phenol in yields as high as forty per cent. The benzoyl derivative (m.p. 47–48°) and the α-naphthylurethane (m.p. 118–119°) were prepared and analyzed.

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 81.23; H, 8.45.
Found: C, 81.39; H, 8.21.
Calc'd for $C_{25}H_{29}NO_2$: N, 3.73. Found: N, 3.75.

Tert-butylbenzene was isolated in yields from 17 to 42% depending on conditions, from the condensation of 2,4,4-trimethylpentanol-2 and benzene.

Three to seven grams of *tert*-butylbenzene per quarter-mole of alcohol was also isolated as a by-product in the condensation of 2,3,3-trimethylpentanol-2 with benzene. This was recovered after repeated fractionation of a complex mixture which boiled between 100° and 190° (746 mm.). Identification was carried out by two methods.

(a) Nitration, reduction, and diazotization followed by hydrolysis to give *p-tert*-butylphenol.

(b) Nitration, reduction, and acylation of the amine, by the method of Ipatieff and Schmerling (11) to give a monoacetamino derivative melting at 170°.

Attempts to condense 2,3,4-trimethylpentanol-2 with benzene at a temperature of −15° resulted in a mixture of hydrocarbons which distilled over a wide range below the boiling points of the octylbenzenes. We were unable to isolate 2,3,4-trimethyl-2-phenylpentane.

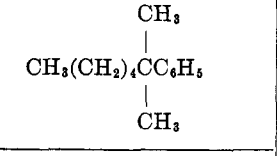
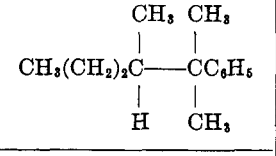
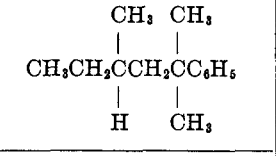
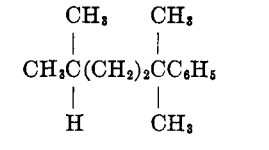
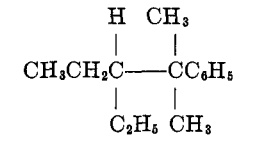
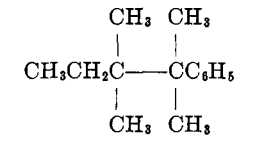
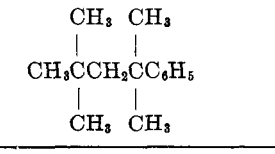
DISCUSSION

Confirming the generalizations drawn from the lower homologs, we have found a marked reduction in yield of octylbenzene from those alcohols in which there is an accumulation of alkyl groups on the carbon adjacent to the carbinol carbon.

Both 2,3,3-trimethylpentanol-2 and 2,4,4-trimethylpentanol-2 gave, in addition to the octylbenzene, hydrocarbons of lower molecular weight, the formation of which might be explained by dehydration of the alcohol with subsequent chain splitting and condensation of the unsaturated fragments with benzene. The isolation of *tert*-butylbenzene as a by-product in the condensation of 2,3,3-trimethylpentanol-2 was something of a surprise. It is suggested that fragmentation of the hydrocarbon chain, in this case, may take place through the intermediate formation of 2,3,3-trimethylpentene-1. Splitting of bonds between the number three carbon and the three alkyl groups attached to it would give isobutene, and a complex mixture of other unsaturated hydrocarbons resulting from the splitting

TABLE III

BOILING POINTS, MOLECULAR WEIGHT, ANALYSIS, INDICES OF REFRACTION, AND MOLECULAR REFRACTION

NO.	FORMULA	B.P., °C. AT *p*. MM.	MOLECULAR WT. CALC'D 190.18	ANALYSIS CALC'D C, 88.35 H, 11.65		n_D^{20}	MR_D^{20} CALC'D 63.25
				C	H		
I		243 at 748 116–118 at 16	185.3	88.23	11.57	1.4951	63.36
II		236 at 748 105–107 at 14	187.2	88.26	11.53	1.4961	62.71
III		238 at 748 112–115 at 17	190.9	88.30	11.67	1.4920	63.22
IV		237 at 748 113–116 at 19	190.	88.24	11.56	1.4939	63.18
V		236 at 748 103–106 at 12	191.5	88.37	11.68	1.4942	62.98
VI		235 at 748 110–113 at 17	191.1	88.28	11.53	1.5031	62.9
VII		234.5 at 748 103–106 at 15	188.5	88.23	11.4	1.4938	62.89

off of methylene and ethylene. Similar mechanisms may be involved in the catalytic breakdown of *tert*-amyl chloride to form *tert*-butyl chloride (15).

Assignment of structure to the *tert*-octylbenzenes is based upon considerations outlined in an earlier publication and upon their conversion to *p-tert*-octylphenols (9).

It is worthy of note that we were unable to obtain an octylbenzene from 2,3,4-trimethylpentanol-2 but were able to effect condensation of this alcohol with phenol (9).

Densities and molecular volumes are shown in Table IV. The difference between the observed and calculated molecular volume of 2-methyl-2-phenylheptane is somewhat greater than in the case of 2-methyl-2-phenylhexane (1). This is in agreement with the stepwise differences of the lower homologs, and indicates a greater effect of the accumulation of

TABLE IV

PHYSICAL PROPERTIES OF OCTYLBENZENES

SUBSTANCE	DENSITIES d_4^{20}	MOLECULAR VOLUME CALC'D 220.76	γ^{20}	PARACHORS	
				Calc'd	Found
I	0.8756	217.24	32.13	516.4	517.3
II	.8861	214.64	32.99	513.4	514.4
III	.8729	217.89	31.01	513.4	514.2
IV	.8749	217.39	31.19	513.4	513.7
V	.8782	216.23	31.17	513.4	511.0
VI	.8939	212.77	32.51	510.4	508.1
VII	.8803	216.06	31.05	510.4	510.0

methyl groups on the carbon adjacent to the ring, with an increase in length of the normal chain.

The boiling points of both of these compounds (Table III) is higher than would be expected from their densities. 2-Methyl-2-phenylheptane boils higher than any of its isomers. These are of approximately the same or higher density. The maximum difference between calculated and observed molecular volumes of these octylbenzenes is found in 2,3,3-trimethyl-2-phenylpentane, in which there is the greatest possible accumulation of methyl groups on adjacent carbon atoms. The molecular volume of 2,3-dimethyl-2-phenylhexane, which has only one methyl group on the third carbon atom, is intermediate between that of 2,3,3-trimethyl-2-phenylpentane and 2-methyl-2-phenylheptane. The largest molecular volumes are found in 2,3-dimethyl-2-phenylhexane and 2,5-dimethyl-2-phenylhexane, where accumulation of methyl groups is on non-adjacent carbons. The molecular volume of 2,4,4-trimethyl-2-phenylpentane is smaller than theory would predict.

Parachors (also shown in Table IV) were calculated using the constants of Mumford and Phillips, together with decrements for chain branching and for attachment of alkyl to the benzene ring. The greatest difference between calculated and observed values is found in 2,3,3-trimethyl-2-phenylpentane. This difference is closely followed by that of 2-methyl-3-ethyl-2-phenylpentane in which there is also branching on the third carbon.

The other isomer in which branching occurs on the third carbon atom, 2,3-dimethyl-2-phenylhexane, shows close agreement between calculated and observed parachors, indicating in this case complete compensation in the surface tension for the branching effect. In spite of the relatively high density of 2,4,4-trimethyl-2-phenylpentane, the observed parachor is in close agreement with the calculated.

Molecular refractions (Table III). The greatest deviations between calculated and observed values which may be attributed to chain branching are found in 2,3,3-trimethyl-2-phenylpentane, in 2,3-dimethyl-2-phenylhexane and in 2-methyl-3-ethyl-2-phenylpentane. The high density of 2,4,4-trimethyl-2-phenylpentane gives a small lowering of the molecular refraction. The highest molecular refraction is shown by 2-methyl-2-phenylpentane which contains the longest carbon chain. The same relationship was found to hold in the heptylbenzenes (1). These high molecular refractions are coincident with relatively high boiling points and may be taken as indicating increased polarizability with lengthening of the chain.

SUMMARY

1. Several known isomeric dimethylamyl carbinols have been prepared in quantity and their physical constants determined.

2. The isomeric amyldimethyl carbinols condense with benzene in the presence of aluminum chloride to give, with one exception, *tert*-octylbenzenes. In cases where the amyl radical was highly branched, alkyl benzenes of lower molecular weight were formed.

3. Physical constants of the alkyl benzenes have been determined and derivatives have been prepared.

4. Several new procedures for condensing benzene and tertiary alcohols in the presence of aluminum chloride have been suggested.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. I. SYNTHESIS OF β-SUBSTITUTED $\Delta^{\alpha,\beta}$-BUTENOLIDES FROM ω-METHOXYMETHYL KETONES

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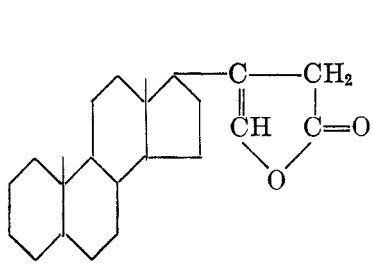
The group of naturally occurring substances known as the cardiac drugs forms an interesting division of the large group of steroids. These substances have been grouped together on the basis of a common pharmacodynamic action on the heart. The investigations, chiefly of Jacobs, Windaus, Tschesche, and Stoll, have provided ample evidence, which has been adequately reviewed in numerous publications (1), for assigning structures to the more important members of the group. With the exception of the toad venoms and a few other substances of alkaloidal nature, the drugs are all non-nitrogenous glycosides which on hydrolysis with acid break with greater or less ease into the aglycones and constituent sugars. The major portion of the physiological action of the glycosides has been found to reside in the aglycone portion of the molecule, although the nature of the sugar moiety plays a definite but relatively minor part in determining the quantitative action of the drugs (2). For purposes of chemical classification it is convenient to subdivide the group of aglycones on the basis of the structure of the side chain. Thus one finds a large group of aglycones, which can be called the "digitalis-strophanthus group," characterized by a side chain consisting of the lactone of an enolized β-aldehydo acid carrying the cyclopentanophenanthrene ring system as a substituent on the β-carbon atom (type formula I), and a second and smaller group, which may be designated the "squill-toad venom group," in which the side chain is an α-pyrone substituted in the 5-position (type formula II).



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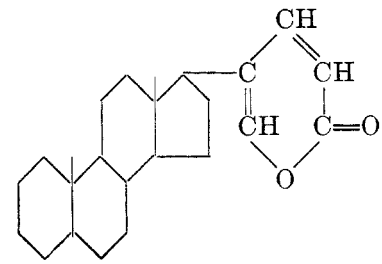
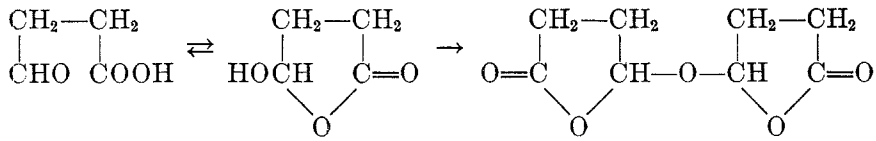


II

Information at hand concerning the relationship between structure and physiological activity of the aglycones is scanty, the recent investigations of Chen and co-workers (3) providing most of our knowledge on this point. It was felt that more adequate information along this line could be obtained if synthetic methods could be made available by which one could vary the molecule at will, with the ultimate object in mind of preparing one or more of the natural aglycones by transformations of other steroids. The results here presented record the exploration of one possible approach to the synthesis of model unsaturated lactones related to the digitalis-strophanthus group, a preliminary note dealing with which has already appeared (4).

Although the γ-substituted $\Delta^{\alpha,\beta}$- and $\Delta^{\beta,\gamma}$-angelica lactones and their homologs have been known for some time (5, 6), the isomeric β-substituted unsaturated lactones analogous to the cardiac lactones have not been prepared, although Blaise and Courtot (7) describe α, α, β-trimethyl -$\Delta^{\beta,\gamma}$-butenolide and α,α-dimethyl-β-phenyl-$\Delta^{\beta,\gamma}$-butenolide. The presence of the two α-methyl groups, which effectively block a possible double bond shift in these lactones, makes them uncertain for study in the present connection. It has been postulated (8) that a lactone of the type under discussion can arise by enolization and lactonization of β-formyl acids in a manner analogous to the formation of the angelica lactones from γ-keto acids. However, experience of previous workers indicates that such lactone formation with aldehydo acids is not as simple as with keto acids. Von Ungern-Sternberg (9) showed that the simplest aldehydo acid of this type, β-formylpropionic acid, first prepared by Perkin and Sprankling (10), exists as an equilibrium mixture of the free aldehydo acid (III) and its cyclic saturated hydroxy lactone (IV). Attempted dehydration (9, 11) of the latter form to the unsaturated lactone resulted in the formation of a bimo-

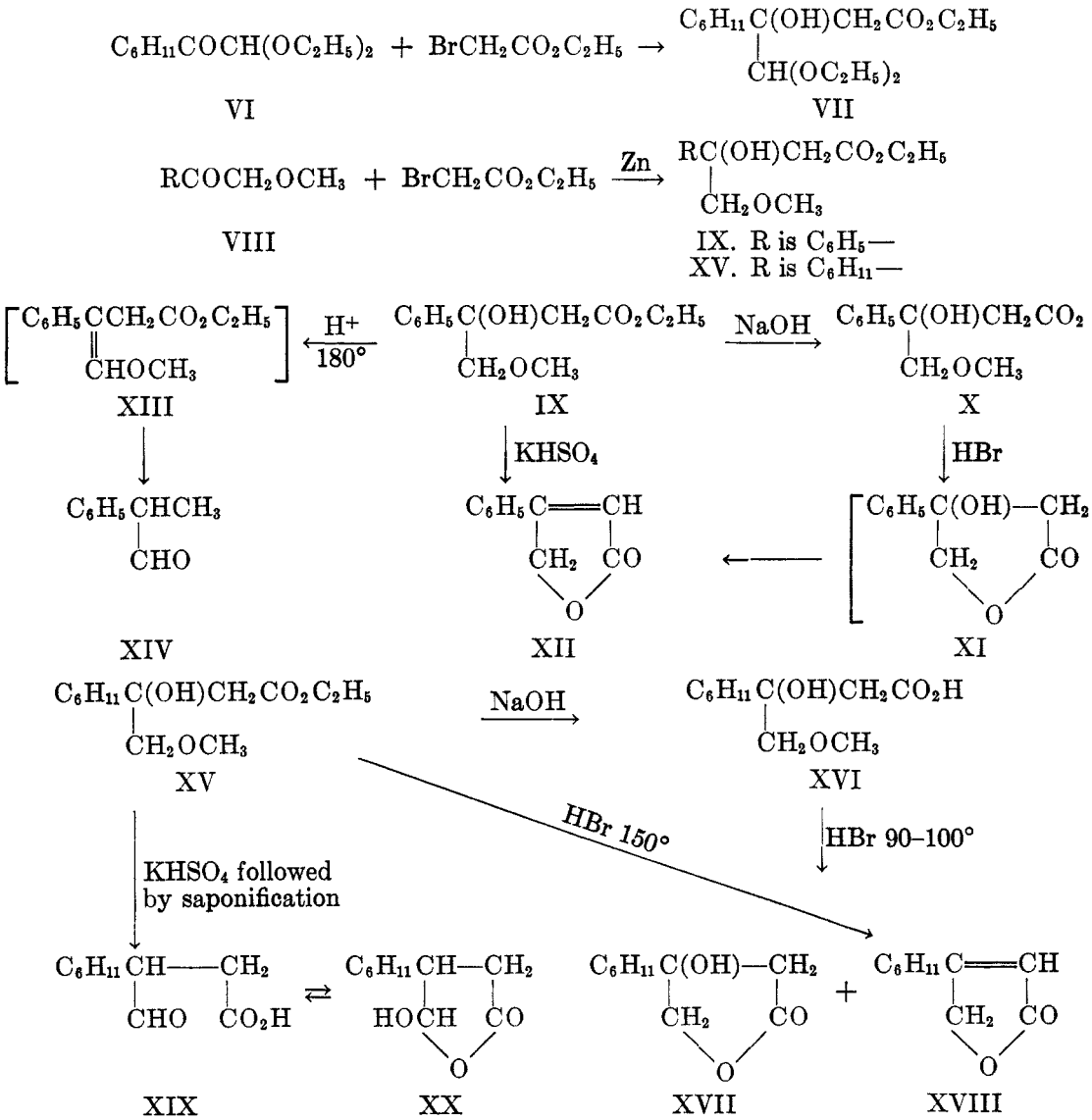


III IV V

lecular compound (V) by elimination of water from two molecules of hydroxy lactone. In any event, the approach to the problem of the synthesis of such unsaturated lactones from this direction demands the preparation of β-formyl acids as necessary intermediates. Such substances have not been obtained previously, with the exception of the one discussed above, although unsuccessful attempts at their synthesis have recently been reported (12). In the present paper we report a successful synthesis for these acids which constitutes part of a general program under way in these laboratories.

In this connection, a possible synthesis of β-cyclohexyl-β-formyl-

propionic acid, based on observations of the corresponding phenyl derivative (13), was attempted. Ethyl β-cyclohexyl-β-hydroxy-γ,γ-diethoxybutyrate (VII) was prepared by condensation of the diethylacetal of cyclohexylglyoxal (VI) with ethyl bromoacetate by the Reformatzky method. Great difficulty was experienced in eliminating the hydroxyl group from this substance, and the synthesis has been abandoned in view of the relatively easy accessibility of the desired β-formyl acid as described below.



The observation of Stoermer (14) that half-ethers of primary-tertiary glycols are converted smoothly and in good yield to aldehydes when heated with acids or when fused with potassium acid sulfate (15) appeared to offer a more promising approach to the synthesis of the desired lactones. ω-Methoxymethyl ketones (VIII) were readily prepared by interaction of an appropriate Grignard reagent with methoxyacetonitrile according to Henze and Rigler (16). These, on condensation with ethyl bromoacetate by the Reformatzky procedure, gave good yields of the desired half-ethers of the glycol esters (IX). By this method we have prepared such glycol ether esters containing phenyl, *n*-butyl, cyclohexyl, and cyclopentyl substituents as representative type substances containing aromatic, aliphatic, and hydroaromatic substituents.

In the subsequent decomposition of the glycol ethers some differences were noted depending on the nature of the substituent present, on the exact experimental conditions, and on whether the ester was hydrolyzed prior to splitting the glycol ether. In the case of IX, where R is phenyl, treatment of the free acid (X) with a solution of hydrogen bromide in glacial acetic acid gave β-phenyl-$\Delta^{\alpha,\beta}$-butenolide (XII). Evidence for the structure assigned to XII was obtained by its synthesis by ring closure of the substance prepared by oxidation of ethyl β-methylcinnamate with selenium dioxide (13) and also by ring closure and dehydration of ethyl β-phenyl-β-hydroxy-γ-acetoxybutyrate (17). The formation of XII can then be pictured as resulting from the series of reactions IX–XII. Definite corroboration for this view was obtained with the analogous cyclohexyl derivative as described below.

Inasmuch as hydrolysis of the blocking ether group in IX apparently occurred before cleavage of the glycol ether ester in the desired sense when hydrogen bromide was used, attempts were made to accomplish the reaction by other reagents and prior to hydrolysis of the ester group in IX. When IX was heated with very dilute sulfuric acid at 180°, cleavage in the desired manner apparently took place to a certain extent, but the instability of the intermediate prevented the isolation of the $\Delta^{\beta,\gamma}$-lactone. Two products were isolated from the reaction-mixture: the above $\Delta^{\alpha,\beta}$-unsaturated lactone (XII), and an aldehyde which has been identified as homotropic aldehyde (XIV). Inasmuch as the first step in the conversion of the half-ether of such a glycol to an aldehyde is apparently the formation of an enol-ether (XIII) (15), the formation of homotropic aldehyde can be readily explained by a decarboxylation of the enol ether ester (or acid) in a manner analogous to the very easy formation of 1,1,2-trimethyl-2-phenylethylene by distillation of ethyl α,α-dimethyl-β-phenylvinylacetate (18). When IX was heated with potassium acid sulfate (15) the $\Delta^{\alpha,\beta}$-unsaturated lactone (XII) was formed exclusively.

A study of the decomposition of the cyclohexyl glycol ether ester (XV)

furnished conclusive proof of the structure of the lactone formed as well as of the manner by which the lactone originates. When the acid, XVI, was heated with a solution of hydrogen bromide in glacial acetic acid at 90–100°, two products were formed. One has been assigned the structure of β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (XVIII). Evidence for this structure was obtained from the ultraviolet absorption curve which closely resembles that for ethyl crotonate (19) and from the molecular exaltation, which indicates conjugation of the double bonds. However, the second product isolated from the above reaction-mixture provided ample confirmatory evidence for this conclusion. This substance is the saturated hydroxy lactone (XVII) formed by hydrolysis of the blocking ether group and subsequent lactonization. As such it was neutral, but took up one equivalent of alkali on saponification; it was saturated and gave neither the nitroprusside nor Tollens' color reactions both of which are characteristic of the unsaturated lactones. This hydroxy lactone therefore represents an intermediate between the glycol ether ester and the unsaturated lactone, and its formation shows conclusively that under the influence of hydrogen bromide cleavage of the glycol ether does not take the anticipated and desired course. When, however, the ester, XV, or the acid, XVI, was similarly treated with hydrogen bromide at higher temperatures or for a longer time, only the unsaturated lactone could be isolated. Likewise, further treatment of the saturated hydroxy lactone with hydrogen bromide in acetic acid resulted in the formation of the unsaturated lactone in practically quantitative yield.

In contrast to the experience with the phenyl derivative, cleavage of the glycol ether in XV by potassium acid sulfate resulted in the formation of the ester of the desired aldehydo acid. The acid is formulated as an equilibrium mixture of the free acid (XIX) and the hydroxy lactone (XX) in accordance with the experience of von Ungern-Sternberg (9) and Harries and Alefeld (11). The substance was characterized by its 2,4-dinitrophenylhydrazone, and its structure was shown by preparation of the semicarbazone of its methyl ester.

The attempted lactonization of the above acid, as well as a detailed discussion of the properties of the unsaturated lactones here described are given in a succeeding paper (19).

EXPERIMENTAL

All melting and boiling points are corrected for stem exposure.

Ethyl β-methoxymethyl-β-phenyl-hydracrylate. To a mixture of 50.1 g. of ω-methoxyacetophenone, prepared from phenylmagnesium bromide and methoxyacetonitrile (20), 21.8 g. of granulated zinc, and 250 cc. of dry benzene in a flask provided with an efficient reflux condenser was added 55.7 g. of freshly distilled ethyl bromoacetate. On gentle warming, a vigorous exothermic reaction set in, and after this moderated

the mixture was refluxed for 2 hours. The mixture was cooled and the zinc compound was decomposed with ice-cold dilute sulfuric acid. The benzene layer was separated, dried with sodium sulfate, and the solvent was removed. The product was then distilled at 18 mm. pressure through a short column. The first fraction consisted of 5.6 g. of ethyl β-methoxymethylcinnamate and boiled at 158–159°.

Anal. Calc'd for $C_{13}H_{16}O_3$: C, 71.0; H, 7.3.
Found: C, 71.0; H, 7.1.

The pressure was then decreased and 54 g. or 68% of ethyl β-methoxymethyl-β-phenylhydracrylate boiling at 111–113° at 2 mm. was obtained; n_D^{25} 1.4989.

Anal. Calc'd for $C_{18}H_{18}O_4$: C, 65.5; H, 7.6.
Found: C, 65.6; H, 7.6.

β-Methoxymethyl-β-phenylhydracrylic acid (X). The above ester was saponified by boiling with a 5% solution of sodium hydroxide in 50% alcohol. The acid was extracted with ether, and slowly crystallized after removal of the solvent. After recrystallization from petroleum ether (Skellysolve B) it melted at 60°.

Anal. Calc'd for $C_{11}H_{14}O_4$: C, 62.9; H, 6.7; OCH_3, 14.8.
Found: C, 63.1; H, 7.0; OCH_3, 13.5.

Neutralization equivalent calc'd: 210; found: 209.

The p-*bromophenacyl ester* melted at 92–93° after recrystallization from alcohol.

Anal. Calc'd for $C_{19}H_{20}BrO_5$: C, 56.0; H, 4.7.
Found: C, 55.9; H, 4.8.

β-Phenyl-$\Delta^{\alpha,\beta}$-butenolide (XII). Twenty-one grams of ethyl β-methoxymethyl-β-phenylhydracrylate was refluxed with 60 cc. of glacial acetic acid, which had been previously saturated with dry hydrogen bromide at 0°, for 1 hour. On pouring the cooled solution into three times its volume of ice water, the crystalline lactone separated. A further amount may be obtained by neutralizing and concentrating the mother liquor. The lactone crystallizes as needles from dilute alcohol and melts at 94°. It has a fragrant, coumarin-like odor, reduces Tollens' reagent and gives the characteristic red color with alkaline sodium nitroprusside solution (Legal test). The yield was 85%.

Anal. Calc'd for $C_{10}H_8O_2$: C, 75.0; H, 5.0.
Found: C, 75.0; H, 5.3.

Saponification equivalent calc'd: 160; found: 160.

The lactone was also obtained by similar treatment of the hydracrylic acid. However, the over-all yield is better if one proceeds directly from the ester.

The same lactone was also obtained by heating the hydracrylic ester with potassium acid sulfate (15). Ten grams of the ester was heated in a Claisen flask with 5 g. of freshly fused potassium acid sulfate for 30 min. at 180–200°. The cooled, dark brown mass was thoroughly extracted with ether. The material extracted by the ether was distilled at reduced pressure. A small amount of unchanged ester came over first at 110–115° at 2 mm., followed by the rapidly crystallizing lactone, which boiled at 155° at 2 mm. The yield was 3.5 g. or 52%. The substance melted at 94° and the melting point was not depressed when this material was mixed with the lactone prepared by the hydrogen bromide method.

Cleavage of ethyl β-methoxymethyl-β-phenylhydracrylate with dilute sulfuric acid. Five grams of the ester was heated in a sealed tube with 10 cc. of water containing 2 drops of conc'd sulfuric acid at 180–200° for 3 hours. The contents of the tube were extracted with ether. Removal of the ether left a residue which deposited 1.5 g., or 45%, of crystalline material on standing. This was filtered from the accompanying oil and identified as the above unsaturated lactone by mixed melting

point. The oily filtrate from the lactone was distilled at reduced pressure and gave 0.8 g. of a pale yellow, pleasant-smelling oil which boiled at 50° at 2 mm. It gave a bisulfite addition-compound and a positive fuchsine aldehyde test. The semicarbazone was prepared for identification and melted at 153–154°. Homotropic aldehyde semicarbazone melts at 153° (21).

Anal. Calc'd for $C_{10}H_{13}N_3O$: C, 62.8; H, 6.9; N, 21.9.
Found: C, 62.7; H, 7.0; N, 22.5.

Methoxymethylcyclohexyl ketone. To a well cooled solution of 1 mole of cyclohexylmagnesium chloride in 400 cc. of dry ether was added dropwise a solution of 71 g. of methoxyacetonitrile (22) in 200 cc. of dry ether. After standing overnight, the addition-compound was decomposed as usual with ice and dilute sulfuric acid. The material extracted with ether was steam distilled for removal of steam volatile impurities. The ketone was extracted from the non-volatile residue with ether and was distilled at reduced pressure. It boiled at 110–111° at 21 mm.; n_D^{25} 1.4552. The yield was 51 g. or 33%.

Anal. Calc'd for $C_9H_{16}O_2$: C, 69.2; H, 10.3.
Found: C, 69.2; H, 10.4.

The *semicarbazone* melted at 102° after recrystallization from 50% alcohol.

Anal. Calc'd for $C_{10}H_{19}N_3O_2$: C, 56.5; H, 8.9; N, 19.7.
Found: C, 57.0; H, 9.0; N, 19.8.

Ethyl β-methoxymethyl-β-cyclohexylhydracrylate (XV), boiling at 116° at 3 mm. was prepared in 59% yield by a process similar to that used for the analogous phenylhydracrylic ester; n_D^{25} 1.4615.

Anal. Calc'd for $C_{13}H_{24}O_4$: C, 63.9; H, 9.9.
Found: C, 63.7; H, 10.0.

β-Methoxymethyl-β-cyclohexylhydracrylic acid (XVI) was obtained as a viscous syrup which slowly crystallized, on alkaline saponification of the above ester. The acid was recrystallized from petroleum ether (Skellysolve B), and melted at 48°.

Anal. Calc'd for $C_{11}H_{20}O_4$: C, 61.1; H, 9.3; OCH_3, 14.3.
Found: C, 61.3; H, 9.3; OCH_3, 13.4.

The p-*bromophenacyl ester* melted at 90° after recrystallization from alcohol.

Anal. Calc'd for $C_{19}H_{25}BrO_5$: C, 55.2; H, 6.0.
Found: C, 55.4; H, 6.4.

β-Cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (XVIII). A mixture of 21.6 g. of the above acid and 60 cc. of glacial acetic acid which had been previously saturated with dry hydrogen bromide at 0° was refluxed for 2 hrs., cooled, and poured into 300 cc. of ice-water. The aqueous solution was neutralized with sodium carbonate and extracted with ether. The material extracted by the ether was distilled under reduced pressure and gave the unsaturated lactone as a clear, colorless oil which boiled at 134° at 4 mm. It gave the characteristic color reaction with Tollens' reagent and with alkaline nitroprusside solution. The yield was 7.5 g. or 45%.

Anal. Calc'd for $C_{10}H_{14}O_2$: C, 72.5; H, 8.5.
Found: C, 72.5; H, 8.8.

Saponification equivalent calc'd: 166; found: 167. n_D^{25} 1.5059; d_4^{25} 1.0985 M_D calc'd: 45.05; M_D found: 45.94.

β-Cyclohexyl-β-hydroxybutyrolactone (XVII) was obtained along with the above unsaturated lactone by treating the hydracrylic acid as follows. A mixture of 110 g. of the acid and 210 cc. of an acetic acid solution of hydrogen bromide was heated under reflux in an oil-bath at a bath temperature of 95–100° for 1.5 hours. After cooling, the mixture was poured into ice-water and the resulting solution was neutral-

ized with sodium carbonate. At this point the saturated hydroxy lactone separated as a crystalline solid. The mixture was extracted with ether and, after removal of the ether, an oil which crystallized for the most part on scratching and chilling, remained. The crystalline material was separated from the oil as well as possible by filtration, and was recrystallized first from ether and then from water. β-Cyclohexyl-β-hydroxybutyrolactone as thus obtained melted at 112°. The yield was 33.5 g. or 36%. The lactone was saturated toward catalytically activated hydrogen and gave negative Tollens' and Legal tests.

Anal. Calc'd for $C_{10}H_{16}O_3$: C, 65.3; H, 8.8.
Found: C, 65.7; H, 8.8.

Saponification equivalent calc'd: 184; found: 186.

The oil from which the crystalline hydroxy lactone was removed was distilled at reduced pressure, and gave 13.5 of g. or 16% of the unsaturated lactone boiling at 132–135° at 4 mm.

When the hydroxy lactone was refluxed with an acetic acid solution of hydrogen bromide in an oil-bath at 140–150° for 2 hours a 92% yield of the unsaturated lactone was obtained.

A similar experiment, wherein 30 g. of ethyl β-methoxymethyl-β-cyclohexylhydracrylate was refluxed with 85 cc. of an acetic acid solution of hydrogen bromide over a free flame for 2 hours, gave 4 g. or 18% of the saturated hydroxy lactone and 6.5 g. or 32% of the unsaturated lactone.

Ethyl β-cyclohexyl-β-formylpropionate. A mixture of 45 g. of ethyl β-methoxymethyl-β-cyclohexylhydracrylate and 15 g. of freshly fused potassium acid sulfate was heated in a Claisen flask at 160–180° for 40 min., and then distilled at 10 mm. pressure. The entire distillate was dissolved in ether and shaken for several hours with a saturated solution of sodium bisulfite. No appreciable amount of bisulfite compound was formed. The ether solution was washed with water, dried, and the residue, after removal of the solvent, was fractionally distilled at reduced pressure. After a fore-run of about 15 g. which boiled up to 140° at 5 mm., a fraction of 21.5 g. boiling at 140–144° at 7 mm. was obtained. This was redistilled at 5 mm. pressure and the fraction boiling at 142–144° was taken as ethyl β-cyclohexyl-β-formylpropionate; n_D^{25} 1.4682; d_4^{25} 1.0288 M_D calc'd: 57.3; found: 57.2.

Anal. Calc'd for $C_{12}H_{20}O_3$: C, 67.8; H, 9.5.
Found: C, 67.4; H, 9.7.

The failure of the above aldehyde ester to form a bisulfite addition-compound was checked with the pure material. However, it gave a positive Schiff test.

The *2,4-dinitrophenylhydrazone* melted at 128–128.5°.

Anal. Calc'd for $C_{18}H_{24}N_4O_6$: C, 55.0; H, 6.2; N, 14.3.
Found: C, 54.7; H, 6.1; N, 14.4.

The presence of an ester group in the above aldehyde ester was shown by a quantitative saponification. Saponification equivalent calc'd: 213; found: 212. The acid from this saponification was converted to the methyl ester with diazomethane. From this the semicarbazone, which melted at 119–119.5°, was prepared. The 2,4-dinitrophenylhydrazone melted at 143°. Neither of these derivatives showed a depression in melting point when mixed with the corresponding derivatives of the methyl ester prepared as described in a following paper (19).

Methoxymethylcyclopentyl ketone, boiling at 86–87° at 14 mm. n_D^{25} 1.4486, was prepared in 22% yield as in the case of the analogous cyclohexyl ketone.

Anal. Calc'd for $C_8H_{14}O_2$: C, 67.5; H, 9.9.
Found: C, 67.1; H, 9.9.

The *2,4-dinitrophenylhydrazone* melted at 129.5° after recrystallization from dilute alcohol.

Anal. Calc'd for $C_{14}H_{18}N_4O_5$: N, 17.4. Found: N, 17.5.

From this were prepared, by essentially the same method used for the cyclohexyl derivatives, *ethyl β-methoxymethyl-β-cyclopentylhydracrylate*, boiling at 121–123° at 3 mm., n_D^{25} 1.4557, in 67% yield,

Anal. Calc'd for $C_{12}H_{22}O_4$: C, 62.6; H, 9.7.
Found: C, 62.9; H, 9.7.

and *β-methoxymethyl-β-cyclopentylhydracrylic acid*, melting at 42° from petroleum ether (Skellysolve B), in 92% yield,

Anal. Calc'd for $C_{10}H_{18}O_4$: C, 59.4; H, 9.0.
Found C, 59.6; H, 9.3.

the p-*bromophenacyl ester* of which melted at 78° after crystallization from dilute alcohol.

Anal. Calc'd for $C_{18}H_{23}BrO_5$: C, 54.2; H, 5.8.
Found: C, 54.4; H, 5.8.

β-Cyclopentyl-$\Delta^{\alpha,\beta}$-butenolide was prepared in 15% yield by cyclization and dehydration of the above acid as in the preceding case. It boiled at 130–132° at 1.5 mm. and gave the characteristic Tollens and Legal tests; n_D^{25} 1.5049.

Anal. Calc'd for $C_9H_{12}O_2$: C, 71.0; H, 8.0.
Found: C, 70.4; H, 7.9.

Ethyl-β-hydroxy-β-methoxymethylheptanoate, boiling at 101–103° at 3 mm. was prepared in 62% yield as in the preceding cases.

Anal. Calc'd for $C_{11}H_{22}O_4$: C, 60.5; H, 10.2.
Found: C, 60.4; H, 10.3.

From this were prepared *β-hydroxy-β-methoxymethylheptanoic acid*, boiling at 148–150° at 3 mm.,

Anal. Calc'd for $C_9H_{18}O_4$: C, 56.8; H, 9.5.
Found: C, 56.8; H, 9.8

and β-n-*butyl-$\Delta^{\alpha,\beta}$-butenolide*, boiling at 102° at 1 mm.

Anal. Calc'd for $C_8H_{12}O_2$: C, 68.5; H, 8.6.
Found: C, 68.2; H, 9.0.

Saponification equivalent calc'd: 140; found: 139. n_D^{25} 1.4617; $d_4^{2.5}$ 0.9950; M_D calc'd: 38.01; M_D found 38.69. The lactone gave the characteristic color tests.

Cyclohexylglyoxal. A suspension of 111 g. of selenium dioxide in a mixture of 600 cc. of dioxane and 20 cc. of water in a 1-l. 3-necked flask equipped with a reflux condenser was warmed on the water-bath with mechanical stirring until solution of the selenium dioxide was complete. To this solution 126 g. of cyclohexylmethyl ketone was added and the mixture was refluxed with stirring for 4 hours. The cooled solution was filtered from precipitated selenium, the solvent was removed at atmospheric pressure, and the residue was fractionated under reduced pressure. Cyclohexylglyoxal distilled as a viscous yellow oil at 71–72° at 17 mm. The yield was 83 g. or 59%. The substance showed a strong tendency to polymerize and therefore was not analyzed as such, but converted directly to the more stable acetal as rapidly as possible.

Diethylacetal of cyclohexylglyoxal (VI). The above glyoxal was added to 300 g. of absolute alcohol containing 3% of dry hydrogen chloride, and the mixture was allowed to stand 24 hours at room temperature. The hydrogen chloride and alcohol were removed under reduced pressure, and the residue was fractionally distilled under reduced pressure. A fore-run of 28 g. of unreacted glyoxal came over first, followed

by 67 g. or 80% (based on the glyoxal reacted) of colorless cyclohexylglyoxal diethylacetal which boiled at 127–128° at 18 mm.

Anal. Calc'd for $C_{12}H_{22}O_3$: C, 67.2; H, 10.4.
Found: C, 67.4; H, 10.4.

Ethyl β-hydroxy-β-cyclohexyl-γ,γ-diethoxybutyrate (VII). A mixture of 44 g. of the diethylacetal of cyclohexylglyoxal, 22.9 cc. of freshly distilled ethyl bromoacetate, 13.7 g. of granulated zinc, and 150 cc. of dry benzene was allowed to stand until the initial violent reaction had moderated, and was then refluxed for 1.5 hours. The zinc complex was decomposed by shaking the reaction-mixture with successive portions of saturated ammonium chloride solution rather than with mineral acid, in order to avoid hydrolysis of the acetal. Fractional distillation of the product at reduced pressure gave 22 g. of unreacted glyoxal acetal and 23 g. of the desired material which boiled at 117–120° at 0.5 mm.

Anal. Calc'd for $C_{16}H_{30}O_5$: C, 63.5; H, 10.1.
Found: C, 63.7; H, 10.0.

Unpromising results at attempted dehydration of this hydroxy ester have caused this approach to the synthesis of the $\Delta^{\beta,\gamma}$-unsaturated lactone to be temporarily discontinued.

The microanalyses reported in this paper were performed by Mr. Saul Gottlieb of these laboratories.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

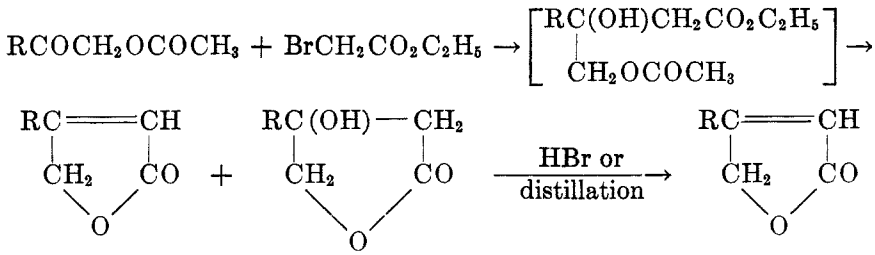
STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. II. SYNTHESIS OF β-SUBSTITUTED $\Delta^{\alpha,\beta}$-BUTENOLIDES FROM ω-ACETOXYMETHYL KETONES

ROBERT G. LINVILLE AND ROBERT C. ELDERFIELD

Received December 5, 1940

In the preceding paper the synthesis of β-substituted $\Delta^{\alpha,\beta}$-butenolides proceeding from methoxymethyl ketones was described. Inasmuch as the original starting materials in this synthesis are halides, it was felt that for purposes of preparing such lactones with larger ring systems as substituents, some other primary starting derivative would be useful in cases where difficulty is experienced in securing the requisite halide or Grignard reagent derived therefrom. To this end we have investigated the use of acetoxymethyl ketones rather than methoxymethyl ketones for the preparation of the butenolides. The former are readily prepared by the action of diazomethane on the appropriate acid chloride at low temperatures, which gives intermediate diazomethyl ketones. These in turn are converted to the acetoxymethyl ketones by reaction with acetic acid. The literature on this reaction, which was first noted by Bradley and Robinson (1), has been tabulated by Arndt and Eistert (2). To this should be added a reference to the use to which the reaction has been put in the synthesis of desoxycorticosterone by Steiger and Reichstein (3).

The series of reactions utilized is shown in the accompanying formulas. The acetoxymethyl ketones were treated with zinc and ethyl bromoacetate according to the general Reformatzky procedure. On decomposition of the zinc complex, it was not possible to isolate the primary reaction-product. Rather, this apparently underwent lactone formation and partial dehy-



dration, leading to the formation of a mixture of saturated hydroxy lactone and unsaturated lactone. Where R is cyclohexyl, it was possible to isolate the saturated hydroxy lactone. This proved to be identical with the saturated hydroxy lactone obtained by gentle treatment of ethyl β-methoxymethyl-β-cyclohexylhydracrylate with hydrogen bromide in acetic acid as described in the preceding paper (4). Where R is phenyl or β-naphthyl it was not possible to separate the two lactones. Further treatment of the crude reaction-mixtures of saturated hydroxy lactone and unsaturated lactone either by distillation or with hydrogen bromide in acetic acid resulted in complete conversion of the former to the latter. From the mode of formation of the unsaturated lactones, little doubt remains that they possess the structure assigned to them.

EXPERIMENTAL

All boiling points and melting points are corrected for stem exposure.

ω-Acetoxyacetophenone. A solution of 30 g. of freshly distilled benzoyl chloride in 60 cc. of dry ether was added drop-wise to a solution of 15–16 g. of diazomethane, prepared from 60 g. of nitrosomethylurea (5), the temperature of the mixture being kept at −10°. The temperature was held at this point for 1 hour, and the mixture was then allowed to stand overnight at room temperature. After removal of the ether, the crude diazomethyl ketone was warmed with 150 cc. of glacial acetic acid until evolution of nitrogen ceased. After dilution, the acetoxymethyl ketone was extracted with ether and distilled at 0.7 mm., the fraction boiling at 118–122° being collected. After recrystallization from petroleum ether (Skellysolve B), it melted at 49°. Zincke (6) reports 48–49° as the melting point of ω-acetoxyacetophenone. The yield was 55% based on the benzoyl chloride used.

Reaction of ω-acetoxyacetophenone with ethyl bromoacetate. Ten grams of freshly distilled ethylbromoacetate was added dropwise and with vigorous stirring to a mixture of 10 g. of ω-acetoxyacetophenone, 7.7 g. of granulated zinc, and 70 cc. of anhydrous benzene in a 3-necked flask equipped with a reflux condenser and mechanical stirrer. The mixture was refluxed for 2 hours, and the zinc compound was decomposed as usual with ice and dilute hydrochloric acid. After washing the benzene layer free from acid and removal of the solvent, 10.2 g. of a semi-solid remained. A small test portion of the crystalline material was removed and the accompanying oil was drained off on a porous plate. The remaining crystalline material gave a strong nitroprusside reaction and was identified as β-phenyl-$\Delta^{\alpha,\beta}$-butenolide by mixed melting point (4). It was impossible to isolate the oily hydroxy lactone in a pure state since this lost water very easily on manipulation. Therefore the crude product of the above reaction was refluxed with 30 cc. of an acetic acid solution of dry hydrogen bromide saturated at 0° for 1 hour. The solution was poured into water and the crystalline β-phenyl-$\Delta^{\alpha,\beta}$-butenolide was filtered off and recrystallized from 75% alcohol, with liberal use of decolorizing carbon. The lactone melted at 92° and the melting point was not depressed when the lactone was mixed with that prepared from the methoxymethyl ketone (4). The yield was 44.5%.

β-Naphthylacetoxymethyl ketone was prepared in 72% yield from β-naphthoyl chloride by the same method. It melted at 80° after recrystallization from petroleum ether (Skellysolve B). Madelung and Oberwegner (7) report the acetoxy ketone as melting at 80°.

β-(β-Naphthyl)-$\Delta^{\alpha,\beta}$-butenolide, melting at 126° after recrystallization from alcohol, was prepared in 50% yield from the acetoxy ketone as in the case of the phenyl derivative.

Anal. Calc'd for $C_{14}H_{10}O_2$: C, 80.0; H, 4.8.
Found: C, 80.1; H, 4.8.

Cyclohexylacetoxymethyl ketone was prepared in 64% yield from cyclohexylcarboxylic acid chloride by the same general method. It boiled at 100–101° at 1 mm.

Anal. Calc'd for $C_{10}H_{16}O_3$: C, 65.2; H, 8.7.
Found: C, 65.5; H, 8.8.

The *semicarbazone* melted at 149–150° after crystallization from 50% alcohol.

Anal. Calc'd for $C_{11}H_{19}N_3O_3$: C, 54.6; H, 7.9; N, 17.5.
Found: C, 54.6; H, 8.0; N, 17.5.

When 27.5 g. of the above cyclohexylacetoxymethyl ketone was subjected to the Reformatzky reaction with 20 g. of granulated zinc and 25 g. of ethyl bromoacetate in 175 cc. of benzene, 26 g. of crude product was obtained. This deposited crystals on standing. A small portion of the crystalline material was removed from the mixture, freed from accompanying oil by pressing on a porous plate, and recrystallized from water. The crystalline material melted at 112° and gave no depression with β-cyclohexyl-β-hydroxybutyrolactone prepared from methoxymethylcyclohexyl ketone (4). It was neutral, saturated towards catalytically activated hydrogen and gave negative Tollens' and nitroprusside color tests.

Anal. Calc'd for $C_{10}H_{16}O_3$: C, 65.3; H, 8.8.
Found: C, 65.7; H, 8.8.

The above saturated hydroxy lactone gave β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide, identical in all respects with the unsaturated lactone prepared from cyclohexylmethoxymethyl ketone (4), in 92% yield when refluxed with a saturated solution of hydrogen bromide in acetic acid for one hour. The unsaturated lactone was also obtained when the crude product of the Reformatzky reaction was distilled at 0.7 mm. pressure.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. III. THE PROPERTIES OF β-SUBSTITUTED $\Delta^{\alpha,\beta}$-BUTENOLIDES AND A SUGGESTED REVISION OF THE STRUCTURE OF THE SIDE CHAIN OF THE DIGITALIS-STROPHANTHUS AGLYCONES

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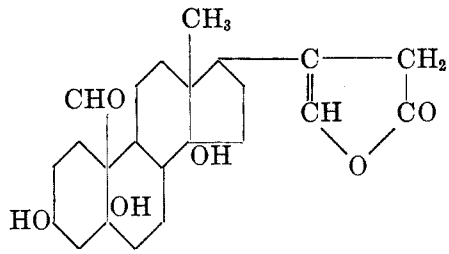
The main structural features of the digitalis-strophanthus group of cardiac aglycones rest on a reasonably firm foundation as a result of the investigations principally of Jacobs, Windaus, and Tschesche and their collaborators. The evidence on which these structures have been assigned has been adequately reviewed on several occasions (1). The main structural features of the molecule of strophanthidin, which may be taken as typical, are given in I.

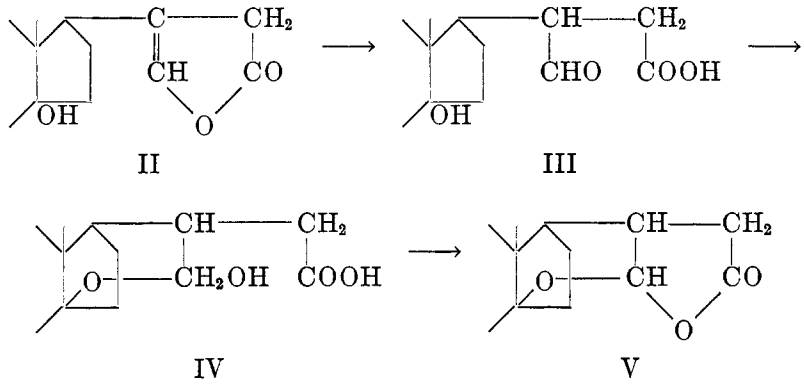


I

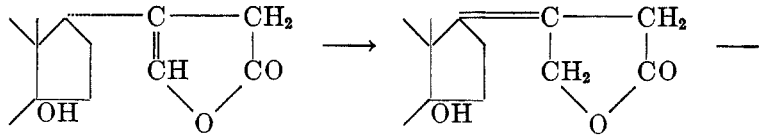
The other members of the group differ in the degree and position of hydroxylation, except that all known members of the group carry hydroxyl groups in positions 3 and 14, and in the nature of the group attached to carbon atom 10, which is aldehydic in strophanthidin but in the form of a methyl group in the other members which have been studied in detail. Perhaps the outstanding structural characteristic of these substances is found in the side chain which has been formulated as the lactone of an enolized β-aldehydopropionic acid to which the cyclopentanophenanthrene ring system is attached through the β-carbon atom. In the present communication we wish to present evidence which we believe suggests that these substances may be more satisfactorily formulated as reduced cyclopentanophenanthrene-$\Delta^{\alpha,\beta}$-butenolides, or as $\Delta^{\alpha,\beta}$-unsaturated lactones, rather than

as lactones of the $\Delta^{\beta,\gamma}$-type as hitherto suggested. For this purpose it will be necessary to review the evidence on which the $\Delta^{\beta,\gamma}$-structure has been based.

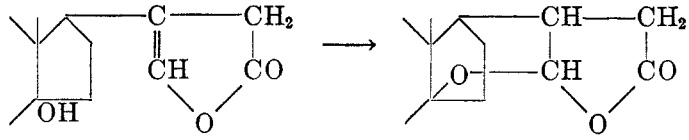
The evidence which indicates the presence of a $\Delta^{\beta,\gamma}$-structure rests largely on a study of the so-called iso-aglycones which result when the aglycones are subjected to the action of a methyl alcoholic solution of potassium hydroxide. For purposes of discussion, strophanthidin (2, 3) will be taken as typical of the other members of the group. For convenience such isomerizing action of alkali may be represented by the series of changes II–V. In this formulation the complete series of changes is



not necessary, as will be discussed below, although the case for the $\Delta^{\beta,\gamma}$-lactone can be more clearly presented on this scheme. The first action of the alkali consists in opening of the lactone ring in II which sets free an aldehyde group (III). This may exist as a lactal (IV) by virtue of the hydroxyl group in reactive proximity on carbon atom 14. The lactal can then undergo lactonization to yield isostrophanthidin (V). However convenient such an explanation may be, it does not accord with the experimental observation of Jacobs and Collins (2) that preliminary saponification of the lactone group of strophanthidin is not necessary for the formation of isostrophanthidin under the action of a methyl alcoholic solution of potassium hydroxide. In order to take this fact into account Jacobs and Elderfield (4) proposed a mechanism for the change in accordance with formulas VI–IX. In this interpretation, the side chain of strophanthidin is pictured as originally in a trans configuration to the hydroxyl group on carbon atom 14. The action of alcoholic alkali then consists in (a) a shift of the double bond to the 17,20-position (VII), (b) a shift of this $\Delta^{17,20}$-double bond back to its original position with an inversion of the configuration of the side chain at carbon atom 17 so that it has now become cis to the hydroxyl group on carbon atom 14 (VIII), and (c) forma-



VI VII



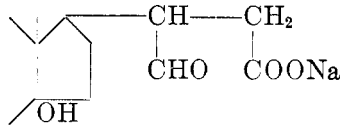
VIII IX

tion of the new oxidic bridge to yield isostrophanthidin (IX), presumably by direct addition of the hydroxyl group at position 14 to the double bond which has now become possible by virtue of the cis relationship of the side chain and the hydroxyl group in question.

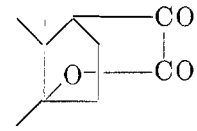
Whatever the mechanism of the formation of iso- derivatives of the aglycones, there is no doubt that the latter are represented by structures V or IX. In support of this, Jacobs and Gustus have succeeded in preparing carbonyl derivatives of saponified iso-aglycones (3, 5), and the lactal form of the saponified iso-aglycones has been oxidized to a lactone in many cases (2, 3, 5, 6, *inter alia*). Largely on the basis of the behavior of the iso-aglycones, the original aglycones have been formulated as $\Delta^{\beta,\gamma}$-butenolides, or as the lactones of enolized β-aldehydo acids. Additional points which have been interpreted as indicating such an arrangement will be developed shortly.

While the $\Delta^{\beta,\gamma}$-formulation satisfactorily accounts for the great majority of the observed experimental facts, a few remain which cannot be adequately explained on this basis. Among these may be cited the failure of certain aglycones, *e.g.* the aglycone of uzarin (7) and allostrophanthidin (8), to yield iso-aglycones under conditions where such a reaction would be expected. This has been ascribed to the occurrence of a trans configuration of the side chain with respect to the hydroxyl group on carbon atom 14, and, in the case of allostrophanthidin, experimental evidence has been obtained in support of this view (9). It is difficult to see why, on the basis of the Jacobs and Elderfield formulation of the formation of iso-aglycones, some such iso-compound should not be formed, since this mechanism postulates a disturbance and re-establishment of asymmetry on carbon atom 17, in which at least a portion of the substance would be expected to assume a cis configuration on the two asymmetric centers in question. A second fact which is difficult to reconcile with the $\Delta^{\beta,\gamma}$-formulation is the structure XI, which has been shown to represent the product of the oxidation of saponified strophanthidinic acid (X) (10). This com-

pound is much better formulated on the basis of a $\Delta^{\alpha,\beta}$-arrangement of the side chain. Indeed it is exceedingly difficult to account for XI on the



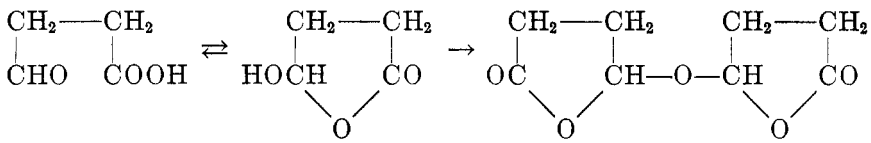
X



XI

basis of the $\Delta^{\beta,\gamma}$-arrangement unless one postulates a shift of the double bond to the $\Delta^{\alpha,\beta}$-position during saponification of the lactone.

Despite the almost overwhelming evidence of Jacobs and his co-workers in favor of the $\Delta^{\beta,\gamma}$-formulation, we were led to investigate the possible application of a $\Delta^{\alpha,\beta}$-formulation in the hope that it would be possible to explain some of the inconsistencies arising from the $\Delta^{\beta,\gamma}$-arrangement and at the same time to retain the unquestionably valid interpretation of the structure of the iso-aglycones. In this we have been guided by a few general observations on record concerning the nature of simple β-aldehydo acids and the products which are formed on attempted lactonization of their enolic forms. The simplest acid of this type, β-aldehydopropionic acid, has been the subject of intensive study by von Ungern-Sternberg (11), Harries and Alefeld (12), and Perkin, Jr. and Sprankling (13). In the course of their investigations, none of these workers was able to accomplish the lactonization of the acid, which they showed existed as an equilibrium mixture of the open aldehydo acid (XII) and the hydroxy lactone (XIII). All attempts at lactonization resulted either in the formation of derivatives of XIII in which the hydroxyl group was attacked, or in the formation of a bimolecular compound (XIV). A similar experience with α,α,β-trimethyl-β-formylbutyric acid and with α,α-dimethyl-β-phenyl-β-formylbutyric acid has been recorded by Blaise and Courtot (14). In this con-



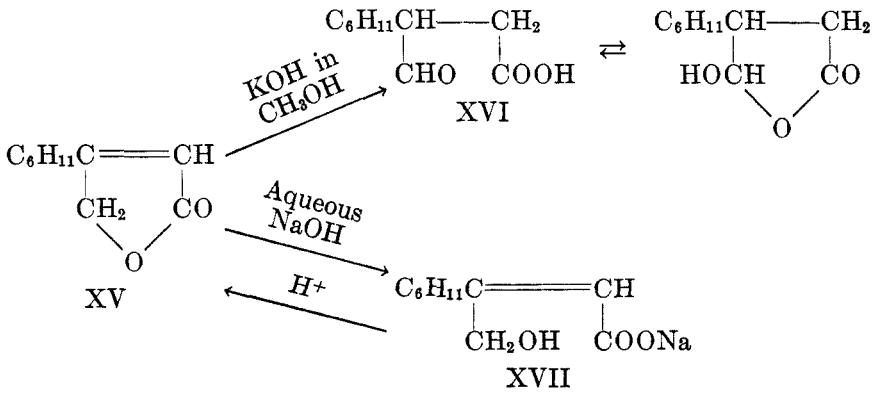
XII XIII XIV

nection it should be noted that the valuable studies of model unsaturated lactones carried out by Jacobs, Hoffmann, and Gustus (15) and by Jacobs and Scott (16) were all done with the lactones of enolized keto acids, with the exception of the lactones of the formyl acids described by Blaise and Courtot (14). The latter lactones were prepared by elimination of hydrogen bromide from saturated bromo lactones rather than by ring closure of the aldehydo acids. No proof of their structure was offered aside from the fact that they yielded aldehydo acids on hydrolysis. In the light of

observations presented in this paper, this proof can not be taken as conclusive. The lactone of enolized β-aldehydopropionic acid can be considered as the ketonic form of α-hydroxyfuran, and the consistent failure of investigators to obtain this from other furan derivatives occasions some doubt as to the existence of stable derivatives of α-hydroxyfuran (17) unless a substituent occurs in the other α-position, which would result in a keto lactone, or unless the molecule is heavily substituted elsewhere. Thus the reported relative stability of the Blaise and Courtot lactones can be explained satisfactorily on the basis of the observation of Boorman and Linstead (18), that the presence of an α-methyl group greatly increases the stability of α-methyl-γ-valerolactone compared to γ-valerolactone. The presence of two stabilizing α-methyl groups in the Blaise and Courtot lactones, therefore, would result in an enhanced stability over that predicted for the unsubstituted derivative, possibly because of the absence of α-hydrogen atoms.

In a preceding paper (19) the synthesis of model β-substituted $\Delta^{\alpha,\beta}$-butenolides has been described. A study of the properties of β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide has revealed information which has led us to consider more seriously the question of a $\Delta^{\alpha,\beta}$-formulation for the unsaturated lactones of the natural cardiac drugs. Catalytic reduction of the cyclohexyl lactone with the platinum oxide catalyst of Adams and Shriner resulted in the absorption of one mole of hydrogen and the formation of β-cyclohexyl butyrolactone. The reduction thus parallels that of the natural aglycones, and contrasts with the behavior of lactones which have a double bond at the point of lactonization. The latter give varying amounts of desoxy acids on catalytic reduction (16). From the natural substances, as well as from our model substance, no acidic products have been isolated.

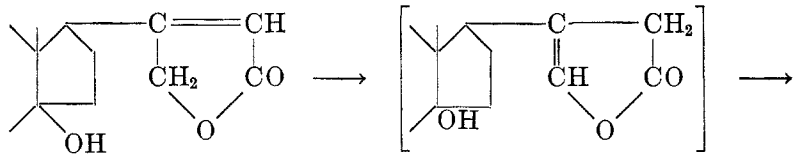
A study of the action of alkali on β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide has yielded information which lends strong support to the hypothesis for the presence of a $\Delta^{\alpha,\beta}$-lactone in the natural aglycones. Two distinct modes of action of alkali, depending on the experimental conditions used, have been noted. These may be represented by formulas XV–XVII:



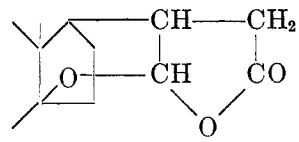
When the unsaturated lactone is subjected to the action of a solution of potassium hydroxide in absolute methyl alcohol at 0°, the characteristic nitroprusside (Legal) reaction disappears on allowing the reaction-mixture to stand for some hours. On working up the reaction-mixture, β-cyclohexyl-β-formylpropionic acid was isolated in practically quantitative yield and was characterized by the preparation of the semicarbazone of its methyl ester. The aldehyde acid showed no tendency to relactonize when subjected to the prolonged action of warm dilute hydrochloric acid. When it was heated in a sealed tube with acetic anhydride-acetyl chloride under conditions which normally lactonize a keto acid, the acetate of the hydroxy lactone form was obtained. Whether the aldehydo acid produced by the action of methyl alcoholic potassium hydroxide on the unsaturated lactone results through the formation of an intermediate methylal, or enol ether, which is decomposed on acidification of the reaction-mixture is a question which must be left open for the present. However the irreversibility of the reaction under these conditions is definite.

On the other hand, when the unsaturated cyclohexyl lactone was treated with alkali in 50% alcoholic solution, the reaction took a different course. While the above aldehydo acid was formed to a greater or less extent, at the same time direct hydrolysis of the lactone to the unsaturated hydroxy acid (XVII) also occurred. The hydroxy acid, in contrast to the aldehydo acid (XVI), readily relactonized on gentle acidification with regeneration of the original $\Delta^{\alpha,\beta}$-lactone. The amount of aldehydo acid formed under these conditions varied with the temperature at which the reaction was carried out. When the unsaturated lactone was shaken with a solution of sodium hydroxide in 50% alcohol at room temperature, the product was almost exclusively the sodium salt of the unsaturated hydroxy acid, with but a trace of the aldehydo acid; on the other hand, when the reaction was carried out at the boiling point of the solvent, both products resulted in the ratio of about one part of the sodium salt of the hydroxy acid to two parts of the aldehydo acid.

We believe that, if the observed experimental facts concerning the varying action of alkali on the natural cardiac aglycones be re-interpreted on the basis of the above behavior of the model $\Delta^{\alpha,\beta}$-unsaturated lactone, a more logical explanation for these findings results. The formation of the iso-aglycones under the influence of a solution of potassium hydroxide in methyl alcohol, thus becomes due merely to an irreversible shift of the $\Delta^{\alpha,\beta}$-double bond to yield an aldehyde acid, possibly through the intermediate transitory formation of a $\Delta^{\beta,\gamma}$-lactone, followed by establishment of the new oxidic bridge on carbon atom 14 (XVIII–XX), in some manner yet to be determined.



XVIII XIX



XX

The possible intermediate formation of XIX is indicated by the transitory character of the positive nitroprusside test shown by the substances in question. In such a formulation for the iso change, no disturbance of the asymmetry about carbon atom 17 is necessary, from which it follows that a trans configuration of the hydroxyl group on carbon atom 14 and the side chain, such as apparently exists in allostrophanthidin, will effectively prevent the formation of an iso compound.

Another observation which can be explained more satisfactorily on the basis of the above experiments is the ready relactonization of saponified pseudostrophanthidin and digitoxigenin when these substances are saponified by shaking with aqueous alcoholic alkali at room temperature (15). If an aldehydo acid were liberated by saponification of a $\Delta^{\beta,\gamma}$-lactone under such circumstances, it is difficult to explain the extremely easy relactonization in the light of our own experience, as well as that of others (11, 12, 13, 14) on the lactonization of aldehydo acids. On the other hand, the isolation of carbonyl derivatives from saponified derivatives of dianhydrostrophanthidin (20, 15) when the saponification was carried out hot is paralleled by the behavior of our model lactone under similar conditions.

Finally, as already indicated, the observed degradation of the side chain when saponified strophanthidinic acid (10) is oxidized by permanganate can only be explained by the presence of a $\Delta^{\alpha,\beta}$-double bond. A completely satisfactory picture of the reported isomonoanhydrostrophanthidin (21) is not possible at present. We are studying a model lactone containing a double bond in the same relative positions to the side chain as have been suggested for monoanhydrostrophanthidin.

Unfortunately, it has not been possible to strengthen the argument for the $\Delta^{\alpha,\beta}$-formulation of the side chain of the natural aglycones by direct oxidative rupture of the double bond, except in the previously reported case of saponified strophanthidinic acid (10). Attempts to cleave the

side chain of representative aglycones using such reagents as ozone, osmic acid, hydrogen peroxide and osmic acid, and Prevost's reagent have led either to the recovery of the original material or to non-crystallizable material. However, the ultraviolet absorption curves for strophanthidin

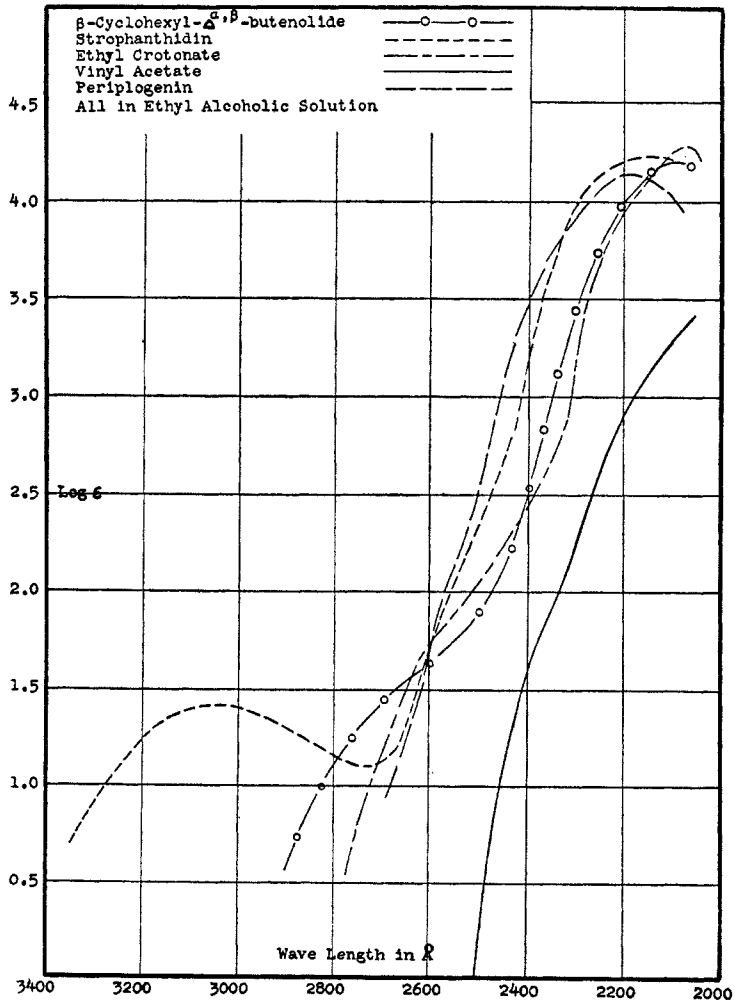


FIG. 1

and for periplogenin supply evidence for the $\Delta^{\alpha,\beta}$-arrangement. In Fig. 1 are shown the curves for the two aglycones together with similar curves for β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide, ethyl crotonate and vinyl acetate. The curves for the first four substances are closely similar with strong maxima between 2100–2150 Å, which are due to the presence of the conjugated

system. Vinyl acetate, which possesses the same arrangement of ethylenic and carbonyl double bonds as would obtain in a $\Delta^{\beta,\gamma}$-lactone furnished a curve radically different from those of the $\Delta^{\alpha,\beta}$-derivatives.

The presence of an apparently reactive methylene group in the aglycones has been offered as supporting evidence for the $\Delta^{\beta,\gamma}$-formulation. Such would, indeed, be expected by virtue of the position of the hydrogen atoms on the α-carbon atom which is situated between the carbonyl double bond and the ethylenic double bond. The evidence in favor of the presence of such a reactive methylene group rests first on the nature of the characteristic nitroprusside (Legal) and Tollens reactions, and secondly on the apparent formation of a mole of methane under the conditions of the Zerewitinoff procedure.

In a study of the model α- and β-angelica lactones, Jacobs, Hoffmann, and Gustus (15) noted a well defined difference between the $\Delta^{\alpha,\beta}$- and $\Delta^{\beta,\gamma}$-angelica lactones both with regard to the speed of development of the Tollens test and to the speed of development and duration of the Legal test. From their observations the promptness of the appearance of the nitroprusside test indicated that the aglycones are $\Delta^{\beta,\gamma}$-lactones, while the gradual reduction of Tollens' reagent suggested the $\Delta^{\alpha,\beta}$-form. On the logical assumption, based on Thiele's observations (22) that the $\Delta^{\alpha,\beta}$-isomer is transformed into $\Delta^{\beta,\gamma}$-angelica lactone under the influence of the reagents used in the tests, they interpreted the positive tests given by the $\Delta^{\alpha,\beta}$-angelica lactone as in reality being due to a small amount of the other isomer formed during the tests. While these studies of the angelica lactones are of value, the fact must be emphasized that the two unsaturated lactones are in equilibrium. On the other hand, as is now shown, the corresponding $\Delta^{\beta,\gamma}$-lactone of an aldehydo acid presumably is capable of but short life, at best, and the equilibrium between the $\Delta^{\alpha,\beta}$- and $\Delta^{\beta,\gamma}$-forms in such a case is irreversible. In contrast to the reported behavior of $\Delta^{\alpha,\beta}$-angelica lactone, we now find that β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide shows exact resemblance to strophanthidin in both the Tollens and Legal tests. In applying the nitroprusside color test, we have noted that the intensity and duration of the color produced is closely dependent on the acidity or alkalinity of the solution. By employing a technique slightly different from that usually used in these tests, we have succeeded in bringing out more sharply the similarity of the tests exhibited by strophanthidin and the cyclohexylbutenolide, and the contrast shown by $\Delta^{\beta,\gamma}$-angelica lactone in comparison with the two former substances. Inasmuch as the production of the color in the nitroprusside test is apparently due to an oxidation phenomenon, it was felt that a still sharper differentiation could be obtained if a reagent of slightly lower oxidation potential could be found. This has been done by using potassium ferricyanide. In alkaline solution no

color is obtained with $\Delta^{\beta,\gamma}$-angelica lactone, whereas both strophanthidin and β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide give a reddish-brown color which was indistinguishable in the two cases.

At first glance the reported formation of a mole of methane from the side chain of the aglycones in the Zerewitinoff test (23) appears difficult to re-interpret on the basis of the $\Delta^{\alpha,\beta}$-formula, although, from time to time certain abnormalities have occurred with certain aglycone derivatives. For convenience the necessary data for re-interpretation of this point are shown in Table I. At the outset, a discrepancy between the reported behavior of the intact side chain of the aglycones and the observed production of about 0.4–0.5 moles of methane from the analogous cyclohexyl

TABLE I

SUBSTANCE	MOLES CH_4 PER MOLECULE
Digitoxigenin (26)	3.04
Strophanthidinic acid methyl ester (26)	4.27
Digitoxigenin acetate (26)	2.09
Dianhydrodilactone from strophanthidin (26)	1.09
Dihydrostrophanthidin (26)	2.92
Isostrophanthidin (26)	2.07
α-Anhydrodigitoxigenin (26)	1.42
β-Anhydrodigitoxigenin (26)	1.42
Tetrahydrodilactone from strophanthidin (26)	0.57
Dihydromonoanhydrostrophanthidin (27)	2.1
Cyclohexyl benzoate (27)	0.06
Cyclohexyl acetate (27)	.70
β-Cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (27)	.43
β-Cyclopentyl-$\Delta^{\alpha,\beta}$-butenolide (27)	.39
β-Phenyl-$\Delta^{\alpha,\beta}$-butenolide (27)	.55
Strophanthidin *p*-bromobenzoate (27)	2.45

model appears. This discrepancy may be rationalized on the basis of observations dealing with the behavior of various classes of compounds under the conditions of the Zerewitinoff procedure which indicate that extreme caution must be used in interpreting data obtained by this method. Thus, in substances where enolization is possible, one frequently observes the formation of a fraction of a mole of methane. For example, catechol diacetate gives 0.24 moles of methane, benzoin acetate gives 0.58 moles, and acetic anhydride gives 0.54 moles (24). We have confirmed this trend for cyclohexyl acetate. On the other hand, where enolization is impossible, as with cyclohexyl benzoate, no significant amount of methane was observed. Likewise the presence of a hydrogen atom on a carbon atom situated between two ethylenic double bonds has been found to be

responsible for the formation of a mole of methane from cyclopentadiene, indene, and fluorene (25). We have been unable to find information on the behavior of an open system of the type C:C·C·C:C in the Zerewitinoff determination. However it seems reasonable to expect somewhat less activation of the hydrogens in question in such a substance than is the case with the similar highly activated cyclic compounds. With the aid of this information we believe that it is now possible to reconcile the observed active hydrogen data with the $\Delta^{\alpha,\beta}$-lactone structure in the majority of cases as shown in Table II.

Dihydrostrophanthidin and isostrophanthidin need not be considered in this connection, except as controls, since the side chain double bond is absent in these substances. In justification of the assumption of an

TABLE II

SUBSTANCE	MOLES CH_4 PER MOLECULE OBSERVED	SOURCE OF CH_4
Digitoxigenin acetate	2.09	1 OH; 0.43 moles from side chain; 0.7 moles from acetate. Total: 2.13 moles.
α-Anhydrodigitoxigenin	1.42	1 OH; 0.43 moles from side chain. Total: 1.43 moles.
β-Anhydrodigitoxigenin	1.42	Same as for α-derivative.
Dianhydrodilactone from strophanthidin	1.09	0.43 Moles from side chain; balance from activated nuclear double bond.
Tetrahydrodilactone from strophanthidin	0.57	All from side chain.
Strophanthidin *p*-bromobenzoate	2.45	2 OH; 0.45 from side chain. Total: 2.45 moles.

activated nuclear methylene group in the dianhydrodilactone from strophanthidin, the following available information may be cited. The nuclear double bonds in dianhydrostrophanthidin show no evidence of conjugation from the absorption spectra and color test with diazotized *p*-nitroaniline (28). One of these double bonds may logically be placed in the $\Delta^{5,6}$-position by analogy with other steroids and on the basis of the value for the optical rotation (28b), and the second double bond can be assigned the $\Delta^{8,14}$-position on the basis of the observations of Jacobs and Elderfield (29). Such an arrangement leaves the hydrogen atoms on carbon atom 7 activated. The active hydrogen values for digitoxigenin and for strophanthidinic acid methyl ester are obscure and can perhaps be accounted for by retention of solvent by these substances, which are notoriously difficult to dry. Finally we have subjected strophanthidin *p*-bromobenzoate to the Zere-

witinoff determination. This derivative was chosen in preference to the benzoate because it can be readily dried, whereas strophanthidin benzoate retains water of crystallization very tenaciously. The result obtained with the *p*-bromobenzoate is in accordance with the prediction based on the $\Delta^{\alpha,\beta}$-formulation.

One other piece of evidence is at hand in favor of the revised structure. Jacobs, Hoffmann, and Gustus (15) report bromine titrations on a number of the aglycones and derivatives. In these no noticeable absorption of bromine could be detected. The substances thus exhibit the behavior of $\Delta^{\alpha,\beta}$-unsaturated esters.

In summary, we here present evidence which we believe suggests that the cardiac aglycones of the digitalis-strophanthus group may be more satisfactorily formulated as $\Delta^{\alpha,\beta}$-unsaturated lactones rather than as $\Delta^{\beta,\gamma}$-lactones as heretofore accepted. The application of the proposed new formula to gitoxigenin and its derivatives will be presented at another time.

EXPERIMENTAL

Action of methyl alcoholic potassium hydroxide solution on β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide. Ten and two-tenths grams of the unsaturated lactone was dissolved in a solution of 6 g. of potassium hydroxide in 250 cc. of absolute methyl alcohol which had been previously chilled to 2°. After standing for 6 hours at 2–3° the mixture was allowed to come to room temperature, and after about 13 hours the nitroprusside test was negative. The solution was then made faintly acid by addition of the calculated amount of acetic acid, diluted with water, and extracted with ether. The ether solution was washed with water and dried with anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled and practically all boiled at 152–154° at 1 mm. The yield was practically quantitative. n_D^{25} 1.4928; d_4^{25} 1.1290; M_D calc'd for the hydroxy lactone: 47.27; for the aldehydo acid: 47.88; found: 47.34.

Anal. Calc'd for $C_{10}H_{16}O_3$: C, 65.2; H, 8.8.
Found: C, 65.7; H, 8.9.

The above acid (1.7 g.) was treated with an ethereal solution of diazomethane. After removal of the solvent, the residue was refluxed for 15 min. with an alcoholic solution of semicarbazide prepared from 1.4 g. of semicarbazide hydrochloride and 1.03 g. of fused sodium acetate. After concentration to about 5 cc. the solution was diluted and the *semicarbazone of the methyl ester* crystallized on rubbing. After recrystallization from dilute alcohol it melted at 120°.

Anal. Calc'd for $C_{12}H_{21}N_3O_3$: C, 56.4; H, 8.3.
Found: C, 56.5; H, 8.5.

Hydrolysis of β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide in aqueous alkali at room temperature. A suspension of 0.549 g. of the unsaturated lactone in 49.8 cc. of 0.1060 *N* sodium hydroxide solution and 10 cc. of neutral alcohol was shaken at room temperature for 11 hours at the end of which time the nitroprusside test was negative. The solution was then back-titrated against phenolphthalein with 0.1108 *N* hydrochloric acid and 32.9 cc. of acid was consumed. Calculated for 1 equivalent: 33.1 cc. Saponification of the lactone was therefore complete. The neutral solution was then acidified to Congo red with hydrochloric acid and a faint nitroprusside test was immediately apparent. The intensity of the test increased on standing as relactonization oc-

curred. In order to complete the relactonization, the acid solution was warmed at 50° for 4 hours after which it was cooled and extracted with ether. The material left after removal of the ether and thorough pumping off to remove traces of solvent showed n_D^{25} 1.5043. n_D^{25} for β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide is 1.5042; n_D^{25} for β-cyclohexyl-β-formylpropionic acid is 1.4928. The recovered substance, therefore is the original lactone.

When the above crude product was treated successively with diazomethane and semicarbazide, a faint trace of semicarbazone was obtained. This was too small in amount for a melting point determination.

Action of hot aqueous alkali on β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide. A mixture of 0.5 g. of the unsaturated lactone, 50 cc. of 0.1 *N* sodium hydroxide solution, and 12.5 cc. of alcohol was refluxed for 1 hour. The cooled solution was made just acid to Congo red, warmed at 50° for 4 hours, and extracted with ether. After drying with anhydrous magnesium sulfate, the ether was removed from the extract, leaving a thick viscous residue with the characteristic odor of the above described aldehydo acid. The material was pumped off at 0.5 mm. and 100° in order to remove traces of solvent, and then showed n_D^{25} 1.4973. If the relative amounts of aldehydo acid and unsaturated lactone in mixtures can be approximated by assuming a linear relationship in the refractive indices, this corresponds to about two-thirds aldehydo acid. The presence of some unsaturated lactone was shown by the positive nitroprusside reaction given by the mixture. On treatment of the crude reaction-product successively with diazomethane and semicarbazide, a copious amount of the semicarbazone of the methyl ester of the aldehydo acid was obtained. This melted at 119° and the melting point was not depressed on admixture with a known sample.

Anal. Found: C, 56.0; H, 8.2.

Action of lactonizing agents on β-cyclohexyl-β-formylpropionic acid. A solution of 4 g. of β-cyclohexyl-β-formylpropionic acid in 36 cc. of acetic anhydride and 4 cc. of acetyl chloride was heated in a sealed tube at 110° for 14 hours. The acetic anhydride and acetyl chloride were removed from the reaction-mixture under reduced pressure. The residue was distilled at 1 mm., and boiled at 163–167°. The analytical figures corresponded to the acetate of the saturated hydroxy lactone.

Anal. Calc'd for $C_{12}H_{18}O_4$: C, 63.8; H, 8.0.
Found: C, 64.2; H, 8.4.

Saponification equivalent calc'd: 113; found: 116.

The aldehydo acid was recovered unchanged after warming in dilute hydrochloric acid at 50°, and showed no tendency to lactonize under these conditions.

Catalytic reduction of β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide. A solution of 4.183 g. of the unsaturated lactone in glass-distilled alcohol was shaken in an atmosphere of hydrogen with the platinum oxide catalyst of Adams and Shriner. After 558 cc. of hydrogen at 0° and 760 mm. had been absorbed, reduction ceased. Calc'd for 1 mole: 566 cc. The nitroprusside test on the product of the reduction was negative. The product was distilled, and boiled at 121.5–123° at 1 mm.; n_D^{25} 1.4794. Analyses corresponded to β-cyclohexylbutyrolactone.

Anal. Calc'd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6.
Found: C, 71.5; H, 9.7.

Two-tenths of a gram of the above lactone was heated on the steam-bath with 5% sodium hydroxide solution for 20 min., at the end of which time the lactone was completely saponified. On careful acidification to litmus with nitric acid, the solution became turbid and deposited prisms on standing. After crystallization from water this material melted at 94.5–95°. Analyses corresponded to β-cyclohexyl-γ-hydroxybutyric acid.

Anal. Calc'd for $C_{10}H_{18}O_3$: C, 64.5; H, 9.8.
Found: C, 64.7; H, 9.8.

The silver salt of the above hydroxy acid was prepared as usual. It darkened above 127° and did not exhibit a sharp melting point.

TABLE III

	$\Delta^{\beta,\gamma}$-ANGELICA LACTONE	β-CYCLOHEXYL-$\Delta^{\alpha,\beta}$-BUTENOLIDE OR STROPHANTHIDIN
Color reactions with sodium nitroprusside		
	At the start the solutions are strongly acid	
1st drop NaOH	Immediate deep red color fading slowly to orange-red which persists	Immediate deep red color; lasts less than 1 sec. and fades to colorless solution
2nd drop NaOH	Intensity of color increases slightly	Immediate deep red color; lasts less than 2 sec.
	Both solutions at this point are acid to Congo red	
3rd drop NaOH	Same intense red color	Immediate deep red color; fades in 15–30 sec. if on alkaline side
4th drop NaOH	Same intense red color	No further color developed
1st drop nitroprusside	No change; intense red which persists	Intense red color which fades in 15–30 sec.
Successive drops of nitroprusside	No change	Transient intense red color until finally no return of color when lactone is all oxidized
Acidification	Blue-green color	Pure blue color
Color reactions with potassium ferricyanide		
	At the start the solutions are strongly acid	
1st drop NaOH	Pale pink	Pale brown
2nd and 3rd drop NaOH	Pale pink	Pale brown
7th drop NaOH	Clear solution	No effect; pale brown
1st drop ferricyanide	Clear solution; no effect	Red-brown color
2nd drop ferricyanide	Clear solution	Color increases
3rd drop ferricyanide	Clear solution	Color persists

Anal. Calc'd for $C_{10}H_{17}AgO_3$: Ag, 36.8. Found: Ag, 36.8.

When β-phenyl-$\Delta^{\alpha,\beta}$-butenolide was similarly reduced, 4 moles of hydrogen were absorbed and the same cyclohexylbutyrolactone was obtained. As thus prepared it boiled at 122–123° at 1 mm., n_D^{25} 1.4792.

Comparative color tests on the unsaturated lactones. If the Legal test is carried out in a slightly different fashion from that ordinarily used, the similarities between the synthetic $\Delta^{\alpha,\beta}$-lactone and strophanthidin, and the contrast between them and $\Delta^{\beta,\gamma}$-angelica lactone are more pronounced. The Legal test as now developed is carried out as follows: The substance to be tested (10–12 mg.) is dissolved in 1 cc. of alcohol or pyridine. To this solution are added 3 drops of 10% hydrochloric acid and 1 drop of 0.5% aqueous solution of sodium nitroprusside. Ten per cent sodium hydroxide solution is now added dropwise to the test solution, an interval of 2 min. being allowed between addition of successive drops, until the solution is on the alkaline side. Sodium nitroprusside solution is then added in the same manner with a 2 min. interval between addition of successive drops.

The same technique was employed in the tests using potassium ferricyanide except that the test solutions were made strongly alkaline before the second addition of the ferricyanide solution.

The results of these tests are tabulated in Table III.

The Zerewitinoff determinations were carried out in dry pyridine in an atmosphere of dry nitrogen according to the procedure given in Hans Meyer, "Analyse und Konstitutionsermittlung organischer Verbindungen," 6th Ed. Berlin, 1938.

The ultraviolet absorption spectra measurements were done with a Hilger rotating sector quartz spectrophotometer using Eastman special ultraviolet plates, type 111-O-UV for the far ultraviolet region.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. IV. PREPARATION OF β-PHENYL-$\Delta^{\alpha,\beta}$-BUTENOLIDE FROM PHENYLGLYOXAL AND FROM ETHYL β-METHYLCINNAMATE

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In the preceding papers (1) successful syntheses for representative β-substituted $\Delta^{\alpha,\beta}$-butenolides have been described and evidence has been presented (2) which suggests that the natural cardiac aglycones are best represented by such a structure rather than by that of a $\Delta^{\beta,\gamma}$-butenolide. Concurrently with these investigations we have studied other possible methods by which the $\Delta^{\beta,\gamma}$-butenolides might be prepared. These projected syntheses involved, for the most part, the preparation of β-substituted-β-aldehydopropionic acids and subsequent ring closure through the enolic form. It now seems probable as a result of our own observations (2), as well as earlier ones of others (3, 4, 5), that ring closure of such an aldehydo acid to a $\Delta^{\beta,\gamma}$-unsaturated lactone is at best exceedingly difficult if not impossible. Although the desired β-aldehydopropionic acids are now readily available (1, 2) we wish to present the results of the exploration of a number of suggested syntheses of these substances.

The most direct route to such aldehydo acids appeared to be based on the work of Perkin and Sprankling (6) who prepared β-aldehydopropionic acid by condensation of bromoacetal with sodio malonic ester and decarboxylation of the product. The logical extension of this synthesis would involve a similar condensation of the acetal of any appropriate α-bromoaldehyde. In an exploratory investigation we have attempted the condensation of α-bromoheptaldehyde diethyl acetal with sodio malonic ester. The condensation could not be made to proceed as desired under a variety of experimental conditions, and either the original materials were recovered, or extensive resin formation took place under more drastic conditions. We therefore conclude that the condensation of bromoacetal with sodio malonic ester represents a special case and that the reaction is not a general one for α-bromoaldehyde acetals. Along the same line, condensation of the cyclohexyl or cyclopentyl derivative of malonic ester with bromoacetal, or of cyclohexyl bromide with acetal malonic ester, gave only mixtures of undesired by-products or cleavage products.

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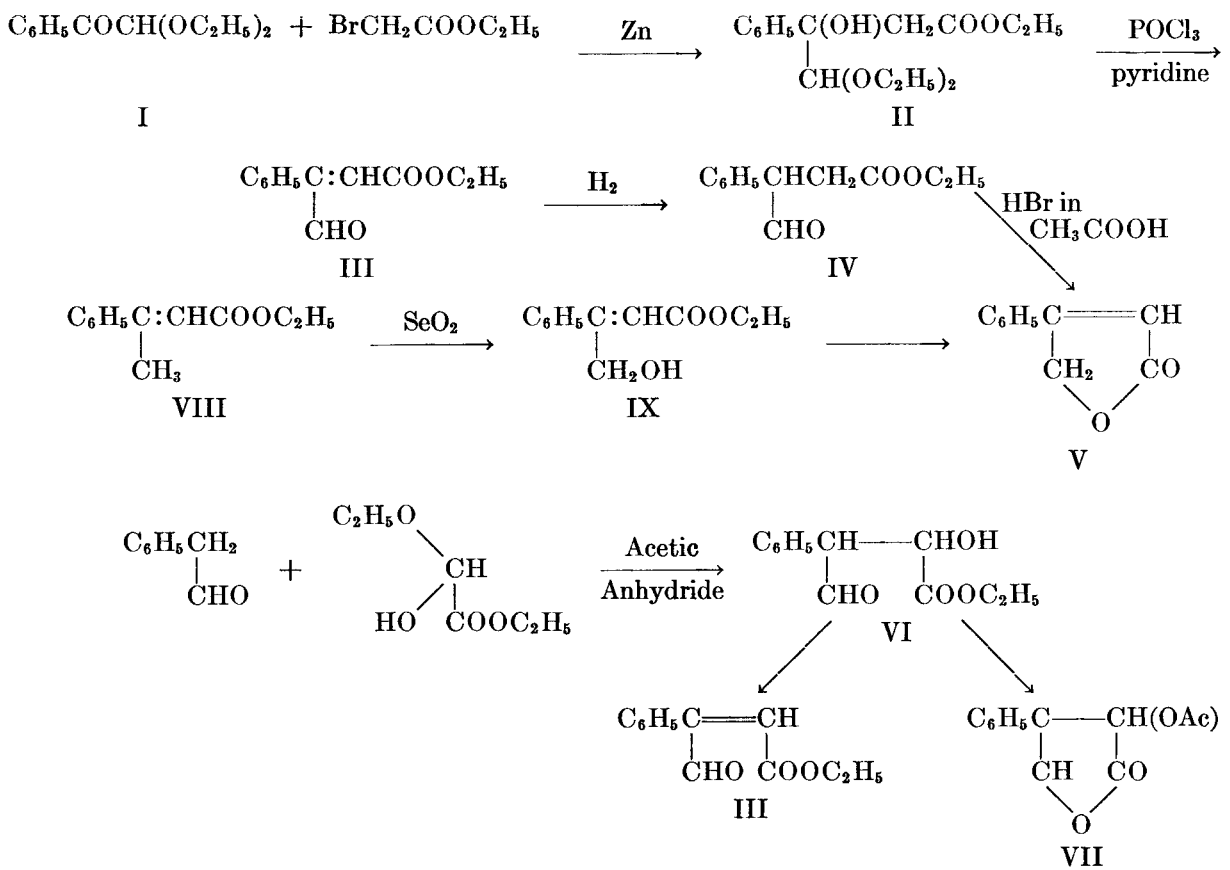
Other attempted avenues of approach to β-aldehydopropionic acids involved use of the Darzens glycid rearrangement and reduction of β-cyano esters (or acids) by the Stephen method. As a model the preparation of β-phenyl-β-formylpropionic acid was chosen because of the accessibility of the starting material. In the attempted application of both of these methods, serious difficulties were encountered at one stage or another, as a result of which these syntheses do not appear to be practical.

Better success attended the application of the Reformatzky reaction to the acetal of phenylglyoxal, although in comparison with the methods presented in earlier papers (1, 2) this scheme possesses serious disadvantages. Nevertheless, it seems of interest to present at this time our experiences dealing with phenylglyoxal and its derivatives, in view of the experiments along the same line recently reported by Shemyakin and Red'kin (7). The diethyl acetal of phenylglyoxal (I) readily undergoes the Reformatzky reaction with ethyl bromoacetate to yield ethyl β-phenyl-β-hydroxy-γ,γ-diethoxybutyrate (II), the structure of which was shown by conversion to phenylmalic acid. Elimination of the tertiary hydroxyl group in II presented unexpected difficulties. The compound was remarkably stable to the usual dehydrating agents, and only by the use of phosphorus oxychloride in pyridine was it possible to eliminate the hydroxyl group in question. The product thus obtained consisted largely of the aldehydo ester, III, although analyses indicated contamination with varying amounts of unhydrolyzed acetal or hemiacetal. Catalytic reduction of the double bond in III and hydrolysis of contaminating acetals gave ethyl β-phenyl-β-formylpropionate (IV). Ring closure of this aldehydo ester provided interesting information on the stability of β-phenyl-$\Delta^{\beta,\gamma}$-butenolide. Shemyakin (7) reports that condensation of the hemiacetal of ethyl glyoxylate with phenylacetaldehyde in the presence of acetic anhydride results in the formation of the intermediate ethyl α-hydroxy-β-phenyl-β-formylpropionate (VI) which then either loses water to yield ethyl β-phenyl-β-formylacrylate or undergoes ring closure and acetylation to yield α-acetoxy-β-phenyl-$\Delta^{\beta,\gamma}$-butenolide (VII). No proof of structure of the latter substance was offered. In contrast to this reported behavior of the α-hydroxy aldehyde ester, the unhydroxylated ester, IV, yielded β-phenyl-$\Delta^{\alpha,\beta}$-butenolide (V) on ring closure. The latter was identical with the lactone previously described (1, 2). The easier ring closure to, and greater stability of the α-hydroxy lactone apparently represents another case of the stabilizing effect of an α-substituent (8, 2). As far as we are aware, the reported ring closure of the aldehyde ester of Shemyakin is the only case on record of such a ring closure with an aldehydo acid. With the unsubstituted derivative, the tendency for the unsaturated lactone to assume a structure representing maximum conjugation of the double bonds makes the existence of a stable $\Delta^{\beta,\gamma}$-lactone doubtful.


C6H5COCH(OC2H5)2 + BrCH2COOC2H5
Zn
C6H5C(OH)CH2COOC2H5
CH(OC2H5)2
POCl3
pyridine
I
II
C6H5C:CHCOOC2H5
CHO
H2
C6H5CHCH2COOC2H5
CHO
HBr in
CH3COOH
III
IV
C6H5C:CHCOOC2H5
CH3
SeO2
C6H5C:CHCOOC2H5
CH2OH
C6H5C
CH
CH2
CO
O
VIII
IX
V
C6H5CH2
CHO
+
C2H5O
CH
HO
COOC2H5
Acetic
Anhydride
C6H5CH
CHOH
CHO
COOC2H5
VI
C6H5C
CH
CHO
COOC2H5
III
C6H5C
CH(OAc)
CH
CO
O
VII

In the course of the above work it has been found that if phenylglyoxal hydrate be treated with alcoholic hydrogen chloride, the hemiacetal (X) results. The latter substance undergoes the usual transformation under the influence of alkali which results in the formation of *d,l*-mandelic acid (XI). This apparently is a special case of the benzilic acid rearrangement.

$$C_6H_5COCH(OH)(OC_2H_5) \rightarrow C_6H_5C(OH)_2CH(OH)(OC_2H_5) \rightarrow$$
$$\text{X}$$
$$C_6H_5CH(OH)COOH$$
$$\text{XI}$$

In order to circumvent the difficult dehydration of the hydroxy acetal ester, II, ethyl β-methylcinnamate (VIII) was oxidized with selenium dioxide, with the object of taking advantage of the activation of the hydrogens of the methyl group by the double bond and thus proceeding directly to the unsaturated aldehydo ester III. However, the oxidation proceeded only to the alcohol stage (IX), and the only product isolated was the $\Delta^{\alpha,\beta}$-lactone V. This experiment is of significance, however, in that it provides rigid confirmatory evidence for the structure assigned to this lactone both in this paper and in a preceding one (1).

EXPERIMENTAL

Diethyl acetal of phenylglyoxal (I). A solution of 396 g. of phenylglyoxal (9) in 3 l. of absolute alcohol containing 3% of hydrogen chloride was allowed to stand 36 hours at room temperature and was then refluxed for 10 hours. After neutralizing the solution with basic lead carbonate and filtering off the lead salts, the solvent was removed and the residue was fractionally distilled at 7 mm. After a fore-run of 46 g. which boiled up to 127° and consisted of unreacted phenylglyoxal, the acetal was collected from 129–132°. The yield was 389 g. or 65%, based on the glyoxal reacted. n_D^{25} 1.5012.

Anal. Calc'd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7.
Found: C, 69.3; H, 7.5.

Hemiacetal of phenylglyoxal (X). When crude phenylglyoxal, as directly obtained from the selenium dioxide oxidation of acetophenone (9) and containing considerable amounts of the hydrate, was subjected to the same treatment with alcoholic hydrogen chloride, the hemiacetal, boiling at 133–137° at 12 mm. was obtained in 56% yield, based on the acetophenone used. n_D^{25} 1.5110.

Anal. Calc'd for $C_{10}H_{12}O_3$: C, 66.6; H, 6.7.
Found: C, 66.8; H, 7.0.

Mandelic acid from the hemiacetal of phenylglyoxal. The hemiacetal was refluxed for 5 hours with an excess of a 4% solution of sodium hydroxide in 50% alcohol. The cooled reaction-mixture was acidified, some of the alcohol was removed under reduced pressure and the aqueous solution was extracted with ether. Upon removal of the ether, *d,l*-mandelic acid was obtained which melted at 117–118° after recrystallization from ether-petroleum ether (Skellysolve B). The acid is reported as melting at 118° (10).

Anal. Calc'd for $C_8H_8O_3$: C, 63.2; H, 5.3.
Found: C, 63.3; H, 5.5.

The *anilide* melted at 150.5–151°, which compares with a value of 151–152° reported by Bischoff and Walden (11).

Anal. Calc'd for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.8.
Found: C, 73.9; H, 6.1.

Ethyl β-phenyl-β-hydroxy-γ,γ-diethoxybutyrate (II). A 5-l. 3-necked flask was equipped with a mechanical stirrer and two very efficient reflux condensers. In the flask were placed 164 g. of granulated zinc (20 mesh), 350 g. of the diethyl acetal of phenylglyoxal, 283 g. of freshly distilled ethyl bromoacetate, and 1200 cc. of sodium-dried benzene. A pinch of good zinc dust and a crystal of iodine were added and the contents of the flask were gently warmed without stirring until the reaction started. The mixture was allowed to reflux spontaneously without stirring for 2 hours. The stirrer was then started and, on breaking up the zinc cake in the bottom of the flask, the reaction became more vigorous. When the reaction had moderated, the mixture was refluxed with stirring for 2 hours and allowed to stand overnight at room temperature. It was poured into 2 l. of 20% hydrochloric acid, the benzene layer was separated and washed successively with dilute hydrochloric acid, sodium carbonate solution, and water. After drying with anhydrous magnesium sulfate and removal of the solvent, the residue was fractionally distilled at 1 mm., the fraction boiling at 145–157° being collected. This was redistilled at 0.4 mm., and gave 170 g. of the product which boiled at 136–140°; n_D^{25} 1.4838.

Anal. Calc'd for $C_{16}H_{24}O_5$: C, 64.8; H, 8.2.
Found: C, 64.6; H, 8.0.

It was possible to obtain the *acetal acid* from the above ester as follows. Twenty-five grams of the ester was refluxed for a few minutes with 75 cc. of 50% alcohol containing 3.4 g. of sodium hydroxide. Hydrolysis of the ester was prompt and the solution turned deep brown. The alcohol was removed and the aqueous solution was extracted with ether for the removal of any unchanged ester. The alkaline solution was then chilled to 0°, carefully acidified with ice-cold dilute hydrochloric acid, and immediately extracted with ether. After thorough washing of the ether extract and removal of the solvent, the acetal acid remained as a reddish-brown oil which could not be crystallized. The acetal group was still intact, as shown by the negative Tollens test displayed by this substance in dilute pyridine solution. However, after warming the acetal acid with 50% acetic acid a prompt strong Tollens test was obtained.

The above acetal acid was converted to the *methyl ester* with diazomethane. The ester boiled at 127–132° at 0.4 mm., n_D^{25} 1.4867.

Anal. Calc'd for $C_{15}H_{22}O_5$: C, 63.8; H, 7.9.
Found: C, 63.8; H, 7.9.

On warming the above methyl ester with 2,4-dinitrophenylhydrazine in dilute alcoholic hydrochloric acid solution, hydrolysis of the acetal occurred and the 2,4-*dinitrophenylhydrazone* of the aldehyde ester was formed. It melted at 179.5–180°.

Anal. Calc'd for $C_{18}H_{18}N_4O_7$: C, 53.7; H, 4.6; N, 14.0.
Found: C, 53.9; H, 4.6; N, 14.1.

Oxidation of β-phenyl-β-hydroxy-β-formylpropionic acid to phenylmalic acid. The acetal and ester groups in ethyl β-phenyl-β-hydroxy-γ,γ-diethoxybutyrate (2 g.) were hydrolyzed by boiling for several hours with dilute sulfuric acid. The free aldehydo acid was extracted with ether and oxidized by stirring with silver oxide, prepared from 1.9 g. of silver nitrate and 0.5 g. of sodium hydroxide in 25 cc. of water, for 12 hours. The phenylmalic acid was extracted from the filtered solution with ether and crystallized from ether-petroleum ether (Skellysolve B). It melted at

186–187° with decomposition, which compares with 187–188° reported by Alexander (12).

Anal. Calc'd for $C_{10}H_{10}O_5$: C, 57.1; H, 4.8.
Found: C, 57.0; H, 5.1.

On drying at 100° and 10 mm. over phosphorus pentoxide, the acid lost water and gave phenylmaleic anhydride which melted at 119–119.5°. Alexander (12) reports the melting point 119° for the substance.

Dehydration of ethyl β-hydroxy-β-phenyl-γ,γ-diethoxybutyrate. In a 500 cc. flask equipped with a reflux condenser were placed 27 g. of the acetal ester and 150 cc. of dry pyridine. To this mixture 23 g. of freshly distilled phosphorus oxychloride was added gradually and with shaking. The solution was then heated for 8 hours in an oil-bath at 135°. After cooling, the contents of the flask were poured into a mixture of ice and excess dilute sulfuric acid, and the dark mixture was extracted with several portions of ether. The combined ether extracts were washed with dilute sulfuric acid, then with sodium carbonate solution, and finally with water. The residue after drying and removal of the ether was fractionally distilled at reduced pressure, and a fraction of 3 g. of material which boiled at 130–138° was obtained. This material was a mixture of the aldehyde ester with some acetal and hemiacetal. The acetal was partially hydrolyzed during manipulation of the product.

Anal. Calc'd for $C_{16}H_{22}O_4$: C, 67.5; H, 8.0.
for $C_{14}H_{18}O_4$: C, 67.2; H, 7.3.
for $C_{12}H_{12}O_3$: C, 70.6; H, 5.9.
Found: C, 68.6, 68.8; H, 6.2, 6.7.

In accordance with this view, the product of the reaction gave a faint Tollens test. The removal of the hydroxyl group was shown by the preparation of the *2,4-dinitrophenylhydrazone of ethyl β-phenyl-β-formylpropenoate* from the reaction-product. This melted at 163–163.5° after recrystallization from alcohol.

Anal. Calc'd for $C_{18}H_{16}N_4O_6$: C, 56.3; H, 4.2; N, 14.6.
Found: C, 56.3; H, 4.3; N, 14.5.

The effect of the ethoxyl groups in hindering removal of the hydroxyl group in the hydroxy acetal ester is rather remarkable. A similarly situated hydroxyl group in ethyl β-phenyl-β-methylhydracrylate is eliminated without difficulty with hydrochloric acid (13). In the above case we have tried to accomplish the dehydration with a variety of reagents without success.

Ethyl β-phenyl-β-formylpropionate (IV). When the aldehyde ester, III, was reduced with hydrogen in alcoholic solution using platinum oxide as catalyst, one mole of hydrogen was rapidly absorbed and a second mole more slowly. If the hydrogenation was interrupted at the one mole stage, ethyl β-phenyl-β-formylpropionate, boiling at 116–120° at 0.3 mm., n_D^{25} 1.5120, was formed. The compound gave a slow but definite Tollens test.

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8.
Found: C, 69.8; H, 7.2.

The 2,4-*dinitrophenylhydrazone* melted at 108.5–109° after recrystallization from dilute alcohol.

Anal. Calc'd for $C_{18}H_{18}N_4O_6$: C, 55.9; H, 4.7.
Found: C, 55.5; H, 4.7.

Ring closure of ethyl β-phenyl-β-formylpropionate to β-phenyl-$\Delta^{\alpha,\beta}$-butenolide. A solution of 1 g. of the ester in 2 cc. of glacial acetic acid which had previously been saturated with dry hydrogen bromide at 0° was heated under reflux in an oil-bath at 120° for 2 hours. After pouring the mixture into ice-water and neutralizing with

sodium carbonate, β-phenyl-$\Delta^{\alpha,\beta}$-butenolide was extracted with ether. After recrystallization from water it melted at 91–92°, and the melting point was not depressed when the lactone was mixed with a sample prepared as previously described (1).

Oxidation of ethyl β-methylcinnamate with selenium dioxide. A solution of 44 g. of ethyl β-methylcinnamate (13) in 140 cc. of dioxane and 4.5 cc. of water was heated to boiling under reflux in a 3-necked flask equipped with a mechanical stirrer. To this was added 26 g. of selenium dioxide over the course of 35 min. The mixture was refluxed with stirring for 4 hours. The reaction-mixture was chilled and decanted from precipitated selenium, and the solvent was removed at reduced pressure. The residue was dissolved in ether and filtered from additional selenium which had precipitated. On concentration of the ether solution, crystallization was copious. The crystalline material was filtered off and recrystallized from water. It melted at 93–93.5° and gave no depression of melting point when mixed with a known sample of β-phenyl-$\Delta^{\alpha,\beta}$-butenolide (1).

Anal. Calc'd for $C_{10}H_8O_2$: C, 75.0; H, 5.0.
Found: C, 75.0; H, 5.2.

The mother liquor from the above crystalline material gave 42% of unreacted ethyl β-methylcinnamate on distillation.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE FORMATION OF DIMERIC PEROXIDES BY OZONIZATIONS OF OLEFINS (1)

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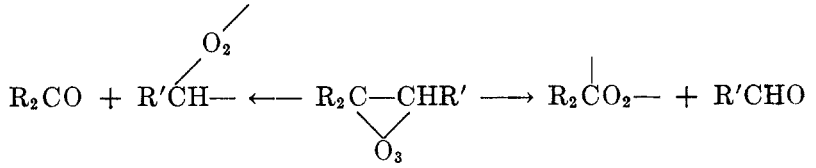
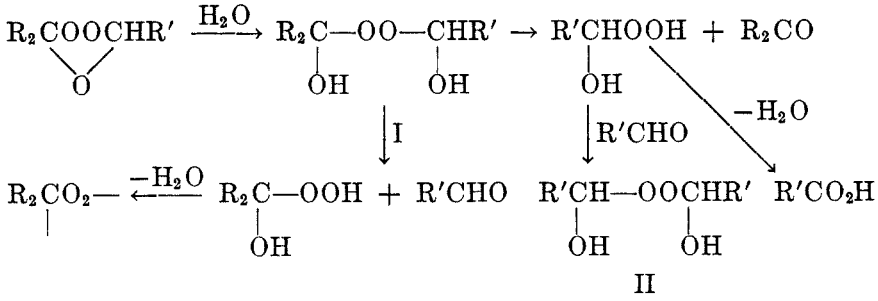
The formation of dimeric diaryl ketone peroxides during the ozonization of arylated olefins (1) has led us to believe that peroxides are to be expected as products of the decomposition of any ozonide. An unsymmetrical olefin ozonide may cleave in either of two ways, and the products isolated



from the ozonolysis mixture will be dependent on the manner in which these possible intermediates dimerize or rearrange. This view is very strongly supported by the work of Briner and his co-workers (2).

Rieche (3) has accounted for the formation of the various products obtained in ozonolysis on the basis of a hydrolytic cleavage which is outlined below

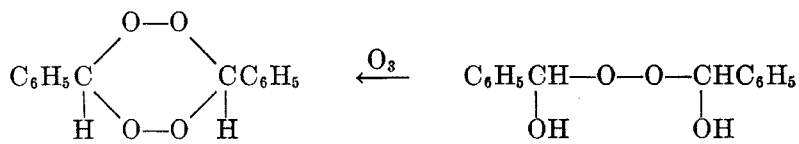


The principal difference between these two schemes for the breakdown is that Rieche believes a dihydroxy peroxide (I) is an intermediate in the formation of the final products whereas the other mechanism does not postulate hydrolysis. Both points of view have supporting evidence in the literature. Perhaps one of the strongest arguments for the Rieche mechanism of cleavage is the occasional isolation of the symmetrical dihydroxy peroxide (II).

In studying the ozonization of various arylated olefins we have secured evidence which we believe supports the former mechanism of ozonide cleavage.

Ozonization of arylated olefins under a wide variety of conditions has shown that approximately the same amount of peroxide is formed from a given olefin whether the ozonization mixture is treated with water or worked up under anhydrous conditions. Ozonization was even carried out in solutions which contained suspended anhydrous copper sulfate to detect the presence or the formation of water and in spite of the apparent absence of water the peroxides were formed as usual.

Ozonolysis of styrene, stilbene, and triphenylethene has in each case yielded the known dimeric benzaldehyde peroxide (4) (III), although this peroxide does not appear to have been previously obtained from an ozonolysis reaction of this type (5). We thought the dimeric benzaldehyde peroxide might be formed by the dehydrogenation by ozone of the corresponding dihydroxydibenzal peroxide (6) (IV) which could be present as a result of complex changes of the type suggested in Rieche's scheme of breakdown of the ozonide. Actually ozonization of dihydroxydibenzal peroxide does



III IV

give low yields of dimeric benzaldehyde peroxide (III) but this does not seem to be the course of the latter in our ozonolysis experiments on styrene, stilbene, and triphenylethene. Attempts were made to isolate the easily characterized dihydroxydibenzal peroxide from styrene and stilbene ozonolysis products but none could be found. That the product of styrene ozonolysis is not sensitive to water was shown by allowing a sample of the styrene ozonide in carbon tetrachloride to stand for two days with water without any evident changes in its properties. Briner and Gelbert (5) have also observed the stability of styrene ozonide towards water.

Treatment of dihydroxydibenzal peroxide with phosphorus pentoxide gave some dimeric benzaldehyde peroxide. It was therefore thought that treatment of the ozonolysis mixture of 1,1-diphenylethene and 1,1-diphenylpropene-1 with phosphorus pentoxide (3) would increase the amount of dimeric benzophenone peroxide if an intermediate such as (I) were formed by hydrolysis of the ozonide. No such increase in dimeric benzophenone peroxide resulted from this treatment.

An attempt to convert dihydroxydibenzal peroxide into stilbene ozonide by dehydration with phosphorus pentoxide was inconclusive. No evi-

dence of ozonide formation was obtained. Yet the products actually isolated from the mixture were identical with those isolated by the decomposition of stilbene ozonide (7).

According to the view that ozonides cleave spontaneously in two directions, it would be logical to assume that the proportion of cleavage in either direction would be influenced by the nature of the substituents on the olefin. That this actually is the case is shown by the yields of peroxides obtained from various arylated olefins. With diarylated compounds of the type $(C_6H_5)_2C{=}CHR$ the yield of dimeric benzophenone peroxide is 4–5% when R = H and 12% when R = n-C_2H_5. When R is phenyl, although a further increase in the yield of dimeric benzophenone peroxide results, dimeric benzaldehyde peroxide is formed simultaneously. This mixture cannot be separated readily. Tetraphenylethylene on ozonolysis gives 53–57% yields of dimeric benzophenone peroxide calculated on the basis that only one molecule of the peroxide can form from one molecule of the olefin.

These results are of some significance in connection with certain ozonolysis reactions which have been suggested as analytical procedures. For example, ozonolysis has been used (8) to convert terminal $=CH_2$ groups to formaldehyde for quantitative determination. Our results indicate that the groups attached to the second carbon of the olefin residue may have a marked effect on the ratio of formaldehyde to formic acid which is produced from the terminal $=CH_2$ group and hence influence the results. Thus we add one more bit of evidence to support Briner's view (9) that this method cannot be expected to give quantitative results.

The list of dimeric diaryl ketone peroxides which have been characterized has been extended to include dimeric p,p'-dichlorobenzophenone peroxide and dimeric di-o-tolyl ketone peroxides. Evidence for the existence of dimeric di-(3,4-dimethylphenyl) ketone peroxide as an ozonolysis product of 1,1-(di-3,4-dimethylphenyl)ethene has been obtained. Dimeric p-methoxyphenyl methyl ketone peroxide has also been characterized (10).

Dimeric benzophenone and di-p-tolyl ketone peroxides have now been synthesized from the corresponding ketones and hydrogen peroxide but the oxidation takes several months. This indicates that the peroxides isolated in ozonolysis of olefins do not result from oxidation of ketones by hydrogen peroxide formed by hydrolysis of the ozonides.

A most surprising result was that ozone oxidized benzaldehyde to give a 15% yield of benzoyl peroxide. Earlier investigators (11) obtained benzoic acid and perbenzoic acid by this reaction. Rupe and Hirschmann (12) did not obtain benzoyl peroxide by the ozonization of benzoic acid and we have likewise failed to do so. Hence, benzoic acid is apparently not an intermediate between benzaldehyde and benzoyl peroxide.

EXPERIMENTAL

Dimeric benzaldehyde and benzophenone peroxides through ozonlysis. Representative experiments in the production of dimeric benzaldehyde and benzophenone peroxides from the ozonolysis of olefins in various solvents with changes in temperatures and times of ozonization are shown in Table I. For this work a concentration of

TABLE I

BENZALDEHYDE AND DIMERIC BENZOPHENONE PEROXIDES FROM THE OZONOLYSIS OF OLEFINS

ALKENE	AMOUNT, G.	SOLVENT	CONDITIONS OF OZONIZATION			YIELD OF PEROXIDE	
			Volume, cc.	Temperature	Time, min.	Grams	Per cent
Styrene	5.0	CCl_4	60	Room	120	0.095	1.7[a]
Stilbene	2.0	C_6H_6	50	"	120	.13	9.6[b]
1,1-Diphenylethene	3.0	n-C_6H_{14}	40	Ice-salt	25	.19	5.8[c]
"	4.0	"	40	"	30	.20	4.5[c]
"	4.0	C_6H_{12}	40	"	35	.24	5.5[c]
"	3.1	CCl_4	40	"	30	.17	5.0[c]
"	3.0	$CH_3CO_2C_2H_5$	30	"	30	.045	1.4[c, d]
"	3.0	CH_3CO_2H	35	20°	30	.03	0.9[c, d]
1,1-Diphenyl-1-butene	2.65	CCl_4	75	Room	300	.4	12.0
Triphenylethene	4.7	CCl_4	40	Ice-salt	45	1.275 (mixture of two not separated)[e]	
"	3.0	$CHCl_3$	75	−40 to −60°	110	0.658	"
"	3.0	C_2H_5Cl	65	−60°	120	1.134	" [e, f]
"	2.5	"	40	−50 to −60°	40	0.975	" [e, g]
Tetraphenylethene	1.9	CCl_4	125	Ice	80	.645	57.0
"	2.0	CCl_4	125	Ice	120	.634	53.0

[a] The dimeric benzaldehyde peroxide melted at 200° with gas evolution and when mixed with a sample of the peroxide prepared by the method of Baeyer and Villiger (4) there was no depression in the melting point.

[b] From the filtrate after isolation of the peroxide, 0.71 g. of benzoic acid was isolated.

[c] The solvent was removed in a vacuum desiccator after ozonization and the peroxide separated with absolute alcohol.

[d] This mixture was still strongly unsaturated towards bromine in carbon tetrachloride after the peroxide had been isolated.

[e] This mixture of dimeric benzophenone and benzaldehyde peroxides melted with gas evolution at about 184°. Benzoic acid was also isolated. The characteristic fragrant odor of crude benzaldehyde peroxide was noted.

[f] Ozonization was continued for about sixty minutes after the appearance of the blue color in the reaction-mixture.

[g] Ozonization was stopped at the first appearance of the blue color.

ozone of 2.5–3.5% and a rate of gas flow of about 18 l. per hour were used. In some experiments ozonizations were continued for thirty to ninety minutes after the appearance of a blue color in the solvent, which was assumed to indicate saturation of the olefin bond with ozone. In others, the mixture of products remaining after separation of the peroxide contained unchanged olefin. In some cases the ozonides were decomposed in the presence of water and the acidic products removed by alkaline extraction; in others, the solvents were removed in a vacuum desiccator and the peroxides separated by virtue of their insolubility in absolute alcohol or ether.

In Table II are shown the yields of peroxides isolated from ozonides which had been treated in carbon tetrachloride solution with phosphorus pentoxide at about 5° for various periods of time prior to aqueous or anhydrous decomposition. The yield from an anhydrous decomposition of the ozonide from 1,1-diphenyl-1-propene which had not been treated with phosphorus pentoxide is included for comparison.

Aqueous decomposition of dihydroxydibenzal peroxide. A suspension of 0.5 g. of dihydroxydibenzal peroxide in 25 cc. of ozone-saturated carbon tetrachloride was treated with 40 cc. of water for fifteen hours and extracted with alkali. The only product isolated was benzoic acid (0.015 g.). From a similar suspension which was

TABLE II

TREATMENT OF OZONIDES WITH PHOSPHORUS PENTOXIDE

ALKENE	AMOUNT, G.	TIME OF OZONIZATION, MINUTES	TREATMENT WITH P_2O_5	YIELD OF PEROXIDE	
				g.	%
1,1-Diphenylethene.....	5.0	60	4–5 days[a]	0.18	3.3
1,1-Diphenyl-1-propene.....	4.0	25	13 hours[b]	.135	2.8
1,1-Diphenyl-1-propene.....	2.5	180	4 hours[a]	.12	4.0
1,1-Diphenyl-1-propene.....	4.5	25	—[b]	.16	3.5

[a] Wet isolation of peroxide.

[b] Dry isolation of peroxide.

treated with 15 cc. of 30% hydrogen peroxide for eighteen hours 0.075 g. of benzoic acid was isolated.

Attempted detection and removal of water formed during ozonization. A solution of 3 g. of styrene in 50 cc. of dry carbon tetrachloride containing a suspension of 0.1 g. of anhydrous copper sulfate was ozonized for one hour and forty minutes in a train in which ingoing and outgoing gases passed through concentrated sulfuric acid. The copper sulfate showed no visible change. The solution was decanted through glass wool *via* a ground-glass joint into a second bottle in the train and subjected to vacuum evaporation under anhydrous conditions. There remained a red viscous residue, from which by treatment with dry ether was separated dimeric benzaldehyde peroxide as dirty white needles, melting with gas evolution at 183–193°, and a red amorphous product not melting below 350°. Other ozonizations carried out over anhydrous copper sulfate gave similar results. One sample exploded harmlessly during evaporation *in vacuo* when it became too warm; dimeric benzaldehyde peroxide was identified in the residue.

Attempted isolation of dihydroxydibenzal peroxide from the decomposition of styrene ozonide. A solution of 3.5 cc. of styrene in 50 cc. of carbon tetrachloride was ozonized for two hours with ice-salt cooling. The solvent was removed *in vacuo* at room tem-

perature under a carbon dioxide atmosphere, and the residue was washed by decantation with dry hexane. It was then treated with 0.5 cc. of water in 10 cc. of anhydrous ether for two hours, during which time a slow evolution of gas was perceptible. By fractional crystallization only benzoic acid and benzaldehyde peroxide were isolated. No indication of the presence of dihydroxydibenzal peroxide was observed. Other ozonizations in carbon tetrachloride and hexane with ice-salt or acetone-dry ice cooling gave similar results. In one instance the oily filtrate remaining from the isolation of benzoic acid and benzaldehyde peroxide reacted vigorously with dilute solutions of sodium bisulfite or sodium hydroxide, probably due to the presence of undecomposed ozonide.

p,p'-*Dichlorobenzophenone peroxide.* 1,1-Di-*p*-chlorophenylethene was prepared by dehydrating with dilute sulfuric acid the carbinol obtained from methylmagnesium iodide and *p,p'*-dichlorobenzophenone. A product melting at 85–87° (lit. 91–92°) after recrystallization from methanol was used for ozonization.

A solution of 6.5 g. of the ethene in 100 cc. of carbon tetrachloride was ozonized for two and one-half hours with acetone-dry ice cooling. At this time saturation of the olefin bond was indicated by the blue color of ozone in the carbon tetrachloride solution. The mixture was decomposed with a solution of hydrogen peroxide and the acidic products were removed with dilute sodium hydroxide. *p*-Chlorobenzoic acid, m.p. 240° (lit. 236°, 243°) and oxalic acid, precipitated as calcium salt in acetic acid solution, were isolated from the alkaline extract. The residue from the carbon tetrachloride solution was dissolved in acetone and cooled. *p,p'*-Dichlorobenzophenone crystallized. The filtrate, concentrated and again cooled, gave 0.31 g. (4.5%) of *p,p'*-dichlorobenzophenone peroxide, which after recrystallization from acetone melted with gas evolution at 217.5–218.5°.

Anal. Calc'd for $C_{26}H_{20}Cl_4O_4$: C, 58.45; H, 3.02.
Found: C, 58.62; H, 3.08.

The product remaining after evolution of gas from the peroxide had ceased melted at 144–145° and a mixed melting point with an authentic sample of *p,p'*-dichlorobenzophenone, m.p. 147–148°, showed no depression.

Di-o-tolyl ketone peroxide. Difficultly separable liquid mixtures containing 1,1-di-*o*-tolylethene were obtained by dehydrating the addition-product from *o*-tolylmagnesium bromide and ethyl acetate. A fraction of 5.9 g. of impure ethene, boiling at 125–127° (4 mm.) n_D^{20} 1.5854, in carbon tetrachloride solution was ozonized for three and one-fourth hours and decomposed by the usual aqueous treatment. Alkaline extraction gave 1.09 g. of a mixture of solid acids, from which was isolated by solution in hot water 0.23 g. of *o*-toluic acid, melting at 90–99°, and 0.54 g. of a light yellow acid, insoluble in hot water, melting at 157°, N.E. 252, which was not further identified. By concentration of the carbon tetrachloride solution and addition of alcohol impure di-*o*-tolyl ketone was obtained, m.p. 65–72° (lit. 72°). After several months standing, the filtrates from several ozonolysis mixtures yielded about 0.035 g. of very impure peroxide, which melted with gas evolution at 175–180°. The amount of purified product, m.p. 183° was not sufficient for an analysis.

Ozonolysis of 1,1-(di-3,4-dimethylphenyl)ethene. 1,1-(Di-3,4-dimethylphenyl)-ethene was prepared essentially according to the directions of Bistrzycki and Reintke (13).

A 2.5 g. sample of the ethene in 60 cc. of carbon tetrachloride was ozonized for two hours and forty minutes with ice-salt cooling. On working up the ozonization mixture in the usual manner there was obtained chiefly di-(3,4-dimethylphenyl) ketone, m.p. 140°, plus a small amount of 3,4-dimethylbenzoic acid, m.p. 165.5–166°, N.E.

153 (calculated 150), and some oxalic acid. The more impure ketone fractions melted with slow evolution of gas to a temperature of 190°. However, when recrystallized these gave either the ketone or a product melting at 164–165° without gas evolution. The quantities of the latter compound were too small for further investigation. Other ozonolysis mixtures gave similar results.

Synthesis of dimeric diaryl ketone peroxides from the ketones and hydrogen peroxide. Dimeric benzophenone peroxide. A mixture of 0.55 g. of benzophenone and 30% aqueous hydrogen peroxide was allowed to stand two months. The crystalline material was separated and after digestion with alcohol 0.003 g. (0.5%) of dimeric benzophenone peroxide, m.p. 212.5°, remained undissolved.

A solution of 0.5 g. of benzophenone in 15 cc. of dry ethereal hydrogen peroxide, which was prepared by extracting 30% aqueous hydrogen peroxide with an equal volume of ether and drying the ethereal solution over anhydrous sodium sulfate, was allowed to stand for two months. A few crystals of dimeric benzophenone peroxide, melting and evolving gas at about 212.5°, were isolated.

*Di-*p*-tolyl ketone peroxide.* A mixture of 0.5 g. of di-*p*-tolyl ketone and 20 cc. of 30% hydrogen peroxide was let stand two months and filtered. Digestion of the solid material with ethyl alcohol left 0.004 g. (0.8%) of dimeric di-*p*-tolyl ketone peroxide, melting at 202–205°, undissolved.

A solution of 0.5 g. of di-*p*-tolyl ketone in dry ethereal hydrogen peroxide was let stand two months and the solvent evaporated. The residue gave 0.005 g. (1%) of dimeric di-*p*-tolyl ketone peroxide, melting above 195° with gas evolution.

Attempted synthesis of dimeric di-(3,4-dimethylphenyl) ketone peroxide. A mixture of 0.5 g. of di-(3,4-dimethylphenyl) ketone and 20 cc. of dry ethereal hydrogen peroxide was allowed to stand for three months. The solvent was evaporated and the residue fractionally crystallized from acetone. The last two of five fractions melted at about 130° with gas evolution to 170°. Recrystallization of these fractions gave similar results, but no ketone peroxide could be isolated.

Dimeric p*-methoxyphenyl methyl ketone peroxide.* 1-*p*-Methoxyphenyl-1-methylethene was prepared by dehydrating the product obtained from the addition of methylmagnesium iodide to methyl anisate (10), with 10% sulfuric acid. Since considerable polymerization occurred during fractional distillation of the ethene under 15 mm. pressure, impure samples were used for ozonization.

A 3.8 g. sample of 1-*p*-methoxyphenyl-1-methylethene, n_D^{20} 1.5665, in 60 cc. of carbon tetrachloride was ozonized with ice cooling for two and three-fourths hours. The reaction-mixture was treated with sodium bicarbonate solution and the unchanged precipitate was removed by filtration, and dissolved in acetone. From the decomposition of this precipitate only oxalic acid, identified as the calcium salt, was isolated. Acidification of the alkaline solution gave no solid acid. A gummy, alcohol-insoluble product remained from concentration of the carbon tetrachloride solution at room temperature. Repeated solutions of this residue in alcohol-ether and evaporations *in vacuo* yielded 0.035 g. of dimeric *p*-methoxyphenyl methyl ketone peroxide, which after several recrystallizations from acetone melted at 187.5° with gas evolution.

Anal. Calc'd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.06.
Found: C, 65.25; H, 6.14.

An attempt to isolate *p*-methoxyphenyl methyl ketone from the filtrate as its semicarbazone derivative was unsuccessful. Briner and Nemitz (10) did obtain this derivative in a similar experiment.

Ozonization of dihydroxydibenzal peroxide. A suspension of 0.5 g. of dihydroxydi-

benzal peroxide in 75 cc. of carbon tetrachloride was ozonized for one and one-half hours and the resulting solution treated with 40 cc. of water for twenty hours. The solvent was removed from the carbon tetrachloride solution *in vacuo* and the residue was dissolved in ether and extracted with dilute aqueous sodium hydroxide. The ethereal solution gave a very small amount of benzaldehyde peroxide, which after recrystallization melted at 195° with gas evolution and red discoloration of the melting point tube, and which showed no depression of melting point with an authentic sample of benzaldehyde peroxide. The alkaline extraction gave 0.3 g. of benzoic acid, melting at 121°.

Treatment of dihydroxydibenzal peroxide with phosphorus pentoxide. Samples of dihydroxydibenzal peroxide in suspension or solution were treated with several grams of phosphorus pentoxide with shaking and cooling, and let stand for various periods of time at low temperature. The solutions were then decanted and the solvents removed *in vacuo*. After testing the residues for explosibility in the flame, the

TABLE III

TREATMENT OF DIHYDROXYDIBENZAL PEROXIDE WITH PHOSPHORUS PENTOXIDE

SAMPLE, G.	SOLVENT	TEMPERATURE	TIME, DAYS	YIELD OF BENZALDEHYDE PEROXIDE, G.
0.5	$(C_2H_5)_2O$	Refrigerator (+5°)	2	0.001
2.0	"	"	1	.06 (6.06%)
2.0	"	Acetone-dry ice	2	Trace[a]
3.0	"	Acetone-dry ice	7	0.032[b]
		Ice	¾	
2.0	"	Refrigerator	1	.012[c]
0.5	$CHCl_3$	"	1	.001
2.0	CCl_4	"	2	.061 (6.16%)

[a] After removal of the solvent under a carbon dioxide atmosphere most of the starting material was recovered.

[b] The solvent was removed under a carbon dioxide atmosphere.

[c] Addition of hexane to the concentrated solution produced no precipitate of expected ozonide.

products of the dehydration were fractionally crystallized by treatment with alcohol. The experimental conditions, as well as the quantities of benzaldehyde peroxide isolated, are given in Table III. The characteristic ozonide odor could not be detected in any residue and in no case was a product of explosive character, or of viscous or gelatinous nature, observed. Benzaldehyde and small amount of benzoic acid also were always obtained.

Ozonization of benzaldehyde. A solution of 5 cc. of purified benzaldehyde in 60 cc. of carbon tetrachloride was treated with ozone with ice cooling for one and one-quarter hours. A precipitate, partly crystalline and partly resinous, separated during this time. To the mixture was added 80 cc. of water. After standing overnight, the carbon tetrachloride layer was washed with sodium carbonate. From this alkaline extract 85% of the theoretical amount of benzoic acid was isolated. The carbon tetrachloride solution was evaporated under reduced pressure at room temperature, and the residue was treated with alcohol. A crystalline residue weighing 0.771 g. (15%) of benzoyl peroxide, m.p. 105°, remained. This product showed no depression in melting point when mixed with authentic benzoyl peroxide.

SUMMARY

1. Dimeric diaryl ketone peroxides have been obtained by the ozonolysis of arylated olefins without the introduction of water at any stage of the reaction. This is considered to be evidence in favor of the view that ozonides cleave directly to give the usual products of ozonolysis.

2. Some new dimeric diaryl ketone peroxides and an alkyl aryl ketone peroxide have been characterized.

3. Benzophenone and di-*p*-tolyl ketone have been converted to the corresponding peroxides by the action of hydrogen peroxide.

4. Ozonolyses of styrene, stilbene, and triphenylethylene have yielded dimeric benzaldehyde peroxide.

5. Benzoyl peroxide has been obtained by the ozonization of benzaldehyde.

URBANA, ILL.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

CONDENSATION PRODUCTS FROM BENZYL ALCOHOL. POLYBENZYLS

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The formation of a hydrocarbon analyzing for $(C_7H_6)_n$ by the action of boron fluoride, boron oxide, sulfuric acid, phosphorus pentoxide, or zinc chloride on benzyl alcohol or benzyl ether was first reported by Cannizzaro (1) in 1854. Compounds of apparently related structure were isolated by Nef (2) from the treatment of benzyl alcohol or various benzyl ethers or esters with sulfuric acid, phosphorus pentoxide, or aluminum chloride. Auger (3) found that sulfuric acid or aluminum chloride converted benzyl alcohol into a hydrocarbon, $(C_7H_6)_n$, having a molecular weight corresponding to 16 to 18 units. By passing benzyl alcohol vapors at 300–360° over various dehydrating oxides, such as those of aluminum, titanium, and chromium, Sabatier and Mailhe (4), and later Mailhe and de Godon (5) using calcined alum at a lower temperature, prepared a yellow insoluble amorphous product also analyzing for $(C_7H_6)_n$, which was apparently the same as a resinous substance previously reported (6, 7). From the treatment of benzyl alcohol or various benzyl ethers with stannic chloride, Zonew (8) obtained a polymeric hydrocarbon of similar analysis. By heating a mixture of benzyl alcohol and sulfuric acid trihydrate, Senderens (9) obtained a hydrocarbon $(C_7H_6)_n$, as did Meerwein and Pannwitz (10) using boron fluoride and the alcohol. Recently, Calcott, Tinker, and Weinmayr (11) reported the isolation of a hydrocarbon from the action of anhydrous hydrofluoric acid on benzyl alcohol.

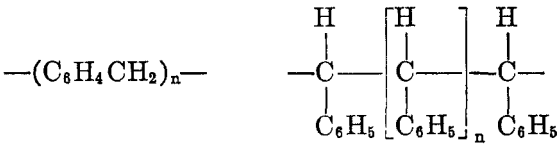
In the presence of numerous catalysts, benzyl chloride also forms a hydrocarbon $(C_7H_6)_n$ which apparently is similar to that obtained from the polymerization of benzyl alcohol. Various metals such as copper (7, 12), nickel (7, 12c), iron (13), aluminum (13), and zinc (13, 14) have all shown activity in polymerizing benzyl chloride. Both the zinc-copper (2, 15) and zinc-sodium (16) couples also react with the chloride to produce the $(C_7H_6)_n$ hydrocarbon. Numerous chlorides, including those of aluminum (2, 3, 13, 17), iron (13, 17h, 18), tin (8, 17h), zinc (3, 13), barium (17g), and nickel (12b, 17g) have also been used to produce resinous hydrocarbons from benzyl chloride under various conditions. Self-condensation of benzyl chloride has also been effected by the action of iron pyrites (18) and of ferric oxide (19).

Benzyl bromide (2, 15, 20) has been polymerized by similar catalysts. Benzyl fluoride (21), in the presence of either hydrofluoric or sulfuric acid, is readily transformed into a colorless glassy resin whose analysis is $(C_7H_6)_n$.

A product of apparently the same general composition can be produced from the condensation of benzene with formaldehyde in the presence of various dehydrating agents (22).

Numerous other workers have reported the formation of hydrocarbon residues in reactions involving benzyl alcohol (9, 23), benzyl ethers (23b, 24), benzyl chloride (12b, 23a, 25), or benzyl mercaptan (26).

All these previous investigations have shown that benzyl alcohol and many of its derivatives do form polymeric substances but very little specific information is available concerning the structure and properties of these products. An examination of the methods of synthesis, and of the elementary formula of the polymeric material would appear to permit of the two possible structures (I) and (II).



I II

The evidence for each of these formulas is somewhat fragmentary. Both *o*- and *p*-benzylbenzyl chloride (17g, 27) have been isolated in reactions involving benzyl chloride and a catalyst. Either of these compounds could be the first step in the formation of a polymer of type (I). In addition, anthracene has been formed in numerous reactions involving benzyl compounds (14, 17a, 24a, 24b, 28). The isolation of the benzylbenzyl chlorides and of anthracene would indicate the possibility that the benzene rings in the polymer chain are linked through methylene groups as in formula (I).

However, stilbene (29) has also been isolated in a number of reactions of benzyl compounds a fact which lends some weight to formula (II). On treatment with aluminum chloride in a manner similar to that used on benzyl chloride in some of the polymerizations reported, stilbene is converted into a compound $(C_{14}H_{12})_x$, originally reported to be a stilbene octamer (30), but later shown to be a trimer (31). This stilbene trimer differs from the hydrocarbon polymer of like analysis formed from benzyl alcohol and its derivatives, in being readily decomposed and oxidized. Some phenanthrene is always found in addition to the stilbene trimer, although as far as is known phenanthrene has never been formed as a product in any of the reactions of benzyl compounds with themselves. This fact, coupled with the auxiliary one; namely, that stilbene has never

been found in any of the reactions of benzyl compounds which also gave rise to the $(C_7H_6)_n$ polymer, would appear to eliminate stilbene as an intermediate in the formation of the hydrocarbon polymer.

The synthesis of 1,2,3,4,5,6-hexaphenylcyclohexane from benzyl compounds has been reported by several investigators (4, 5, 6, 7, 11). This compound could conceivably be formed as a cyclic trimer of stilbene, or by the cyclization of 6 units of formula II. In spite of the many references which have been made to 1,2,3,4,5,6-hexaphenylcyclohexane the evidence presented in support of this formula has been very slight. None of the previous investigators has reported a molecular weight or even a melting point for any of the products so designated. Apparently the material has never been isolated in any save an amorphous form with an empirical analysis corresponding to $(C_7H_6)_n$. The formula given has been based on the analysis of a nitration product. Mailhe (7) originally gave the analysis of this nitration product as $(C_7H_5NO_2)_x$, but later, in collaboration with Sabatier (4), the analysis for the nitro compound was given as $(C_6H_4NO_2)_6C_6H_6$. No molecular weight or melting point was given for this nitration product, which would make it appear that this compound was also obtained in an amorphous state. Bezzi (17i) has shown that by varying the method of nitration on the $(C_7H_6)_n$ hydrocarbon, one can obtain a product containing either less or more than one nitro group per benzyl unit. Thus it would appear that evidence based entirely on nitration is none too reliable. Olivier and Wit (19), working on a similar polymerization problem, have concluded from their results that the supposition of Sabatier and Mailhe that they had hexaphenylcyclohexane is erroneous. Thus all of the evidence favoring formula II is apparently unreliable.

Since the information now at hand, taken in conjunction with what is now known of the phenol-formaldehyde resins, appears overwhelmingly to favor formula I, and since the work to be presented later in this paper gives added evidence favoring formula I, this formula will be used in the subsequent discussion.

In the studies of the polybenzyl hydrocarbons reported to date, both liquid and amorphous solid materials have been formed. The solids have been for the most part red or yellow in color, while the variously colored liquids have usually shown a marked fluorescence. In certain cases highly insoluble products have been formed, while in other instances hydrocarbons soluble in benzene and carbon disulfide have been isolated. Especially for the benzyl alcohol resins, very little information is available pertinent to the experimental conditions to be used in the preparation of one or another of these resinous materials. In view of this fact, part of the earlier work has been repeated and extended.

The first condensation product used in the present investigation was

prepared by adding benzyl alcohol dropwise to a well-stirred, cooled solution of concentrated sulfuric acid. The polymer forms immediately as a salmon-red, stringy, solid mass which floats on the sulfuric acid. This mixture is poured on cracked ice immediately after all of the alcohol has been added. A very insoluble green resin is formed in a short time if the salmon-red polymer is not removed quickly from the concentrated acid solution. The red color is discharged partially from the condensation product as soon as it is added to the cracked ice, and on further standing in the dilute acid solution it usually becomes a light cream color. The condensation product is separated from the liquid by a combination of decanting, centrifuging, and filtering, depending on the rate of coagulation. After being collected on a filter, the condensation product is washed with water until the washings show only a slight cloudiness with barium chloride solution. The solid remaining is air dried and powdered.

All attempts to crystallize this product were unsuccessful. Though it is soluble in chloroform, carbon tetrachloride, benzene, carbon disulfide, toluene, benzaldehyde, ethyl bromide, and mesitylene, evaporation of solutions in these solvents leaves the polymer residue as a gummy mass. Since the condensation product dissolves only partially in dioxane, a separation of the polymer was made based on differences in solubility in this solvent.

The dioxane-soluble portion was purified by repeated precipitation of the dioxane solution with water. The white polymer thus produced had a melting point range of 85–100° and gave no qualitative test for sulfur. Numerous analyses of this dioxane-soluble polymer from different reaction-mixtures showed that the product is not a hydrocarbon as was expected, but that there must be some oxygen still left in the compound. The analytical data indicate that the material is a polybenzyl alcohol of the general composition shown in formula III.

$$C_6H_5CH_2(C_6H_4CH_2)_nC_6H_4CH_2OH$$

III

The combustion analyses suggest that this product has a value of n equal to about 9 for its average composition. Molecular weight determinations by the ebullioscopic method in chloroform and in dioxane gave the average values 952 and 830, respectively. Molecular weights by the viscometer method in benzene solution, using the constant given for polybenzyl by Bezzi (17i), $K_m = 4.01 \times 10^{-4}$, gave the average value 1218. The calculated value for formula III, n = 9, is 1008.

Molecular weight determinations by the ebullioscopic or cryoscopic methods yield number average molecular weights (M_n) whereas the viscosity method gives weight average molecular weights (M_w). The two methods therefore measure different types of average molecular

weights and since the values differ from each other, the polymer is probably rather heterogeneous in regard to chain lengths.

The dioxane-insoluble portion was purified by repeated washings with dioxane and water. The white product thus produced, with a melting point range of 65–90°, also gave no test for sulfur. Analysis indicated it to be a hydrocarbon $-(C_6H_4CH_2)-_n$. While this might be a cyclic product, it is unlikely that such is the case, since the method of preparation was not of the high dilution type, and the formation of a good yield of a cyclic product would be entirely unprecedented. It is, of course, possible that the chain is terminated at each end by a hydrogen atom. However, it appears more likely from analogy with the benzyl chloride polymers which contain no chlorine that the insoluble polybenzyl is terminated by the formation of a stilbene structure (IV), although the existence of the double bond could not be detected by chemical means.

$$C_6H_5CH_2(C_6H_4CH_2)_xC_6H_4CH{=}CHC_6H_4(CH_2C_6H_4)_yCH_2C_6H_5$$

IV

Molecular weights of this dioxane-insoluble polymer by the ebullioscopic method in chloroform gave the average value 1687, and by the viscometer method, a higher value, 2116. These molecular weight values correspond to a chain length of 19 to 24 benzyl units.

It appeared that the simplest method of determining whether the chain was linked through *ortho*, *meta*, or *para* positions was by means of an oxidation to the polyketone followed by an alkaline fusion and isolation of the phthalic acids formed.

$$-(C_6H_4CH_2)_n- \xrightarrow{[O]} -(C_6H_4CO)_n- \xrightarrow{NaOH}$$

V

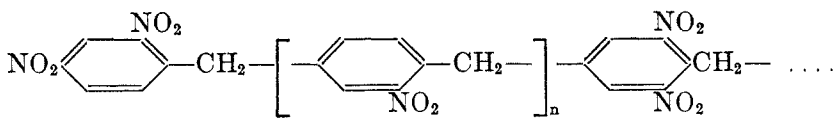
$$C_6H_5CO_2H + C_6H_4(CO_2H)_2$$

In agreement with earlier reports by Nastukoff (22a) and Jacobson (17h) on polybenzyls prepared by other methods, the polybenzyl hydrocarbon showed a remarkable stability to oxidizing agents. Even boiling alkaline, neutral, and dilute acid solutions of potassium permanganate had no noticeable effect on the condensation product. Chromic acid in acetic acid solution at room temperature and selenium dioxide in boiling dioxane for forty-eight hours produced little oxidation. Hot chromic acid and potassium dichromate in sulfuric acid gave oxidation products which could not be purified. However, 1:4 nitric acid readily produced a golden-yellow compound softening between 160–165° which contained no nitrogen. Its analysis and subsequent alkaline fusion products indicate that it is a polyketone (V), which may, from analogy with polybenzyl, be called polybenzoyl. This polyketone is soluble in chloroform, nitro-

benzene, benzyl alcohol, dioxane, and pyridine; slightly soluble in ethanol, Cellosolve, and Carbitol; insoluble in carbon tetrachloride, acetone, and aliphatic and aromatic hydrocarbons. It was insoluble in aqueous alkali indicating that no carboxyl group was at the end of the chain. The average molecular weight of polybenzoyl by the ebullioscopic method in dioxane was found to be 890 and by the cryoscopic method in benzophenone was 1070, which indicates 9 or 10 benzoyl units. It also shows that some degradation had occurred during the oxidation.

Fusion of the polyketone (V) with a mixture of sodium and potassium hydroxides at 260° for twenty-four hours produced a mixture of benzoic acid and two of the phthalic acids. The acids were isolated by direct precipitation from the acidified fusion mixture and through an ether extraction on the acidified solution. Since benzoic and *o*-phthalic acids are fairly soluble in water, while both isophthalic and terephthalic acids are very insoluble in water, a separation of the mixed acids into two groups was easily made by means of this solvent. As a separation of the large excess of benzoic acid could not be made easily from the *o*-phthalic acid, the mixture of the two acids was purified and the amounts of each acid present determined by the neutral equivalent. No isophthalic acid was isolated in any fusion, so either extremely small amounts, or none of the *meta* compound was formed. In one experiment 0.5203 g. of terephthalic acid, 0.0899 g. of *o*-phthalic acid and about 5 g. of benzoic acid were isolated from the alkaline fusion of 20 g. of polyketone. The relative amounts of terephthalic and *o*-phthalic acid suggest a ratio of *para* to *ortho* linkage in the polymer of approximately 6 to 1. These results are necessarily quite inaccurate, not only because of the small amounts of dibasic acids obtained, but also because of differences in the chemical reactivity of the *ortho* and *para* isomers in the oxidation and alkaline fusion reactions.

Nitration of polybenzyl has produced a variety of nitro derivatives depending on the solubility of the polybenzyl and the conditions used (4, 7, 15, 16, 17b, 17c). In addition a mononitropolybenzyl has been prepared by the action of aluminum chloride on *p*-nitrobenzyl chloride (2d). Using fuming nitric acid Bezzi (17i) isolated a compound with 1 nitro group per benzyl unit, except for the end benzyl units, which presumably gained 2 nitro groups each as in formula VI. (The positions of the nitro groups on the rings are indeterminate.)



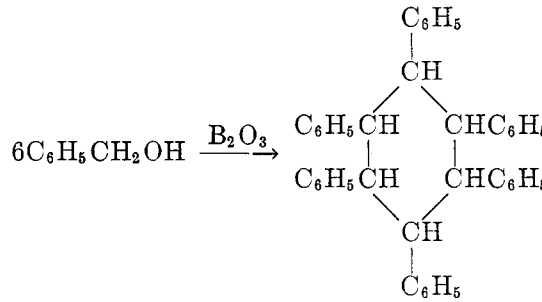
VI

When the condensation product from benzyl alcohol was treated with fuming nitric acid in the cold it produced a nitro derivative containing between 1 and 2 nitro groups per benzyl unit. Analysis of this nitro product for carbon, hydrogen, and nitrogen showed the presence of almost exactly 2 oxygen atoms for each nitrogen atom indicating that little or no oxidation had occurred during the nitration. The present work and other reports of the nitration of polybenzyl show that anywhere from a few nitro groups to a large number may be introduced into the polybenzyl molecule by varying the solubility of the condensation product and the nitrating conditions.

Bromination of the condensation product with iron as a catalyst produced a bromo derivative containing between 1 and 2 bromine atoms per benzyl unit. By extracting the bromopolybenzyl with a small amount of chloroform, a product was separated whose analysis agreed closely with that of 1 bromine atom per benzyl unit. A product of similar analysis was obtained by Boeseken (20), and later by Jacobson (17h), from the polymerization of *p*-bromobenzyl chloride. From the bromination of polybenzyl, Jacobson obtained a bromopolybenzyl containing 1 bromine atom for each pair of benzyl units.

In order to determine the effect of other dehydrating acids on benzyl alcohol, it was treated with perchloric acid in the same manner as it had been with sulfuric acid. A pink colored condensation product was formed when the benzyl alcohol was added dropwise to the perchloric acid. This material becomes white almost immediately when added to ice-water. It is quite soluble in dioxane, and may be purified from dioxane-water mixtures in the same manner as the condensation product from sulfuric acid. The perchloric acid condensation product softens below 60° and tends to darken very readily in air, even at room temperature, so no satisfactory analysis or molecular weight could be made on this material.

When benzyl alcohol was treated with fused boric acid at 180° for about four hours and distilled immediately under reduced pressure an 86% yield of benzyl borate (32) resulted. The same reaction materials were heated for about twelve hours at 180°, cooled, shaken with excess alkali, and extracted with chloroform, dried, and vacuum distilled. Treatment of the distillate with ether gave a small amount of a solid which upon crystallization from benzene yielded colorless needles, m.p. 278–280°. The crystals were soluble in benzene and chloroform, slightly soluble in ether, and insoluble in water, ethanol, and ligroin. Analysis of the material corresponded to $(C_7H_6)_n$, and molecular weight measurements in camphor gave the value 556, indicating that the crystalline material is one of the isomeric 1,2,3,4,5,6-hexaphenylcyclohexanes.



EXPERIMENTAL

Preparation of the condensation product. A 2-liter three-necked flask, containing 500 ml. of concentrated sulfuric acid, is fitted with an efficient mechanical stirrer, a thermometer reaching into the liquid, and a dropping-funnel containing about 75 ml. (0.72 mole) of benzyl alcohol. The acid is cooled to 0° in an ice-salt-bath, and the benzyl alcohol is added dropwise to the well-stirred acid solution over about a thirty minute period, during which time the temperature of the acid mixture rises to about 20°. With the addition of the first drop of the alcohol, a salmon-red, stringy solid which floats on the acid is formed. This color is retained if the acid solution is well stirred and the alcohol is added slowly enough to prevent any local excess of alcohol throughout the addition. If an excess of alcohol does accumulate at any point it will cause the formation of a greenish insoluble product. As soon as all of the benzyl alcohol has been added, the polymer-sulfuric acid mixture is poured with stirring into two 4-liter beakers, each containing about 2000 g. of cracked ice. The polymer is partially precipitated directly, its color usually a red-pink to a very faint pink at first, gradually becoming cream colored to white after standing for some time. The water suspension is permitted to stand overnight or until the ice has melted, and one of the three following methods is used in separating the polymer from the liquid depending on the amount of separation which has taken place during this time.

1. If the condensation product has precipitated only slightly and remains essentially in a colloidal form, the dilute acid-polymer mixture is centrifuged, decanted, and washed with water until the polymer begins to settle fairly rapidly. Then it is collected on a filter and washed with water until the washings give only a slight cloudiness with barium chloride solution.

2. If a considerable portion of the condensation product has settled to the bottom of the beakers, the upper layers are poured into another vessel and allowed to stand until a better separation of liquid and solid materials has occurred. The product which has settled out in the two beakers is combined and washed by nearly filling the beaker with water, stirring vigorously, and allowing the solid to separate out. The mixture is decanted and the washing process is repeated until the solid begins to settle out of solution quite rapidly, which usually takes between five and fifteen such washings. The condensation product is now collected on a filter and washed with water until the washings give only a slight cloudiness with barium chloride solution.

3. If the condensation product has settled out of the dilute acid solution almost completely the supernatant liquid is removed by decantation and the solid collected on a filter and washed with water until the sulfate test is faint.

The solid is now dried by sucking air through it for twelve hours or more, and

then it is spread out and pressed on large sheets of blotting paper. During this partial drying process the polymer often reassumes a light pink color. On removal from the blotting paper the weight of the condensation product varies between approximately 60 and 100 g. (corresponding to a yield of 80–133% by weight depending on the extent of drying). For all of the work except the analysis and molecular weights this material, which will be referred to hereafter as crude, or simply polybenzyl, was used. This crude material starts to soften at 65° and is completely liquid at 77°. Bromine in carbon tetrachloride, potassium permanganate, and bromine water are not decolorized by this product at room temperature.

Purification of the condensation product. Dilute solutions of the polymer were prepared in chloroform, carbon tetrachloride, benzaldehyde, ethyl bromide, and dioxane. About 5 ml. of each of these solutions was added to about 50 ml. of each of the following solvents: 95% alcohol, absolute alcohol, water, ethyl ether, high-boiling petroleum ether, low-boiling petroleum ether, acetone, methyl alcohol, acetic acid, and paraldehyde, except when the two solvents were not miscible. These mixtures were permitted to stand overnight and then examined. Practically none of the mixtures save those of dioxane showed any evidence of the polymer having settled out as a solid, although an oil had separated out in a few cases. The dioxane-acetic acid solution contained a small precipitate of a light pink cream colored material. From the water-dioxane solution a small amount of a white material had precipitated and therefore in all succeeding purifications dioxane-water mixtures were used. Dilute solutions of the polymer were added dropwise with stirring to 40 to 50 volumes of water. The mixture was allowed to stand for twenty-four hours and collected on a filter if it had separated sufficiently. Otherwise it was centrifuged and washed in the centrifuge tube. By repeating the precipitation three times, a white product was isolated which was considered sufficiently pure for analysis. This material started to turn dark at about 80°, began to melt about 95°, and was completely liquid at 110°.

The portion of the crude material which failed to dissolve in the dioxane was separated from the soluble portion by filtration and washed with considerable dioxane to remove all of the soluble portion. The insoluble material remaining was quite gummy but came out as a white amorphous solid when placed in water.

Soluble polymer: Anal. Calc'd for $C_6H_5CH_2(C_6H_4CH_2)_{10}OH$: C, 91.62; H, 6.79 Mol. Wt. 1008.

Found for three separate preparations: C, 91.51, 91.12, 91.68; H, 6.78, 6.87, 6.73.

Molecular weight in chloroform: 963, 941.

Molecular weight in dioxane: 843, 817.

Molecular weight by viscometer; benzene solution, using $K_m = 4.01 \times 10^{-4}$: 1174, 1262.

Insoluble polymer: Anal. Calc'd for $(C_7H_6)_n$: C, 93.29; H, 6.71. Mol. Wt. calc'd for n = 19, 1710; n = 24, 2160.

Found: C, 93.23; H, 6.67.

Molecular weight in chloroform: 1630, 1743.

Molecular weight by viscometer; benzene solution, using $K_m = 4.01 \times 10^{-4}$: 2198, 2033.

Oxidation of polybenzyl with dilute nitric acid. To 5 g. of polymer in a 1-liter round-bottomed flask was added a mixture of 100 ml. of concentrated nitric acid and 400 ml. of water and the combination was heated under reflux for forty-eight hours. After about an hour a yellow-orange solid had separated from the nitric acid as a

hard crust, and this was broken up with a glass rod a few times during the reaction. In other runs, when 20–30 g. of polybenzyl was oxidized at once, after twelve hours the crust was broken up and then collected on a filter, ground, and then returned to the reaction flask with fresh 1:4 nitric acid. The reaction-mixture was cooled and the product collected on a filter. The precipitate, a yellow-orange solid, was repeatedly washed with water to remove the acid. On air-drying the material turned to a beautiful golden-yellow color. It gave no qualitative test for nitrogen. In a melting point tube it began to darken slightly at about 157° and softened completely between 160–165°. It was insoluble in hot alkali.

Anal. Calc'd for $H(C_6H_4CO)_{10}H$: C, 80.60; H, 4.06; Mol. Wt. 1042.
Found: C, 80.64, 80.32; H, 4.55, 4.13.

Molecular weight by boiling point method in dioxane: 876, 903.

Molecular weight by freezing point method in benzophenone: 1036, 1103.

Alkali fusion of polybenzoyl. To 20 g. of polybenzoyl in a 200 ml. iron crucible was added a mixture of 25 g. of potassium hydroxide and 25 g. of sodium hydroxide. The mixture was heated to 260° for twenty-four hours. During this time the hard lumps which formed were broken up as well as possible with a metal rod, but mechanical stirring was impossible due to the size of the lumps formed. The mass was allowed to cool and dissolved in about a liter of water. A separation from insoluble material was made by filtration, the precipitate being washed with hot water until the washings were essentially colorless. At this stage in the process the solution was black in color. Hydrochloric acid was added and then 20 ml. excess of concentrated hydrochloric acid was added and the solution heated to boiling and filtered while hot. The filtrate was colorless and on standing for about twenty-four hours, terephthalic acid precipitated and was collected on a filter and crystallized from absolute ethanol. The remainder of the solution was evaporated down to about a liter, and the organic materials removed by continuous ether extraction for seventy-two hours.

Identification of acids formed from alkali fusion. The terephthalic acid weighed 0.52 g. and gave a neutral equivalent of 83.7 (theoretical 83.0). It failed to melt or sublime in a melting point tube at 340°. When melted with phosphorus pentachloride it gave a diacid chloride melting at 80.5°, which in mixture with pure terephthalyl chloride melted at 81°. When treated with methanol a dimethyl ester formed, melting at 139°, which gave no depression in mixed melting point with a known sample of dimethyl terephthalate.

The ether solution from the continuous extraction was evaporated to dryness. The residue crystallized in colorless plates from water and weighed 5.2 g. It melted between 112° and 119° and a mixed melting point with benzoic acid gave a rise. The presence of *o*-phthalic acid was shown both by the formation of fluorescein and phenolphthalein. By sublimation, crystals were isolated melting at 130°, which gave no depression with pure phthalic anhydride. A neutral equivalent of very nearly 122 was obtained on the original material. By repeated crystallizations from water the phthalic acid was concentrated in the mother liquor, and finally 1.8 g. of the acid mixture was isolated by evaporating the filtrates using compressed air, air-drying, and then drying in a desiccator over magnesium perchlorate. This material gave a neutral equivalent of 119.3 on three trials. This neutral equivalent corresponds to 4.8% *o*-phthalic acid and 95.2% benzoic acid or a total weight of 0.0899 g. of *o*-phthalic acid. Thus the ratio by weight of the dibasic acids isolated was 0.52 g. of terephthalic to 0.0899 g. of *o*-phthalic, corresponding to a ratio of nearly 6 *para* to 1 *ortho* linkage in the original polybenzyl.

Nitration of polybenzyl. To 50 ml. of fuming nitric acid in a 100-ml. beaker cooled

to 0° by an ice-salt-bath was added 2 g. of polybenzyl and the mixture was stirred for one minute and then poured on cracked ice. The light yellow nitration product was collected on a filter and washed with water to remove all of the acid. The nitro derivative softened at 117° and was completely melted at 132°. It gave none of the usual tests for a polynitro compound.

Anal. Calc'd for $(C_7H_5NO_2)_n$: C, 62.22; H, 3.73; N, 10.37.
Calc'd for $[C_7H_4(NO_2)_2]_n$: C, 46.61; H, 2.24; N, 15.56.
Found: C, 52.58; H, 3.18; N, 12.96.

Bromination of polybenzyl. In a 500-ml., round-bottomed flask fitted with an efficient reflux condenser bearing an outlet tube held above the surface of water was placed 10 g. of crude polybenzyl, 3 g. of iron powder, and 10 ml. of bromine dissolved in 200 ml. of chloroform. The mixture was refluxed overnight, or until hydrobromic acid stopped coming off. After cooling, the mixture was filtered to remove iron, shaken with a solution of sodium bisulfite, and then the chloroform was evaporated. The product was collected on a filter and washed with alcohol. The brominated material started to soften at 152° and was completely melted at 180°.

Anal. Calc'd for $(C_7H_5Br)_n$: C, 49.74; H, 2.98.
Calc'd for $(C_7H_4Br_2)_n$: C, 33.90; H, 1.63.
Mixed product, found: C, 39.16, 39.16; H, 2.29, 2.39.
Soluble product, found: C, 49.49; H, 3.37.

Pyrolysis of polybenzyl. Ten grams of polybenzyl was heated in a distilling flask up to 300°. A small amount of a liquid distilled over up to 200°, but no visible change occurred later even when the temperature was raised to 300° and kept there for a few hours. The residue was a dark brown thermoplastic resin. The distillate was mainly water and a small amount of benzene. The latter was identified by extraction with ether, evaporation of the ether, and nitration of the residue with fuming nitric acid. When poured on ice and crystallized from alcohol the product melted at 88° and a mixed melting point with *m*-dinitrobenzene gave no depression.

Preparation of polybenzyl by use of perchloric acid. To 200 ml. of perchloric acid in a 400-ml. beaker cooled to 0° by an ice-salt-bath was added dropwise with stirring, 5–10 ml. of benzyl alcohol. The precipitate which formed immediately was at first white and then a light pink. The mixture was poured into 600 g. of cracked ice with stirring. After the ice had melted the precipitate which had settled was decanted from the supernatant liquid, washed thoroughly with water, and then collected on a filter and air dried. This white amorphous material readily decomposed on standing in air, especially after drying, possibly due to occluded perchloric acid, and in a melting point tube was completely softened below 60°. When dissolved in dioxane and reprecipitated by water, a soft material which hardened on standing in a vacuum desiccator was formed. When pulverized, this material softened between 60–65°. It was somewhat soluble in benzene but insoluble in ethanol, acetone, and ligroin.

The crude polybenzyl prepared from the alcohol with perchloric acid was oxidized readily to a yellow product with 1:4 nitric acid on refluxing for twenty-four hours, just as was the polybenzyl from sulfuric acid. This oxidation product appeared to decompose somewhat on standing in air. It softened between 100–115°, and was soluble in dioxane and chloroform and insoluble in water, ethanol, ligroin, and carbon tetrachloride.

Anal. Calc'd for $(C_7H_6O)_n$: C, 79.22; H, 5.70.
Found: C, 79.54; H, 5.59.

Reaction of benzyl alcohol with boric oxide. To a 100-ml. beaker in an oil-bath heated to 180° was added 10–25 g. of fused boric acid and 50 ml. of benzyl alcohol. The mixture was covered with a watch glass and heated four to twelve hours.

When the hot reaction-mixture after four hours time was distilled *in vacuo*, the temperature rose to 135° at 4 mm. pressure, and a few grams of benzyl ether distilled. Then the temperature rose to 206° at the same pressure and 46 g. (86% of theoretical) of benzyl borate distilled. It gave a refractive index at 20° of 1.5544. The residue decomposed when the temperature was raised any higher.

In one run, the reaction-mixture after twelve hours heating was treated with an excess of alkali to remove boric acid and anhydride, and then with alcohol and ether to remove benzyl ether. The residue was dried at 140° for twenty-four hours, but the remainder was a small amount of a dark brown very viscous liquid which could not be crystallized. A small amount of liquid distilled from this when heated *in vacuo*, together with a very small amount of solid which appeared to be carried over with the liquid.

When the reaction-mixture was heated for twelve hours, cooled and shaken with excess alkali, and extracted with chloroform, dried, and vacuum distilled, a small amount of a solid distilled over between 160–200° at 4 mm. together with a small amount of liquid. This solid was separated from the liquid by shaking with ether, in which the solid is insoluble, and filtering. The solid on crystallization from a small amount of benzene yielded needles, m.p. 276–280° (corr.). It is soluble in benzene and chloroform, slightly soluble in ether, and insoluble in water, ethanol, and ligroin. Repeating this work in a sealed tube gave the same results.

Anal. Calc'd for $(C_7H_6)_n$: C, 93.29; H, 6.67.
Found: C, 93.53; H, 6.74.

Molecular weight, calc'd for 1,2,3,4,5,6-hexaphenylcyclohexane: 540.
Molecular weight found in camphor: 556.

SUMMARY

A polymeric condensation product was formed when benzyl alcohol was treated with cold concentrated sulfuric acid. This product was a mixture of at least two types of polymers.

1. A polybenzyl alcohol with analysis and molecular weight corresponding to the average composition:

$$C_6H_5CH_2(C_6H_4CH_2)_9C_6H_4CH_2OH$$

2. A hydrocarbon whose analysis and molecular weight indicates a polybenzyl with the average composition:

$$—(C_6H_4CH_2)_{18-23}$$

The condensation product was oxidized by 1:4 nitric acid to a polyketone. Cleavage of the latter by fusion with alkali yielded benzoic acid, *o*-phthalic acid, and terephthalic acid, which shows the presence of both *ortho* and *para* linkages in the original polymer.

Nitration of the condensation product yielded a material containing between one and two nitro groups per benzyl unit. Bromination also produced a derivative containing one to two bromine atoms per benzyl unit.

A condensation product of character similar to the polybenzyl from

sulfuric acid was isolated when benzyl alcohol was treated with perchloric acid.

Treatment of benzyl alcohol with fused boric oxide at 180° also produced polymeric condensation products. From this reaction there was isolated a small amount of a pure crystalline compound whose analysis and molecular weight indicate that it is one of the isomeric 1,2,3,4,5,6-hexaphenylcyclohexanes.

URBANA, ILL.

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THE RELATIONSHIP BETWEEN OPTICAL ROTATORY POWER AND CONSTITUTION OF THE STEROLS

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It is well known that the carbohydrate chemist has made extensive application of the physical property of optical rotatory power in the elucidation of molecular structure. This has been made possible by the discovery, chiefly by Hudson, of several rules relating the structure and rotatory power of carbohydrates. Sterol molecules are also optically active, and it is apparent that the development of analogous quantitative relationships between the structures and the rotatory powers of these substances should be of similar great value to the worker in this field.

It is the purpose of this paper, first to investigate the possibilities of the steroid molecule in this connection from the standpoint of modern theories of optical rotatory power, and then to apply the results of this investigation to the establishment of a reliable and general method of calculating the rotatory power of any molecule from a knowledge of its structure and of the rotatory powers of other molecules.

Several investigators have already pointed out definite relationships between rotatory power and the constitution of the sterols. In 1936, Callow and Young (1), compiled data to show that when a certain structural element (*e.g.*, a double bond) is introduced at a given position in a steroid molecule, there is usually a definite directional change in the rotatory power. Unfortunately, the changes in rotatory power observed by them were not such as to make their method quantitative, and, furthermore, a sufficient number of discrepancies were found to reduce considerably its value in elucidating structure. Lettré (2), by employing the principle of optical superposition to partially dehydrogenated sterol molecules, attempted to correlate the absolute configurations of the hydroxyl group at the C_3 position in sterol molecules with that in *ac*-tetrahydro-β-naphthol. Ruzicka, Hofmann, and Meldahl (3) have observed that the transformations of a Δ^5-3,17-diol into a Δ^4-3-keto-17-ol results in an increase in positive rotation (sodium D light) of 140° to 160° in alcoholic solution. In several other investigations (4), use has been made of the sign and magnitude of the optical rotatory power in support of, or in opposition to suggested structures of sterols, and every experi-

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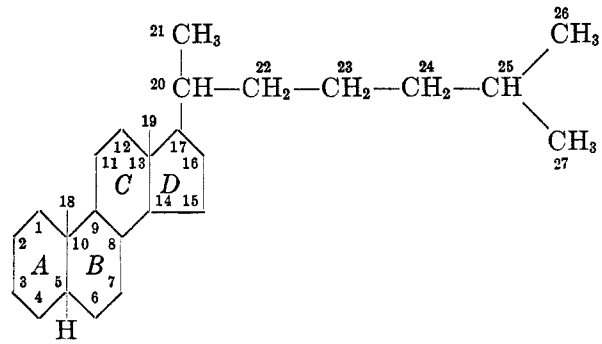
enced worker in this field now has preconceived ideas concerning the magnitude and signs of the rotatory powers of various types of sterols which are based on his every-day experience.

It has been shown (5) that the validity of Hudson's Rules in carbohydrate chemistry is the result of certain very special conditions to which the structures of carbohydrate molecules readily conform. It is to be pointed out here, however, that steroid molecules in general cannot possibly fulfill these conditions. Therefore, no method of attack in the manner of the principle of optical superposition can succeed except in very special cases such as that considered by Lettré (2). Thus, it will not be valid to assign numbers to individual asymmetric carbon atoms and to attempt to calculate the changes in rotations when the configurations about different asymmetric carbon atoms are changed. Indeed, even if such a procedure were valid, it would be of little use to the organic chemist in this field, since one is usually not at liberty to change the configurations about most of the asymmetric atoms in the steroid molecule. Furthermore, the worker in this field is generally more interested in knowing the change in rotation in going from one type of substance to another with or without different functional groups, and as a consequence the principle of superposition is of little use. We conclude, therefore, that little help will be given by attacking the problem from this point of view.

In our opinion the most promising starting point is to be found in the following statements of fact:

(A) Construction of space models for steroid molecules, as for example cholestane (6), reveals that certain parts of the molecule are widely sep-



Cholestane

arated from one another. Thus, the ring system *A B C D* does not curl up, but is more or less flat. Consequently positions 3 and 17 are at relatively great distances (more than 8 Å) from one another.

(B) Introduction of double bonds does not alter this flatness appreciably.

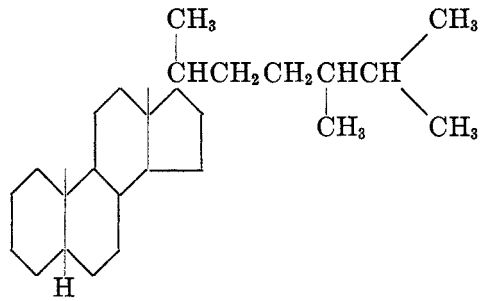
(C) Only very few of the stereoisomers theoretically possible are encountered, and these are of such a nature that the major portion of their chemical reactions involves transformations on a fixed framework. For example, cholestane and coprostane, which differ solely at the C_5 position, have no appreciably differences in regard to the flatness of the molecule.

(D) Vicinal actions (*i.e.*, the interactions between groups in optically active molecules which give rise to optical activity) decrease rapidly with distance. Therefore, when two centers of asymmetry are far apart, they do not influence appreciably one another's contributions to the optical rotation. We shall find that it is through the careful use of this rule that we can make such quantitative predictions as are actually possible. The question of just how far apart two groups must be before they cease to have significant influence on each other cannot be answered *a priori* with assurance, but it is very likely that groups as far apart as those attached to C_3 and C_{17} will have little effect on each other.

(E) When a group occurs on an open chain, vicinal actions between it and other groups on the chain are much smaller, and decrease with distance much more rapidly than do those between groups attached to a rigid framework (7). This makes the groups on the side chain more independent of the rest of the steroid molecule.

The procedure which is to be followed in utilizing the above principles in calculating the rotatory powers of steroids is best illustrated by the following example.

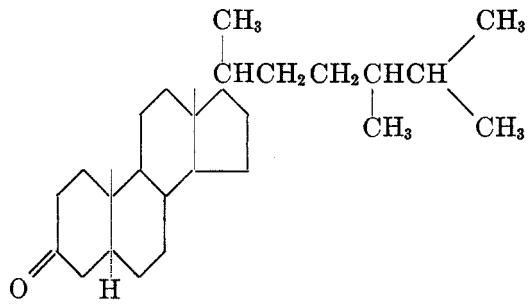
Consider the changes in rotation which occur when one goes from ergostane to ergostanone and from stigmastane to stigmastanone:



Ergostane

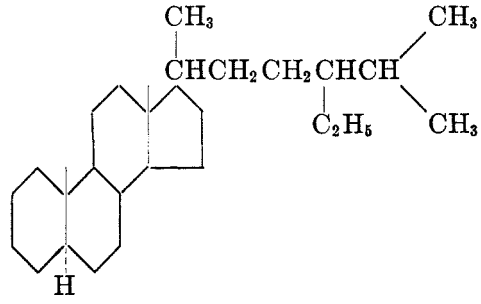
$[M]_D = +7670°$ in $CHCl_3$ [1]

[1] $[M]_D = [\alpha]_D X$ molecular weight (C = 12, H = 1, and O = 16). All molecular rotations have been rounded off in the last figure. It is obvious that all measurements shall have been made in the same solvent in order to reduce disturbances due to solvent effects.



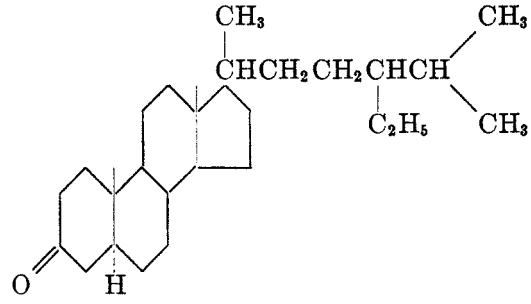
Ergostanone

$[M]_D = +13{,}960°$ in $CHCl_3$



Stigmastane

$[M]_D = +10{,}470°$ in $CHCl_3$



Stigmastanone

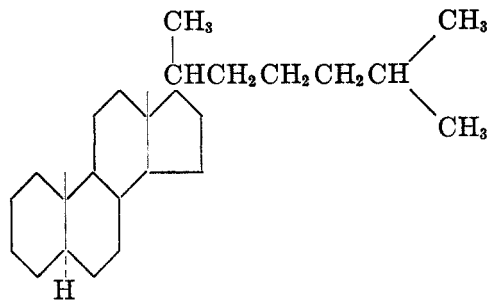
$[M]_D = +17{,}000°$ in $CHCl_3$

Stigmastane and ergostane differ from each other solely at the C_{24} position, the former having a methyl group, and the latter an ethyl group. This changes the rotation of the molecule as a whole from $[M]_D = +7670°$ for ergostane to $[M]_D = +10{,}470°$ for stigmastane. This modification is centered at a point far distant from the C_3 position, and moreover it occurs well out on an open chain. If one considers the side chain and the atoms in the neighborhood of C_3 as two independent regions of asymmetry,

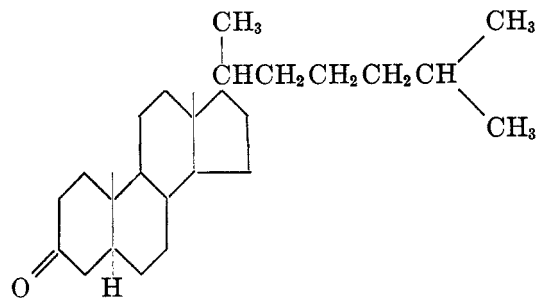
each of which contributes a definite amount to the optical rotatory power of the molecule, then subtraction of the rotation of stigmastane from that of ergostane will give the difference in the contributions to the rotation of a methyl group at the C_{24} position and its environment, and of an ethyl group at that position and its environment. Similarly, subtraction of the rotation of stigmastane from that of stigmastanone will give the difference in the contributions to the rotation of a methylene group at C_3 and its environment, and of a carbonyl group at C_3 and its environment, since the contributions of the side chain regions, which are the same in both molecules, should cancel each other. In the same way, when we subtract the rotation of ergostane from that of ergostanone, the contributions of the side chains cancel one another, leaving again only the difference in rotation of the methylene and carbonyl groups at the C_3 position. Therefore, the difference in rotation between ergostane and ergostanone should be the same as that between stigmastane and stigmastanone. This is, indeed, found to be the case:

Ergostanone.....	+13,960	Stigmastanone.....	+17,000
Ergostane.....	+7,670	Stigmastane.....	+10,470
	+6,290		+6,530

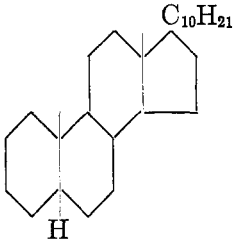
Again, we should expect increases in the positive rotation of about 6400° in going from cholestane to cholestanone, and from γ-sitostane to γ-sitostanone:



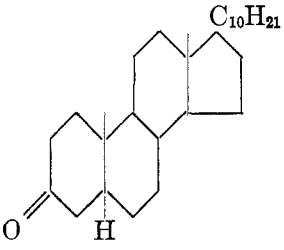
Cholestane



Cholestanone



γ-Sitostane

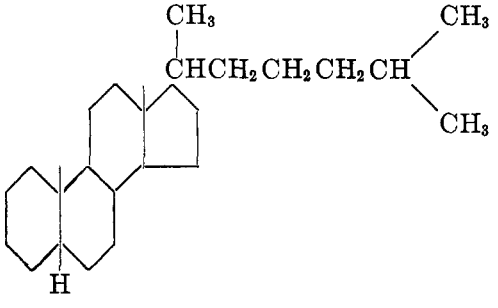


γ-Sitostanone

Since an error in the measurement of $[\alpha]_D$ of only 2.5° would result in an error of about 1000° in $[M]_D$, we see that in this case also our expectations are fulfilled within experimental error.

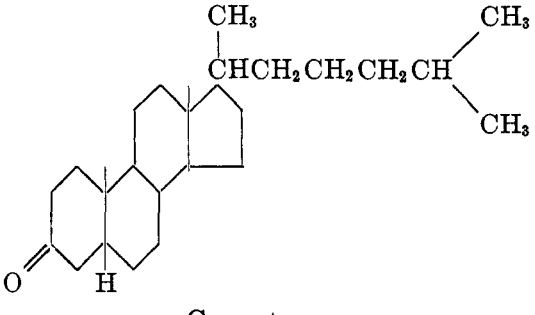
Cholestanone	+15,840	γ-Sitostanone	+15,760
Cholestane	+9,160	γ-Sitostane	+8,090
	+6,680		+7,670

It is interesting in this connection to point out that in all of the above compounds, the hydrogen at C_5 is conventionally taken to be trans to the



Coprostane

$[M]_D$ = +9430° in $CHCl_3$



Coprostanone

$[M]_D$ = +14,010 in $CHCl_3$

C_{10} methyl group. A comparison of the above differences with the differences in the rotations of coprostane and coprostanone types of compounds, where this hydrogen is cis to the C_{10} methyl group illustrates what happens when the environment at the C_3 position has been altered. Here an agreement is not to be expected in the difference (4580°) and indeed is not so found.

In order to be able to carry out this procedure for any molecule it will be convenient at this time to set up a system of notation. Let us arbitrarily select cholestane as our reference compound. The rotation of this substance will be denoted by the symbol C (Table I). In the change from cholestane to cholestanone, there will be a change in rotation which will be denoted by the symbol[2] K_{3t}; we can write, therefore, the rotation of cholestanone as $C + K_{3t}$. The value of C is +9160, this being the molecular rotation of cholestane itself (Table I). Since the rotation of cholestanone is +15,840, it follows that $C + K_{3t} = +15,840$, and hence $K_{3t} = +6680$. Similarly, in the change from cholestane to ergostane we change the rotation by an amount denoted by the symbol Erg, and since the rotation of ergostane is + 7670° it follows that $C + Erg = +7670$, and therefore $Erg = -1490°$.

Now if we wish to express the rotation of ergostanone precisely in terms of these constants, we must write its rotation as $C + K_{3t} + Erg + \epsilon$, where C, K_{3t} and Erg have the values given above, while ϵ is a factor which takes into account the difference in the interactions of the ergostane and cholestane side chains with the carbonyl and methylene groups at the C_3 position. As we have seen, ϵ should be insignificant, so that we can express the rotation of ergostanone as $C + K_{3t} + Erg = +14,350°$, as compared with the observed value of + 13,960°. Thus the neglect of this term, ϵ, under the proper circumstances can be said to provide the basis for the present method of calculation.

In Table I there is given a series of constants whose values have been derived in the same manner as that outlined above. Each constant represents the change in rotation which occurs when an indicated change is made in the structure of cholestane. Rotations measured in chloroform have been used in deriving the constants, since this is the solvent most used in this field. Only measurements with sodium D light have been utilized. It should be noted that other solvents and other wave lengths, if used consistently, would, of course, be no less suitable than those selected, but indiscriminate use of solvents and wave lengths obviously is to be avoided.

The system used in assigning symbols in Table I is as follows: N and

[2] This symbol signifies that there is a carbonyl (*K*etone) at the C_3 position and that the hydrogen at C_5 is *t*rans to the C_{10} methyl.

TABLE I

SUBSTANCE USED IN OBTAINING CONSTANT	ENVIRONMENTAL CHANGE, CHOLESTANE AS REFERENCE	$[M]_D$ ($CHCl_3$)[a]	REF.	$[M]_D$ IN TERMS OF CONSTANTS	SYMBOL FOR CONSTANT	VALUE OF CONSTANT
Cholestane	—	+9160	8	C	C	+9160
Coprostane	C_5—H(cis)	+9430	8	$C + B$	B	+270
Coprostanol	C_3—OH(cis) C_5—H(cis)	+9580	8, 9	$C + N_c$	N_c	+420
Cholestanol	C_3—OH(cis)	+8920	1, 8, 10	$C + N_t$	N_t	−240
Epi-coprostanol	C_3—OH(trans) C_5—H(cis)	+12260	8	$C + E_c$	E_c	+3100
Epi-cholestanol	C_3—OH(trans)	+11460	8, 10, 11	$C + E_t$	E_t	+2300
i-Cholesteryl methyl ether	C_6—OCH_3 C_3—C_4—C_5—Δ	+21600	12	$C + i_{CH_3O}$	i_{CH_3O}	+12440
Δ^4-Cholestene	F[c]—4:5	+23740	8	$C + D_{4:5}$	$D_{4:5}$	+14580
Δ^5-Cholestene	F—5:6	−20830	8	$C + D_{5:6}$	$D_{5:6}$	−29990
$\Delta^{5:6,7:8}$-Cholestadiene	F—5:6, 7:8	−46740	8	$C + D_{5:6,7:8}$	$D_{5:6,7:8}$	−55900
Cholesterol	C_3—OH(cis) F—5:6	−15250	13	$C + ND_{5:6}$	$ND_{5:6}$	−24410
Epi-cholesterol	C_3—OH(trans) F—5:6	−13120	11	$C + ED_{5:6}$	$ED_{5:6}$	−22280
γ-Cholestenol	C_3—OH(cis) F—7:8	0	8	$C + N_tD_{7:8}$	$N_tD_{7:8}$	−9160
δ-Cholestenol	C_3—OH(cis) F—8:9	+5250	9, 14	$C + N_tD_{8:9}$	$N_tD_{8:9}$	−3910
δ-Coprostenol	C_3—OH(cis) C_5—H(cis) F—8:9	+5790	9	$C + N_cD_{8:9}$	$N_cD_{8:9}$	−3380
α-Cholestenol	C_3—OH(cis) F—8:14	+7900	15	$C + N_tD_{8:14}$	$N_tD_{8:14}$	−1260
β-Cholestenol	C_3—OH(cis) F—14:15	+13120	8	$C + N_tD_{14:15}$	$N_tD_{14:15}$	+3960
7-Dehydrocholesterol	C_3—OH(cis) F—5:6,7:8	−43620	8	$C + ND_{5:6,7:8}$	$ND_{5:6,7:8}$	−52780

7-Dehydro-epi-cholesterol	C_3—OH(trans) F—5:6,7:8	−27070	16	$C + ED_{5:6,7:8}$	$ED_{5:6,7:8}$	−36230
Dehydrocholesterol B_3	C_3—OH(cis) F—7:8,14:15	−55870	8	$C + N_tD_{7:8,14:15}$	$N_tD_{7:8,14:15}$	−65030
Cholestanone-3	C_3—CO	+15830	1	$C + K_{3t}$	K_{3t}	+6670
Coprostanone-3	C_3—CO C_5—H(cis)	+14010	8	$C + K_{3c}$	K_{3c}	+4850
Δ^4-Cholestenone	C_3—CO F—4:5	+33640	1	$C + K_3D_{4:5}$	$K_3D_{4:5}$	+24480
Δ^5-Cholestenone	C_3—CO	−1610	8	$C + K_3D_{5:6}$	$K_3D_{5:6}$	−10770
Δ^4-Ergostenedione-3,6	C_3, C_6—CO F—4:5	−21180	8	$C + Erg + K_3K_6D_{4:5}$	$K_3K_6D_{4:5}$	−28850
Ergostane	C_{24}—CH_3	+7670	8	$C + Erg$	Erg	−1490
Stigmastane	C_{24}—C_2H_5	+10470	8	$C + Stig.$	$Stig.$	+1310
α_1-Sitostanol	C_3—OH(cis) C_{17}—$C_{10}H_{21}$	+11230	4	$C + N_t + \alpha_1\text{-}Sit$	$\alpha_1\text{-}Sit$	+1760
γ-Sitostane	C_{17}—$C_{10}H_{21}$	+8080	17	$C + \gamma\text{-}Sit$	$\gamma\text{-}Sit$	−1080
Stigmasterol	C_3—OH(cis) C_{24}—C_2H_5 F—5:6,22:23	−19780	8	$C + ND_{5:6} + Stig\ D_{22:23}$	$Stig\ D_{22:23}$	−4530
Ergosterol	C_3—OH(cis) C_{24}—CH_3 F—5:6,7:8,22:23	−51590	8	$C + ND_{5:6,7:8} + Erg\ D_{22:23}$	$Erg\ D_{22:23}$	−7800
Allocholanic acid	C_{17}—C_4H_8 COOH	+7990	8	$C + Chol$	$Chol$	−1170
3-Oxo-bisnorcholanic acid	C_3—CO C_5—H(cis) C_{17}—C_2H_4—COOH	+1590	8	$C + K_{3c} + Bisnor$	$Bisnor$	−12420
Allopregnane	C_{17}—C_2H_5	+4320	18, 19	$C + Et_{17}$	Et_{17}	−4840
Cholesteryl *p*-toluene-sulfonate	C_3—OTs F—5:6	−21820	20	$C + TsO_3\text{-}D_{5:6}$	$TsO_3\text{-}D_{5:6}$	−30980

TABLE II

SUBSTANCE	$[M]_D$ IN TERMS OF CONSTANTS	$[M]_D$ CALC. ($CHCl_3$)	$[M]_D$ OBS. ($CHCl_3$)[a]	$[\alpha]_D$ CALC. ($CHCl_3$)	$[\alpha]_D$ OBS. ($CHCl_3$)[b]	REF.
Pregnane	$C + B + Et_{17}$	+4700	+5700	+16.3	+19.8	8, 19
γ-Sitostene	$C + \gamma\text{-}Sit + D_{5:6}$	−21910	−23640	−55.1	−59.4	17
Stigmastanol	$C + N_t + Stig$	+10230	+10190	+24.6	+24.5	8
Epi-stigmastanol	$C + E_t + Stig$	+12770	+10610	+30.7	+25.5	8
Ergostanol	$C + N_t + Erg$	+7430	+6230	+18.5	+15.5	8
Epi-ergostanol	$C + E_t + Erg$	+9970	+5670	+24.8	+14.1	8
γ-Sitostanol	$C + N_t + \gamma\text{-}Sit$	+7840	+7650	+18.8	+18.4	8
β-Sitosterol	$C + ND_{5:6} + Stig$	−13940	−14950	−33.7	−36.1	8
β-Ergostenol	$C + N_tD_{14:15} + Erg$	+11630	+8080	+29.1	+20.2	8
α_1-Dihydrositosterol	$C + N_tD_{8:14} + \alpha_1\text{-}Sit$	+9660	+4510	+23.3	+10.9	4
α_1-Isodihydrositosterol	$C + N_tD_{14:15} + \alpha_1\text{-}Sit$	+14880	+17390	+35.9	+42	4
α-Ergostenol	$C + N_tD_{8:14} + Erg$	+6410	+5760	+16.0	+14.4	1, 8
γ-Sitosterol	$C + ND_{5:6} + \gamma\text{-}Sit$	−16330	−17550	−39.4	−42.4	8
22-Dihydroergosterol	$C + ND_{5:6,7:8} + Erg$	−45110	−43380	−113.3	−109	8
$\Delta^{8:14,22:23}$ Ergostadienol-3	$C + N_tD_{8:14} + Erg\ D_{22:23}$	+100	−7920	+0.3	−19.9	8
Ergosterol B_3	$C + N_tD_{7:8,14:15} + Erg\ D_{22:23}$	−63670	−71480	−160.8	−180.5	8, 21
Dihydroergosterol II (5:6-dihydroergosterol)	$C + N_tD_{7:8} + Erg\ D_{22:23}$	−7800	−3060	−19.6	−7.7	8
Brassicasterol	$C + ND_{5:6} + Erg\ D_{22:23}$	−23070	−24950	−55.9	−62.7	8, 22
22-Dihydrobrassicasterol	$C + ND_{5:6} + Erg$	−16740	−18520	−41.9	−46.3	23
α-Spinasterol	$C + N_tD_{8:14} + Stig\ D_{22:23}$	+3370	0	+9.3	0	24
α-Stigmastenol	$C + N_tD_{8:14} + Stig$	+9210	+10350	+22.5	+25	24, 25
7-Dehydro-β-sitosterol	$C + ND_{5:6,7:8} + Stig$	−42310	−47800	−102.7	−116	8
Stigmastanone	$C + K_{3t} + Stig$	+17150	+17020	+41.4	+41.1	8
Ergostanone	$C + K_{3t} + Erg$	+14350	+13960	+35.9	+34.9	8
γ-Sitostanone	$C + K_{3t} + \gamma\text{-}Sit$	+14750	+15760	+35.6	+38.0	17
Δ^4-3-oxo-bisnorcholenic acid	$C + K_3D_{4:5} + Bisnor$	+21220	+20640	+61.7	+60	8
Cholanic acid	$C + B + Chol$	+8260	+7560	+22.9	+21.0	8
Allopregnane-ol-3	$C + N_t + Et_{17}$	+4080	+4870	+13.4	+16.0	18
Allolithocholic acid	$C + E_t + Chol$	+10290	+10904	+27.4	+29	8
i-Stigmasteryl methyl ether	$C + i_{CH_3O} + Stig\ D_{22:23}$	+17070	+14435	+41.0	+34.7	23
i-Brassicasteryl methyl ether	$C + i_{CH_3O} + Erg\ D_{22:23}$	+13800	+8240	+33.5	+20.0	23
Stigmasteryl p-toluenesulfonate	$C + Ts\text{-}O_3\text{-}D_{5:6} + Stig\ D_{22:23}$	−26350	−26660	−46.6	−47.1	23
Brassicasteryl p-toluenesulfonate	$C + Ts\text{-}O_3\text{-}D_{5:6} + Erg\ D_{22:23}$	−29620	−34000	−53.7	−61.6	23

Footnotes to Tables I and II

[a] In many cases these values represent the mean molecular rotation calculated from specific rotations reported by several different investigators.

[b] In many cases these values represent the mean specific rotation calculated from values reported by several different investigators.

[c] Represents double bond.

E refer to the hydroxyl group at the C_3 position in the "normal" and "epi" configurations, respectively (*i.e.*, cis and trans to the C_{10} methyl group, respectively). The subscripts *c* and *t* refer to the cis-trans relationships of the hydrogen at the C_5 position to the C_{10} methyl group. *D* signifies a double bond system, and its subscript gives its position. The meaning of the other symbols is self-evident.

In Table II, these constants have been utilized in calculating the rotations of a number of known compounds whose rotations have actually been measured. Table II contains only those compounds for which rotations have been measured in chloroform, and for which the constants of Table I were derived from measurements made in chloroform solution.

In Table II, the calculated and observed molecular rotations usually differ by less than 2000° (the equivalent of about 5° in $[\alpha]_D$), and on the whole there can be little question that the results tend to verify our postulates.

A statement should be made at this time concerning the theoretical significance of those cases in which large discrepancies occur between observed and calculated results. Thus, in the calculation of the rotation of epiergostanol an error of about 4300° is found. The calculation involves the replacement of a hydrogen at C_{24} by a methyl group, and this region is at such a great distance from C_3 and C_5 that it is inconceivable that an interaction term, ϵ, is of such a magnitude as to account for the difference between observed and calculated values. The conclusion is inescapable, that in this case either the compound in question is impure,[3] and consequently an error of at least 10° has been made in the measurement of the rotation, or that the structure assigned to this compound is wrong. Similarly in other cases, inspection of the data and of the assumptions involved in the calculations leads to the same conclusions.

In conclusion, we wish to emphasize that it has been our purpose here to indicate a general method of attack rather than to set up a rigid system of calculation. We have left for others the problem of adapting the method to their needs. It should be noted that one can calculate the rotations of many compounds not indicated here. Furthermore, the method may be applied to derivatives of the sterols, such as esters, ethers, oximes, etc., and if proper care is used, to different solvents.

SUMMARY

1. An application of the modern theories of optical rotatory power to the steroids has been discussed.

[3] In view of the great difficulty of obtaining steroids in the pure state, the occurrence of these discrepancies is not too surprising, and it is likely that the greatest practical obstacle to the quantitative use of rotatory powers in determining structure will prove to be just this difficulty of obtaining pure compounds on which to make the necessary measurements.

2. A method of calculating the optical rotatory power of steroids has been developed.

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THE RELATION BETWEEN THE ABSORPTION SPECTRA AND CHEMICAL CONSTITUTION OF DYES. XVII. THE ABSORPTION SPECTRA OF THE COPPER, NICKEL, AND COBALT COMPOUNDS OF SOME SIMPLE *ortho*-HYDROXY AND *ortho*-AMINO AZO DYES[1]

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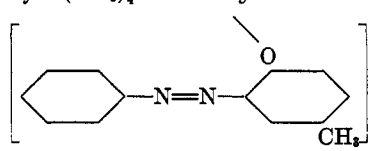
In earlier published papers on the chemistry of the metal compounds of simple *o*-hydroxy and *o*-amino azo dyes (1, 2, 3, 4, 5, 6, 7, 8, 9), no data on the absorption spectra of compounds of this type have been included. The present paper discusses the absorption spectra of a representative group of such compounds.

EXPERIMENTAL

A. Metal compounds of o-*hydroxybenzeneazo-β-naphthol.* The dye was prepared by the method of Charrier and Fererri (10). Its metal compounds were prepared by two methods: (a) The dye in alcoholic solution was treated with a solution of copper sulfate in excess ammonium hydroxide. A red-brown precipitate was formed which contained copper, was insoluble in water, soluble in alcohol and other organic solvents, and did not melt below 300°. Its visible spectrum differed from that of the dye. Attempts to purify it were unsuccessful. (b) *ortho*-Aminophenol was diazotized and to the solution of the diazonium salt was added an excess of a solution of a metal salt. The diazonium salt was then coupled to alkaline β-naphthol. The following salts were used: $CuSO_4$, CrF_3, $CoCl_2$, $NiSO_4$, and $FeSO_4$. In every case a product was obtained which was insoluble in water and did not melt below 300°. The chromium and iron products showed no visible absorption maxima, but the visible absorption spectra of the copper, nickel, and cobalt compounds differed from the spectrum of the dye and from each other. This indicates that definite compounds were formed, although efforts to purify them were unsuccessful.

*B. Metal compounds of mono-*o*-hydroxy and* o*-amino azo dyes.* Three general methods were used in preparing these compounds. A preparation typical of each method is described below and in subsequent discussion these methods will be referred to by number.

I. Action of $M(NH_3)_4^{++}$ *on the Dye in Alcoholic Solution* (3, 4)

Preparation of Cu  . A solution of 5 g. of ben-

[1] An abstract of a portion of a thesis submitted by Maurice L. Ernsberger in partial fulfilment of the requirements for the degree of Doctor of Philosophy at The Ohio State University in 1936.

zeneazo-*p*-cresol in 600 ml. of alcohol was treated with 3 g. of $CuSO_4 \cdot 5H_2O$ in water to which was added 19 ml. of concentrated ammonium hydroxide. The solution was refluxed for one hour and filtered hot. The brown precipitate was washed successively with dilute ammonium hydroxide, alcohol, and water. The product was recrystallized from xylene.

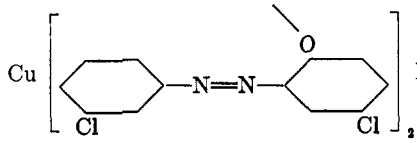
II. Action of the Metal Acetate on the Dye in Alcoholic Solution

A solution of the metal acetate was made by dissolving the salt in a small amount of water and diluting with alcohol. This solution was added to a solution of the dye in hot alcohol. The metal compound of the dye precipitated immediately, was filtered, washed with alcohol, and dried.

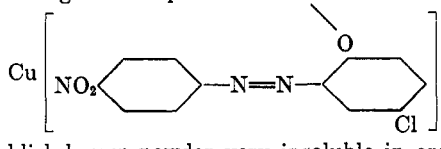
III. Coupling in the Presence of the Metal Salt (11)

Aniline (1.7 g.) was diazotized with an equivalent amount of sodium nitrite. A solution of 5 g. of $CuSO_4 \cdot 5H_2O$ was added to the diazonium salt solution, which was then coupled to β-naphthol in alkaline solution. The insoluble product was filtered off, washed with alcohol and water, and dried.

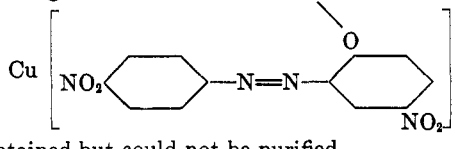
New compounds. The following compounds not previously described were prepared.



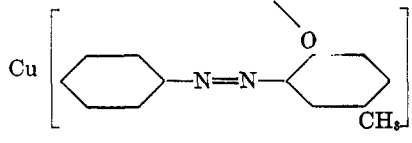
By method II. The product was a brown powder, insoluble in alcohol and only slightly soluble in chloroform; m.p. 228–229° with slight decomposition. Chlorine: calculated, 23.8; found, 23.7, 23.7.



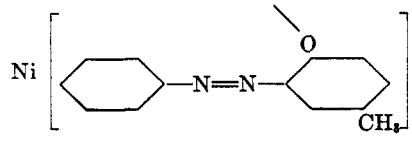
By method II. The product was a reddish-brown powder very insoluble in organic solvents; it decomposed without melting. Chlorine: calculated, 11.5; found, 11.0, 11.2.



By method II. A brown solid was obtained but could not be purified.



By method I. The product was a brown powder, soluble in organic solvents; m.p. 234°. Copper: calculated, 13.1; found, 12.8, 13.1; nitrogen: calculated, 11.5; found, 11.1, 11.9. This compound was prepared and analyzed in the present work in May, 1935, prior to its description by Elkins and Hunter (7). They give its melting point as 230°.



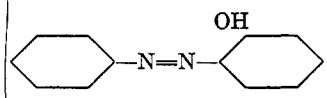
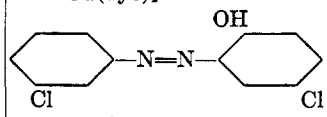
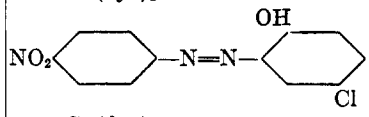
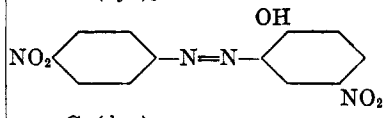
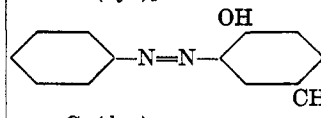
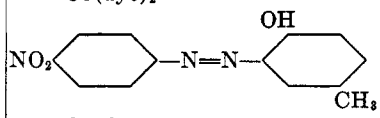
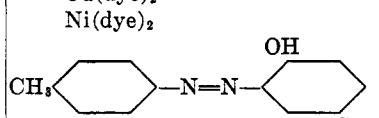
By method I. Green crystals were ob-

tained by recrystallizing the compound from xylene; m.p. 217–220°. Nickel: calculated, 12.2; found, 12.1, 12.2. Molecular weight: calculated, 480; found, 473. Elkins and Hunter (7) give the melting point of this compound as 216°.

TABLE I

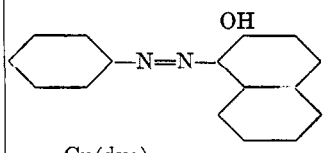
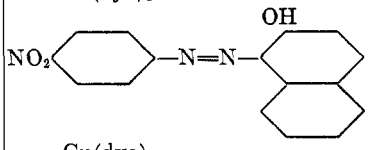
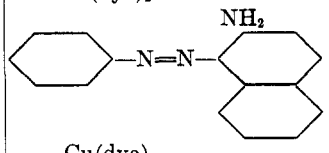
COMPOUNDS INCLUDED IN THE PRESENT WORK

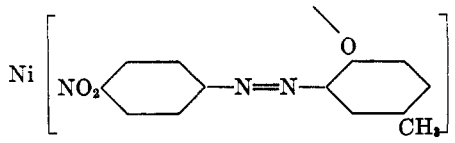
The metal compounds of each dye are listed immediately below the dye

NO.	COMPOUND	METHOD OF PREPARATION	M.P., °C.		LIT. REF.
			Found	Lit.	
I			82.5–83.5	82.5–83	12, 8
	$Cu(dye)_2$	II	226	226	1, 8
II			154–155		
	$Cu(dye)_2$	II	288–289		[a]
III			140–143		
	$Cu(dye)_2$	II	Decomp.		[a]
IV			175–180		
	$Cu(dye)_2$	II	Decomp.		[a]
V			108	108	
	$Cu(dye)_2$	I	234	230	7
	$Ni(dye)_2$	I	217–220	216	7
	$Co(dye)_2$	II	202–203	202	7
VI			191	186	
	$Cu(dye)_2$	II	Decomp.		[a]
	$Ni(dye)_2$	II	280–290		[a]
VII			111–112	112–113	
	$Cu(dye)_2$	II	243–245	242	7
	$Ni(dye)_2$	II	242–243	242–243	7

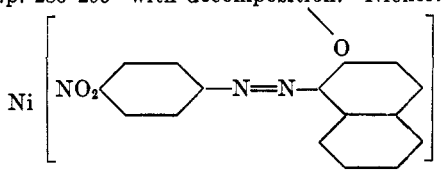
[a] Compound not previously described.

TABLE I—*Concluded*

NO.	COMPOUND	METHOD OF PREPARATION	M.P., °C. Found	M.P., °C. Lit.	LIT. REF.
VIII			133–134	134	
	$Cu(dye)_2$	I	288	289	2, 3, 4, 8
	$Ni(dye)_2$	I	Decomp.	Decomp.	3
	$Co(dye)_2$	I	Decomp.	Decomp.	3
IX			251–252	251–252	
	$Cu(dye)_2$	II	Decomp.		2
	$Ni(dye)_2$	I	Decomp.		[a]
X			103	102–104	
	$Cu(dye)_2$	I	171–174	174	4
	$Ni(dye)_2$	I	248–249	260–265	3
	$Co(dye)_2$	I	200–230	215–265	3



By method II in acetone solution. By recrystallizing it from xylene, the product was obtained as shiny black crystals, m.p. 280–290° with decomposition. Nickel: calculated, 10.3; found, 9.9.



By method I. A gray-green product was obtained which was very insoluble in organic solvents. It could not be purified.

All the compounds included in this study are listed in Table I.

Purity of the dyes was established by their melting points after they were recrystallized several times. The metal compounds, with the exception of one or two which were very well characterized, were analyzed for the metal and in some cases for nitrogen or chlorine, so that they were of known purity. Although some of the metal compounds decompose in solution, determinations of absorption spectra were made rapidly enough to be completed before this decomposition was appreciable.

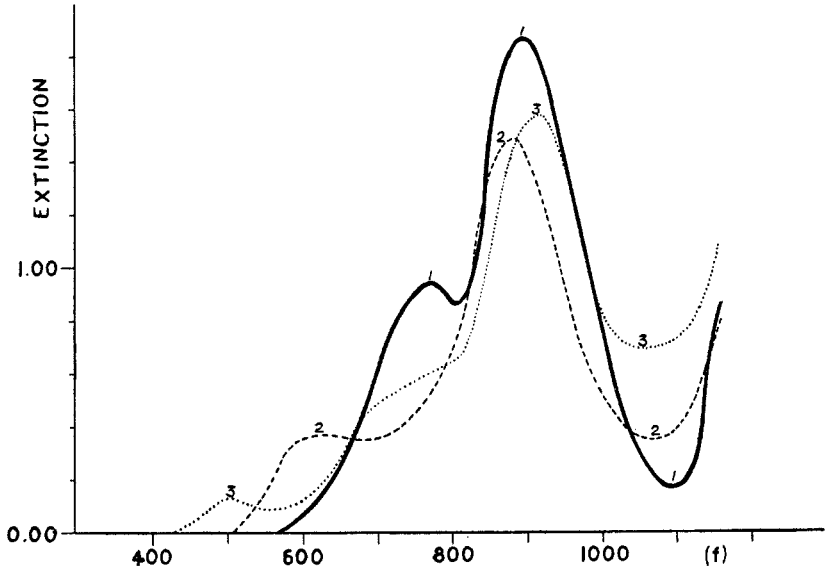


FIG. I. ABSORPTION SPECTRA OF *p*-TOLYLAZO-*p*-CRESOL IN $CHCl_3$
1. Dye 0.0001 M; 2. Cu $(dye)_2$ 0.00005 M; 3. Ni $(dye)_2$ 0.00005 M. cell = 1.0 cm.

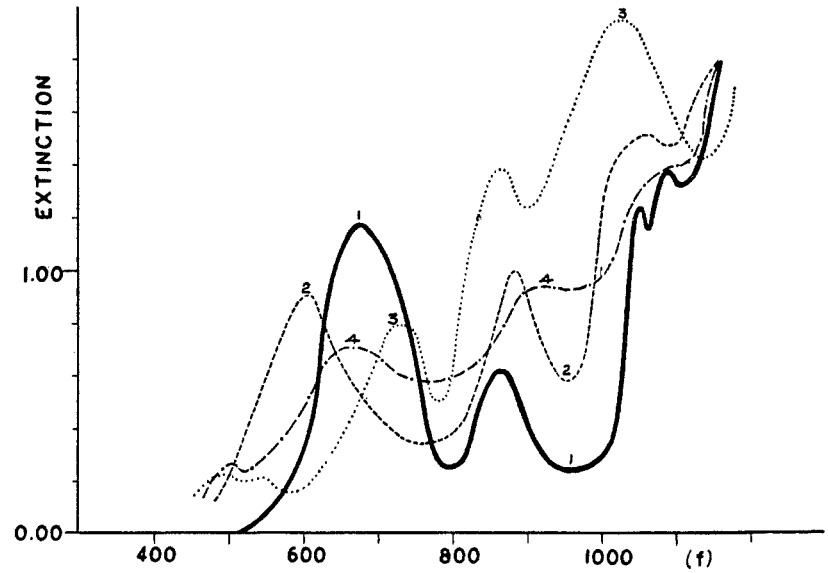


FIG. II. ABSORPTION SPECTRA OF PHENYLAZO-β-NAPHTHYLAMINE IN $CHCl_3$
1. Dye 0.0001 M; 2. Cu $(dye)_2$ 0.00005 M; 3. Ni $(dye)_2$ 0.00005 M; 4. Co $(dye)_2$ 0.00005 M.

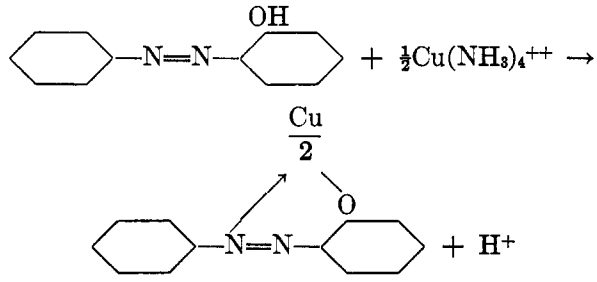
Absorption spectra. Solutions of the dyes were made up to 0.0001 M. in chloroform. Solutions of the metal compounds were made up to 0.00005 M. in chloroform, so that all solutions contained the same amount of azo nitrogen. All the visible absorption spectra were measured in a 1.0 cm. cell, and determined with a Bausch and Lomb spectrophotometer. A Bausch and Lomb quartz spectrograph with a Hilger rotating sector photometer was used for the ultraviolet spectra. The light source was a condensed tungsten spark under water. For a more detailed description of the apparatus see Brode (13) and others (14, 15). Instrumental errors involved in this method are discussed by Brode (13) and by Flexser and co-workers (16). For the broad bands studied in the present work instrumental errors are negligible.

The absorption curves are plotted with values of the extinction coefficient $\left(k = \frac{1}{d} \log \frac{I_0}{I}\right)$ as ordinates, and wave length ($m\mu$ = meters $\times 10^{-9}$) or frequency $\left(f = \frac{3 \times 10^{10}}{\text{cm}} \times 10^{12} = \frac{\text{vibrations}}{\text{seconds} \times 10^{12}}\right)$ as abscissae. The spectra of each dye and its metal compounds were plotted on the same graph so that they could be compared. Two typical graphs are shown (see Figures I and II).

DISCUSSION

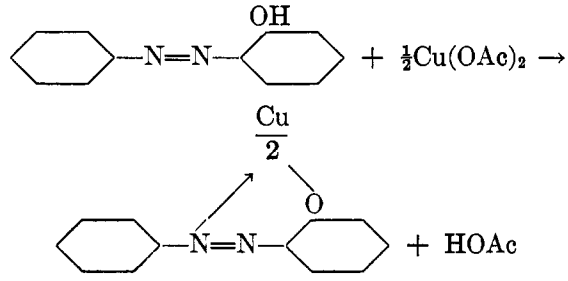
A. Methods of preparation. The reactions used in preparing these compounds may be represented in this manner:

Method I



The hydrogen ion formed is neutralized by the excess of ammonium hydroxide.

Method II



Although these compounds are unstable in the presence of acids, the concentration of acetic acid reached in the reaction is not sufficient to prevent the formation of the compounds.

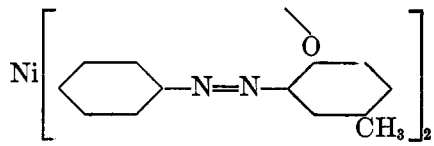
Method III. The nature of the reactions in which the metal compound is formed by carrying out the coupling in the presence of the metal salt is in doubt. There is a possibility that there is chemical combination between the metal and the diazonium salt (17, 18, 19).

Methods I and II were used for the preparation of several compounds in the present work. Elkins and Hunter (7) suggest that method I is unlikely to lead to salt formation, whereas method II (their method) should lead to salt formation. The copper and nickel compounds of benzeneazo-*p*-cresol were prepared in the present work by method I, and the compounds were found to be identical with those prepared by method II.

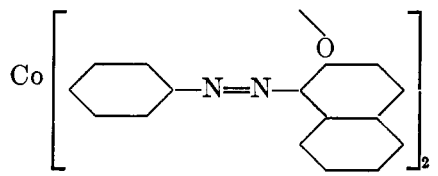
No record of the use of method III was found except in the patent literature and in a brief discussion by Georgievics and Grandmougin (11). In the present work several compounds were prepared by this method and were found to be the same as when prepared by other methods.

In general the new compounds described have properties similar to those of compounds of the type previously described. However, the copper compounds of *m*-chlorobenzeneazo-*p*-chlorophenol, *p*-nitrobenzeneazo-*p*-chlorophenol, *p*-nitrobenzeneazo-*p*-cresol, and *p*-nitrobenzeneazo-*p*-nitrophenol were very insoluble in solvents such as chloroform, ether, benzene, etc., which is contrary to the usual behavior of compounds of this type.

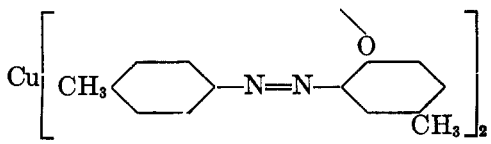
B. Molecular Weights. Values were obtained for the molecular weights of



and



These are the first to be published for compounds of this type. They were determined cryoscopically in benzene, and although the limited solubility of the compounds in cold benzene made it possible to get only a small ΔT_f (less than 0.1°), the values are reliable to within 5%. The nickel compound was found to be monomolecular and undissociated. The cobalt compound was found to be bimolecular; molecular weight, calculated, 553; found, 1080, 1040; $2 \times 553 = 1106$. Less reliable evidence by the boiling point method in chloroform indicates that



is also monomolecular and undissociated. The general behavior and absorption spectra of these particular copper and nickel compounds are typical of the other copper and nickel compounds, which indicates that all of the copper and nickel compounds are probably also monomolecular and undissociated. It was not possible to determine molecular weights of the other compounds because they are too insoluble in cold benzene. A possible explanation of the fact that the cobalt compound is bimolecular is that it may be a cobaltic compound. Other evidence in favor of this suggestion is the fact that Elkins and Hunter (7) recommend the addition of some hydrogen peroxide to the cobalt acetate solution used to prepare cobalt compounds. This causes the pink cobaltous solution to turn dark brown, indicating oxidation.

C. Absorption spectra. The absorption spectra of the products obtained by coupling diazotized *o*-aminophenol to β-naphthol in the presence of metal salts were only qualitative because no definite compounds were isolated. These spectra indicate that there are compounds formed. Further work should result in their isolation.

The absorption spectra of the metal compounds of mono-*ortho*-hydroxyazo dyes show very few differences from the absorption spectra of the corresponding dyes alone. For the compounds of the dyes with the hydroxyl group on a benzene nucleus the ultraviolet spectra of the dyes and the metal compounds are practically identical. In the visible region the spectra of the metal compounds show a weak band not found in the spectra of the dyes alone. The example given (Fig. I) is typical. For the compounds with the hydroxyl group on a naphthalene nucleus, the spectra are more complicated, but the general effect of the metal is about the same as for the simpler dyes. A new visible band is introduced, although at the same time the intensities, but not the positions, of the ultraviolet bands of the dye are altered.

The new band in the visible region shown by the nickel compounds is at about 590 mμ and by the copper compounds at about 490 mμ regardless of the dye with which the metal is combined. Table II gives the maxima of the new bands. Because of the difficulty of their preparation, few cobalt compounds could be obtained pure, so that generalizations about them cannot be made.

D. Conclusions. 1. The new band in the visible region of the absorption spectra of the metal compounds is due to the presence of the metal.

2. The metal has very little effect on the chromophore of the dye, since the dye bands appear unchanged in the absorption spectrum of the metal compound.

3. Because the new bands in the spectra of the dye-metal compounds occur at the same position for a given metal regardless of the dye with which it is combined, it must be concluded that the dye mass has little

effect. Therefore the new band is not due to vibration of the entire molecule, since if it were, the change in mass caused by changing the dye would change the position of the band.

4. The only possibility which remains is that the new band is due to an electronic transition. Since the new band is characteristic of the metal rather than of the dye, the electrons must be associated with the metal, and under its influence. Since the characteristic absorption maxima of the new bands do not correspond to the absorption maxima of water solutions of simple salts of the metals, the electronic configuration must also be influenced by the dye.

5. It is likely, therefore, that the electron (or electrons) which undergoes transition is one of those in the covalent or coordinate covalent bonds

TABLE II

VISIBLE ABSORPTION MAXIMA IN THE SPECTRA OF THE DYE-METAL COMPOUNDS

Compounds included in Table I and not in Table II are those which were too insoluble to permit a determination of their spectra. Numbers of dyes refer to structures shown in Table I.

DYE	COPPER COMPOUND	NICKEL COMPOUND	COBALT COMPOUND
I	475 mμ		
V	490 mμ	580 mμ	460 mμ
VI		590 mμ	
VII	490 mμ	590 mμ	
VIII	490 mμ	580 mμ	500 mμ
			480 mμ
X	495 mμ	600 mμ	600 mμ
		545 mμ	450 mμ

joining the dye and the metal, since those are the electrons directly influenced by both the dye and the metal.

SUMMARY

1. Several copper, nickel, and cobalt compounds of *o*-hydroxy and *o*-amino azo dyes have been prepared and their absorption spectra have been determined.

2. In the ultraviolet region the absorption spectra of the metal compounds do not differ appreciably from the spectra of the corresponding dyes, but in the visible region a new weak band due to the metal is found.

3. It is suggested that this new absorption band may be due to transitions of one or more electrons in the bonds between the dye and the metal.

4. Data on the molecular weights of three of the compounds have been obtained.

COLUMBUS, OHIO.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

THE RELATION BETWEEN THE ABSORPTION SPECTRA AND THE CHEMICAL CONSTITUTION OF DYES. XVIII. THE EFFECT OF POSITION ISOMERISM ON THE ABSORPTION SPECTRA OF HALOGEN DERIVATIVES OF PHENYLAZOPHENOL

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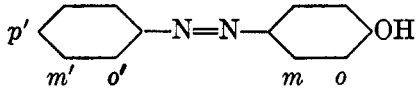
This paper is an extension of an investigation begun a number of years ago, concerning the relation between the absorption spectra and the chemical constitution of simple derivatives of phenylazophenol. In the previous papers of this series (1, 2, 3) it was shown that the positions and magnitudes of the absorption bands of the methyl, nitro, and nitro methyl derivatives were functions of the types, numbers, and positions of substituents present.

In this investigation the methods and technique of the previous studies have been extended to the analogous chlorine and bromine derivatives of phenylazophenol; these included the eleven possible mono- and dichloro derivatives, in which only a single chlorine atom occurs on a benzene ring, and the eleven analogous bromine derivatives.

The positions of substituent elements or radicals are indicated by the notations: *o'*, *m'*, *o*, *o'm*, etc., in accordance with the following formula:



In the mixed-substituent compounds involving methyl and nitro groups, the first symbol designates the methyl position; and the second, the nitro position. The unsubstituted compound is indicated in the tables by the symbol "Ph."

These dyes were prepared from purified intermediates by standard coupling procedures; they were recrystallized from appropriate organic solvents to constant melting points. The melting points of these compounds are given in a preliminary report presented at the Sixth Summer Conference on Spectroscopy (4). Those not previously recorded in the chemical literature were analyzed for their azo nitrogen content by the titanous chloride method of Knecht and Hibbert (5) as modified by Calcott and English (6).

EXPERIMENTAL

Three solvents of different chemical character were employed for the spectroscopic measurements: 95% ethyl alcohol, concentrated hydrochloric acid, and 3% aqueous sodium hydroxide. These solutions were prepared by the methods previously described (2, 3). The dye concentration was about 7.0×10^{-5} g. moles per liter in the alcohol and alkaline solutions and about 3.5×10^{-5} g. moles per liter in the acid solutions. It is to be noted that the acid and alkaline solutions each contained a small amount of alcohol.

The absorption spectra measurements in the ultraviolet were made with a Bausch and Lomb medium quartz spectrograph, equipped with a modified Hilger sector photometer; in the visible region a Bausch and Lomb Universal Spectrophotometer was employed. The methods and system of nomenclature have been previously described (3, 7, 8).

The data were plotted with frequency in fresnels (vibrations/seconds $\times 10^{12}$) as abscissae and extinction ($\log \frac{I_0}{I}$) as ordinates. Each curve was based on from fifty to one hundred points. Due to lack of space, it is not possible to reproduce the sixty-six curves here in sufficient size to show the variations. The frequencies and magnitudes of band maxima have been indicated in Figs. I, II, III, and IV. In these figures, however, for the sake of comparison, the experimental extinction values have been recalculated to a common basis of concentration, the unit chosen being 1.5×10^{-4} g. moles per liter; these values are also calculated to a cell thickness of 0.5 cm., for ready comparison with previously reported values. The experimental thickness was 0.4 cm. in all cases.

In any one solvent, the general shape of the curves is the same, and is quite similar to those previously reported. Significant differences, however, may be noted in both frequency and intensity.

DISCUSSION OF DATA

A. Alcohol solutions. In this solvent the weak band in the violet region found by Brode (3) for the methyl derivatives, but absent in the nitro compounds (1), is present for about half the halogen derivatives. Its presence seems, however, to bear no simple relation to position of substitution. The third band in the extreme ultraviolet has been shifted towards higher frequency so that its maximum does not appear in the region studied. The principal band in the near ultraviolet is present in all cases and this study is confined to its characteristics.

A general shift towards lower frequency with increase of molecular weight may be noted. In many cases, however, the shift is slight, and is within the limits of experimental error, so that no quantitative generalization may be stated.

In Fig. I are plotted the variations of the principal band extinction and frequency shift with position of substitution for the substituting groups studied thus far. The general shape of the curve is very similar in all cases. Closer examination reveals several other interesting facts:

1. A nitro group increases the absorption band extinction in practically

all positions studied, in the disubstituted (nitro methyl) compounds the values are considerably greater than those of any other derivatives.

2. The chloro and bromo curves run practically parallel throughout, with the bromo value being the higher in all cases.

3. The methyl curve, while similar in character to the others, does not bear any constant relation to them, since enhancement and depression effects appear to be of a lower order of magnitude.

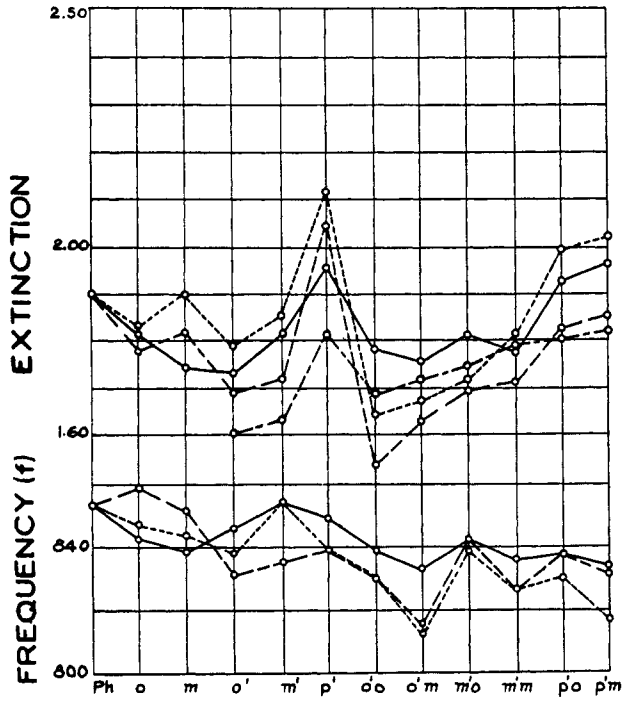


FIG. I. Specific absorption indices (extinction) of the absorption maxima of the alcohol solutions (upper) and frequency of principal band maxima (lower). Substituent positions are indicated by *o*, *m*, *o'*, etc. for CH_3 (——), Cl (— —) Br (-----) and NO_2 and CH_3, NO_2 (— - —) derivatives of phenylazophenol.

4. In every case the maximum extinction value of the monosubstituted series is that of the *p'* isomer.

5. In the disubstituted series the maximum extinction values in every case are those of the *p'o* and *p'm* isomers with the *p'm* values being greater than the *p'o* values.

6. The minimum extinction values for the chloro and bromo derivatives are those of the *o'o* compounds.

7. For the monosubstituted compounds the minimum extinction value is that of the *o'* isomer.

8. The average frequency position of disubstituted derivatives is less than the average frequency position of monosubstituted derivatives indicating a molecular weight effect.

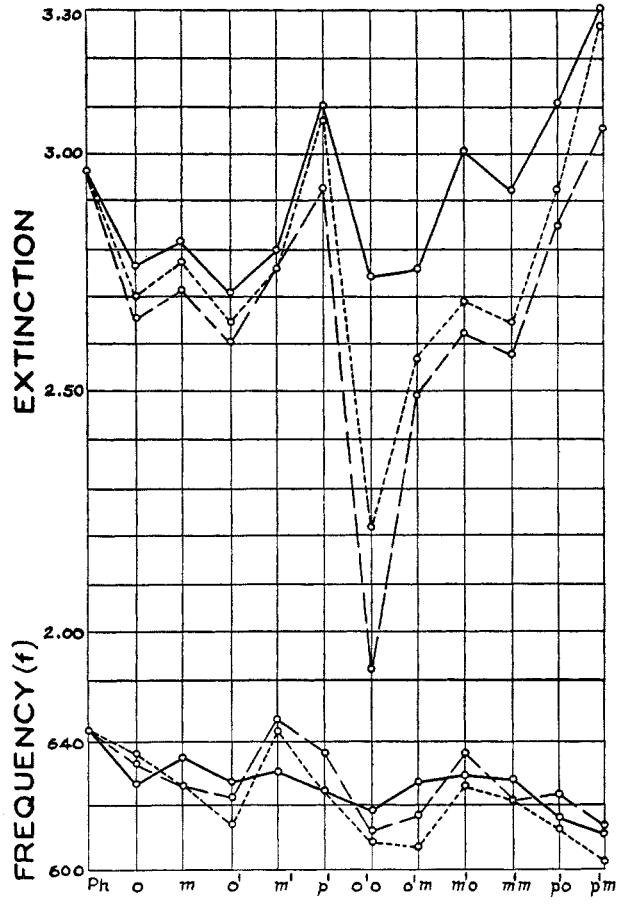


FIG. II. Specific absorption indices (extinction) of the absorption maxima of the concentrated hydrochloric acid solutions (upper) and frequency of principal band maxima (lower). Substituent positions are indicated by *o*, *m*, *o'*, etc. for CH_3 (——), Cl (— —) Br (-----) derivatives of phenylazophenol.

B. Hydrochloric acid solutions. In this solvent the first band noted for the methyl derivatives is entirely missing in the halogen derivatives. As in alcohol, the third band is shifted towards higher frequency, so that its maximum does not appear in the region studied. The second band, which is the principal one, is present in all cases, occurring in the visible region.

Increase of molecular weight again produces a noticeable lowering of frequency, except in the *m* position, where little or no change is evident.

In Fig. II are plotted the changes of the principal band extinction and frequency shift with position of substitution. (The original study on nitro derivatives did not include hydrochloric acid as a solvent, hence that information is lacking in this figure.) Again the curves are strikingly similar in shape, and a study of their characteristics leads to the following generalizations:

1. The chloro and bromo extinction effects are parallel, with the bromo value being the greater in all cases.

2. The methyl curve runs parallel to the halogen values and is greater in extinction.

3. The maximum extinction value for the monosubstituted halogen compounds is that of the *p'* derivative and the minimum value is that of the *o'* derivative in all cases.

4. For the disubstituted halogen compounds the maximum extinction value is that of the *p'm* derivative followed by the *p'o* derivative and the minimum value is that of the *o'o* derivative.

5. Halogen derivatives show greater maximum and minimum extinction effects than the methyl derivatives.

6. The average frequency values of the disubstituted derivatives are less than the monosubstituted derivatives, indicating a molecular weight shift of frequency.

C. Sodium hydroxide solutions. In this solvent two strong bands are present in the ultraviolet region; however, as in the other solvents, the peak of the second band was not included in the region studied. The first band appears to be composed of two components, which together produce the observed principal band.

Since this principal band varies considerably in shape with different compounds, it is difficult to draw any conclusions with regard to the relations between either frequency or magnitude of absorption and chemical constitution. In general, the frequency seems to be shifted toward lower values with increasing molecular weight.

It has been found possible to analyze this principal band into two components (A and B) by the method described by Brode (3). By this means it is possible to determine approximately the frequency and magnitude of the component bands. The general shape of these curves lends support to the hypothesis that the two components of the principal band are produced by two forms of vibration of the molecule, which are present in a variable equilibrium, and that this equilibrium is influenced by the position of the substituting group. In accord with this hypothesis, it is apparent in Fig. III that the extinction values of one of the components (A) do not show the regularity of effect demonstrated in the alcohol and hydro-

chloric acid solutions of these dyes. However, the sums of the extinction values of the absorption bands (A + B) show the same regular variation with position of substitution, as reported for the alcohol and hydrochloric

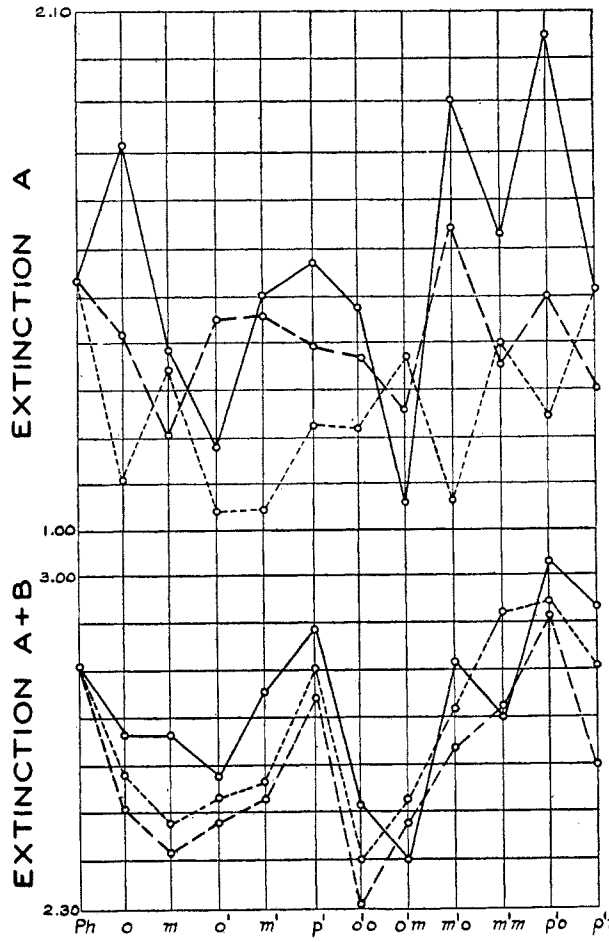


FIG. III. Specific absorption indices (extinction) of the absorption maxima of the "A" component (upper) and the "A" + "B" components (lower) of the bi-component principal band observed in 3% aqueous sodium hydroxide. Substituent positions are indicated by *o*, *m*, *o'* etc. for CH_3 (——), Cl (— —) and Br (-----) derivatives of phenylazophenol.

acid solutions. A study of these curves permits the following generalizations:

1. As noted in the other solvents, the chloro and bromo curves are practically parallel throughout, with the bromo value being the higher in all cases.

2. The methyl curve is roughly parallel to the other two, but shows general significant variations, such as a slightly greater average extinction.

3. In all cases the maximum extinction value of the monosubstituted compounds is that of the p' derivative.

4. In the disubstituted compounds, the maximum extinction value in all cases is that of the $p'o$ derivative. This differs from the other solvents, where the $p'm$ value is the greatest.

5. In the chloro and bromo series, the minimum extinction value is that of the $o'o$ compound, which is in agreement with the results observed in other solvents.

6. In an attempt to classify the equilibrium condition between the "A" and "B" components the proportion of A has been plotted $\left(i.e.\ \frac{A}{A+B}\right)$ against position of substitution (Fig. IV). While the arrangement shows

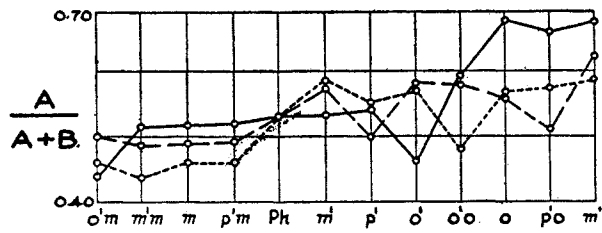


FIG. IV. PROPORTION OF "A" IN THE "A–B" EQUILIBRIUM IN DILUTE AQUEOUS SODIUM HYDROXIDE, I.E., $\frac{A}{A+B}$
CH_3 (——), Cl (— —) and Br (-----)

a definite trend, the results are not as satisfactory as those reported for the methyl derivatives (3).

SUMMARY

The study of the influence of character and position of substituents on the absorption spectra of phenylazophenol has been extended to include twenty-two mono- and di- halogenated compounds in which not more than one halogen is attached to each ring. These measurements have been made in the visible and ultraviolet regions of the spectrum from 400 to 1400 f (750 to 215 mμ) in three solvents; 95% ethyl alcohol, concentrated hydrochloric acid, and 3% aqueous sodium hydroxide.

There is a marked uniformity with regard to the intensity of extinction and the frequency shift as a result of the position of the substituent group in which *para* substitution enhances the extinction. There is a regular shift of maxima position in which the substitution of greater mass shows greater deviations from the mean. Substitution in the p' position produces

an increase in extinction in the order, methyl, chloro, bromo, iodo, and nitro, where the methyl shows the least effect; while substitution in the *o'* position, and in particular *o'o*, produces a marked decrease in both extinction and frequency of the absorption band.

In accordance with the method of analysis of the bi-component alkali band into "A" and "B" factors, it is to be noted that the A values fail to conform with data from other solvents. However, the sum of A and B conforms reasonably well with the data obtained in other solvents. The analysis of the alkali data through the study of the ratio of $\frac{A}{A+B}$ indicates that it is possible to classify the various types of substituent placing through a study of these data.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE CHICAGO CITY COLLEGES AND THE SYNTHETICAL LABORATORIES]

STUDIES IN AMMONOLYSIS. I. THE AMMONOLYSIS OF HALOGEN FATTY ACIDS AND PREPARATION OF α-AMINO ACIDS

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The present paper is one of a series on the investigation of ammonolytic reactions begun in 1933. Although short abstracts of the work have appeared (1), the detailed description of the investigations has been delayed, pending the elucidation of the mechanism of the ammonolytic reactions in which aqueous solutions of ammonia and carbon dioxide are used as the aminating agent. The present paper will deal with the ammonolysis of the lower halogen fatty acids under various conditions and the preparation of α-amino acids from such reactions.

The ammonolysis of the halogen fatty acids has been extensively investigated because of the relative ease by which α-amino acids are prepared by means of such reactions. Schmidt (2) gives an extensive bibliography of the literature on the synthesis of various α-amino acids by the reaction of α-halogen acids with ammonia, therefore references will be given only on works that bear relation to the present study. The reaction of α-halogen acids with ammonia was first reported by Perkin and Duppa (3), and also by Cahours (4). The former heated bromoacetic acid with aqueous ammonia, and the latter chloroacetic acid and alcoholic ammonia, to obtain glycine. It was noted very early that the yields of glycine were 10–15% of the theoretical and it was shown by Heintz (5) that the chief products of the reaction were the secondary and tertiary amino compounds, which were called diglycolamic and triglycolamic acids respectively.

$$ClCH_2COOH + 2\ NH_3 \rightarrow H_2NCH_2COOH + NH_4Cl$$

$$ClCH_2COOH + H_2NCH_2COOH \rightarrow HN(CH_2COOH)_2 + HCl$$

$$ClCH_2COOH + HN(CH_2COOH)_2 \rightarrow N(CH_2COOH)_3 + HCl$$

Nencki (6) attempted to improve the yield of glycine by substituting dry ammonium carbonate for ammonia and heating the mixture of carbonate and chloroacetic acid to 130°, but obtained about 20% yield.

Mauthner and Suida (7) in commenting on the work of Nencki proposed the addition of a metal carbonate to the mixture of chloroacetic acid and ammonia in order to increase the yield. Their experiments reported with sodium carbonate, chloroacetic acid, and ammonia show a 16–18% yield. Later, the same authors state that in order to obtain a considerable yield of glycine at ordinary temperatures, the essential condition lies in the presence of excess of ammonia. Kraut (8) made a review of the previous work and first noted that the yield of the primary amino compound depended on the ratio of the halogen acid and ammonia used. With one mole of acid to 16 moles of aqueous ammonia (26.5%) at 100°, yields of 50–55% were obtained. This method, with slight modifications, has remained the standard procedure for the ammonolysis of halogen acids. Generally, better yields are reported in the ammonolysis of the higher α-halogen acids. For example, Fischer (9) prepared a large number of amino acids and their derivatives, using one-to-twelve mole ratio of acid to ammonia (25% aqueous). The yield of *l*-alanine from *l*-α-bromopropionic acid obtained by Fischer was 65%. Slimmer (10), following Fischer's suggestion, prepared α-aminoisovaleric acid and α-amino-*n*-valeric acid by heating the halogen acid with aqueous ammonia and ammonium carbonate at 100° in an autoclave; yields of 62–70% were obtained. Similar results were reported by Abderhalden (11) and by Adams and Marvel (12) in the preparation of α-aminocaproic acid from the corresponding halogen acid. No explanations are given in the literature for the various empirical modifications that were proposed from time to time in the procedures used in ammonolysis. The reaction of chloroacetic acid and ammonia was again investigated by Druschel and Knapp (13) in 1915. It was found that it did not seem possible to increase the yield of glycine by changing the conditions of the Kraut method in the direction of lowering the temperature or increasing the concentration of ammonia during the reaction.

Robertson (14) reported the first quantitative data on the reaction between chloroacetic acid and ammonia. From rate studies at 40°, it was shown that the amount of the primary amino compound could be increased by the use of higher ratios of ammonia to acid than those proposed by Kraut. The formation of primary amino compounds rises from 58% when a 1:15 mole ratio of acid to ammonia is used, to 95% with a mole ratio of 1:220. For practice, the use of a mole ratio of 1:60 was found convenient. Using this ratio, 63% of glycine was actually isolated; 9% remained in the mother liquor; a total of 72%. It should be noted here that the total glycine originally estimated by determination of amino nitrogen in the reaction mixture was 86% of the theoretical. The difference of 14% was ascribed to loss in manipulation. Robertson further found that high temperatures and runs with 40% ammonia under pressure

did not show any significant improvements except that derived from raising the acid-to-ammonia ratio. Further, it was found that experiments with dilute mixtures, those with alcohol as a solvent, and those with ammonium carbonate instead of ammonium hydroxide gave inferior results. The disadvantage of Robertson's modification of the Kraut method lies in the large quantities of aqueous ammonia required. For example, in order to obtain a kilogram of glycine it is necessary to work with 80 liters of concentrated aqueous ammonia which must be later distilled and concentrated to from 4 to 5 liters before the glycine can be precipitated. The original objective of this investigation (15) was to find a more convenient method for the preparation of glycine, since its therapeutic use had just been reported (16).

In the ammonolysis of any α-halogen fatty acid with 2 to 8 carbon atoms, the main direction of the reaction is towards the formation of primary, secondary, and tertiary amino compounds according to the following equation:

$$RCHClCOO^- + NH_3 \overset{S_1}{\rightleftharpoons} H_2NCHRCOO^- + H^+ + Cl^- \quad (a)$$

$$H_2NCHRCOO^- + RCHClCOO^- \overset{S_2}{\rightleftharpoons} HN(CHRCOO)_2^{=} + H^+ + Cl^- \quad (b)$$

$$HN(CHRCOO)_2^{=} + RCHClCOO^- \overset{S_3}{\rightleftharpoons} N(CHRCOO)_3^{\equiv} + H^+ + Cl^- \quad (c)$$

Since there is always some excess of ammonia in the reaction mixture, the hydrogen ion shown in equations a, b, and c appears in the products as ammonium ion; although a certain amount of hydrolysis would be expected in aqueous media, the α-halogen acid which contains a hydrogen on the same carbon atom as the halogen does not show any appreciable tendency in this direction in excess of ammonia.

During the progress of this work it became apparent that the formation of the amino acid, (a), which is the desired product of the ammonolysis of α-halogen acids, depends on other factors besides the temperature at which the reaction takes place and the concentration of acid and ammonia. The rates S_2 and S_3 of the reactions represented by equations (b) and (c) are markedly influenced by the *p*H of the ammonolytic medium and the presence of ions which are capable of reacting with the amino group.

The p*H effect.* Rate studies in aqueous media at various temperatures and with varying mole ratios of halogen acids and ammonia indicate that at temperatures below 60° increase in the concentration of ammonia produces an increase in the amount of amino acid. Figure 1 summarizes the conversion of chloroacetic acid to glycine at various temperatures and with various mole ratios of ammonia to acid. The extent of conversion of chloroacetic acid to glycine rises steadily with increase in the mole ratio of ammonia to acid at temperatures of 25°, 40°, and 50°; at 60° or above, the

velocities of the secondary reactions are accelerated to a far greater extent than the initial formation of the amino acid so that increase in the concentration of ammonia has no appreciable effect on the conversion of the halogen acid to glycine.

In the initial stages of the reaction between chloroacetic acid and ammonia only the primary amino compound is formed. It is assumed that as soon as an appreciable amount of the amino acid is produced, the amino group reacts with the halogen acid to give the secondary amino compound;

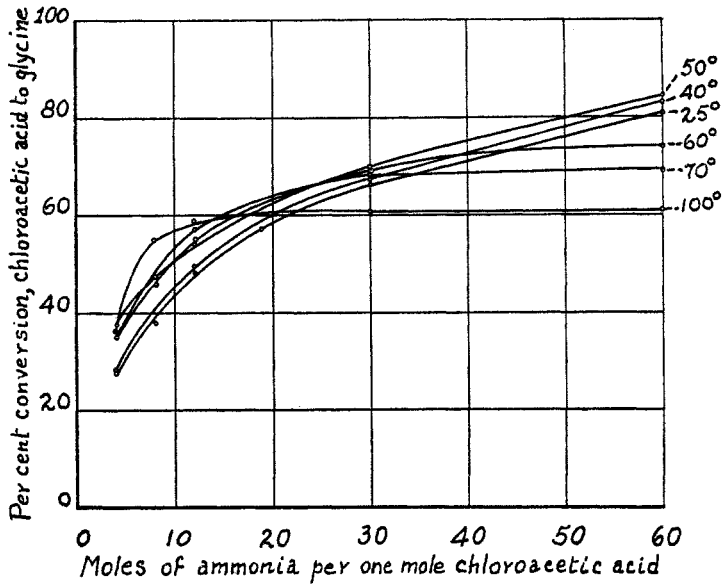

FIG. 1. CONVERSION OF CHLOROACETIC ACID TO GLYCINE AT VARIOUS TEMPERATURES AND WITH VARIOUS MOLE RATIOS OF AMMONIA TO ACID

the reaction involved in the formation of the secondary and tertiary amino compounds may be represented thus:

$$H_3N^+CH_2COO^- + H^+ \rightleftarrows H_3N^+CH_2COOH \qquad (d)$$

$$H_3N^+CH_2COO^- + OH^- \rightleftarrows :NH_2CH_2COO^- + HOH \qquad (e)$$

$$:NH_2CH_2COO^- + ClCH_2COO^- \rightleftarrows :NH(CH_2COO)^{=} + H^+ + Cl^- \qquad (f)$$

$$:NH(CH_2COO)^{=} + ClCH_2COO^- \rightleftarrows :N(CH_2COO)_3^{\equiv} + H^+ + Cl^- \qquad (g)$$

Equation (f) shows that the formation of the secondary amino compound takes place through the reaction of the anion of the amino acid. Increase

in the hydrogen ion concentration of the medium will render the amino group unreactive through the acceptance of a proton by the unshared pair of electrons of the nitrogen atom to form the zwitterion. Accordingly, in the ammonolysis of halogen acid, decrease of the *p*H of the ammonolytic medium would favor the formation of the amino acid.

Evidence for the *p*H effect in the ammonolysis of α-halogen acids has been obtained from rate studies of the reaction between glycine and chloroacetic acid. Table I summarizes the extent of this reaction at various *p*H. The results clearly indicate that the amino acid reacts with the α-halogen acid to form the secondary amino compound through the anion form, (f), and that if the initial *p*H of the ammonolytic medium is decreased below *p*H 10, the formation of the secondary and tertiary amino compounds can be appreciably inhibited.

TABLE I

EXTENT OF REACTION OF ONE MOLE OF GLYCINE WITH ONE MOLE OF CHLOROACETIC ACID FOR 24 HOURS AT 25° AT VARIOUS *p*H OF THE REACTION MIXTURE

INITIAL *p*H OF SOLUTION	*p*H AFTER 24 HOURS	CHLOROACETIC ACID REACTED, %	GLYCINE REACTED, %
13.8	13.8	88.1	60.2
12.7	9.8	85.0	60.1
10.5	9.2	71.0	52.0
9.2	8.5	5.5	4.5
8.5	8.3	4.25	3.5

Further evidence for the *p*H effect is obtained from studies of the ammonolysis of chloroacetic acid with mixtures of aqueous ammonia and various salts. Table II summarizes the extent of conversion of chloroacetic acid to glycine with various mixtures of aqueous ammonia and salts. The mole ratio of acid to ammonia is kept 1:12 throughout the series. With ammonium salts, the ammonium ion is considered capable of taking part in the reaction, and hence it is included in the total mole ratio of acid to ammonia. The increased conversion of chloroacetic acid to glycine by the addition of salts which reduce the *p*H of the ammonolytic medium is evident both at 60° and 100°.

The addition of salts in ammonolytic media was first advocated by Mauthner and Suida (17). Their claim of improvement does not appear to have sufficient experimental basis, for they report a yield of 16–18% of glycine by the addition of sodium carbonate to the mixture of chloroacetic acid and ammonia, while the previous reported yield was 10–15% (18). Addition of ammonium salts, particularly of the carbonate, to solutions of aqueous ammonia has also been reported (19). No clear explana-

tion however has been advanced for the effect of salts in ammonolytic reactions.

The carbamate effect. Solutions of ammonia which contain an appreciable amount of carbon dioxide yield a far greater conversion of halogen

TABLE II

EFFECT OF SALTS ON THE AMMONOLYSIS OF CHLOROACETIC ACID AT 60° AND 100°

ACID MOLES	AQUEOUS AMMONIA[a] MOLES	MOLES OF SALT	*p*H OF THE MIXTURE	MOLE RATIO ACID:NH_3	TEMP.[b] °C.	PRODUCTION[c] OF RNH_2, %
0.01	0.12	0.00	11.7	1:12	60	55.0
.01	.12	.03 Na_2CO_3	12.5	1:12	60	64.5
.01	.12	.06 $NaHCO_3$	8.8	1:12	60	65.0
.01	.12	.06 NaCl	12.0	1:12	60	59.0
.01	.06	.06 NH_4NO_3	8.6	1:12	60	66.5
.01	.06	.06 NH_4Cl	8.8	1:12	60	61.2
.01	.06	.06 $NH_4C_2H_3O_2$	8.6	1:12	60	61.7
.01	.06	.03 $(NH_4)_2CO_3$	8.3	1:12	60	81.5
.01	.12	.00		1:12	100	59.0
.01	.06	.06 NH_4Cl		1:12	100	68.4
.01	.06	.06 NH_4NO_3		1:12	100	65.0
.01	.06	.03 $(NH_4)_2CO_3$		1:12	100	76.0

[a] Strength of ammonia: 27.7%.

[b] Time heated: at 60° for 4 hours; at 100° for 1.5 hours.

[c] Average of 2 to 4 runs. Maximum variation less than 3.0%. The production of halide ion is quantitative.

TABLE III

AMMONOLYSIS OF CHLOROACETIC ACID AT ROOM TEMPERATURE IN THE PRESENCE OF AMMONIUM SALTS

ACID MOLES	AQUEOUS AMMONIA MOLES	AMMONIUM SALT MOLES	MOLE RATIO ACID:NH_3	*p*H[c]	CONVERSION[d] TO RNH_2, %
0.1[a]	0.45		1:4.5	12.1	29.0
.1[a]	.45	0.4 NH_4Cl	1:4.5	9.0	35.2
.1[b]	.45	.4 NH_4NO_3	1:4.5	8.8	42.6
.1[b]	.45	.2 $(NH_4)_2CO_3$	1:4.5	8.7	73.4

[a] The solution of acid and ammonia was mixed at 25°. On standing, the temperature rose gradually to 40° after 1.5 hours.

[b] The solution of acid and ammonia was mixed at 25°. The temperature remained unchanged.

[c] *p*H of the ammonolytic medium before addition of the halogen acid.

[d] Conversion determined after the reaction was complete.

acid to the primary amino compound than is anticipated on the basis of increased acidity. Addition of three moles of ammonium carbonate to six moles of aqueous ammonia at 60° leads to a 40% increased conversion of chloroacetic acid to glycine; the use of an equivalent amount of ammonium

nitrate or ammonium chloride gives only a 20% increased conversion. Data of Table II show the striking difference in the effect of the ammonium carbonate compared to other ammonium salts; the data of Table III indicate that the increased conversion is not entirely due to the *p*H effect. The addition of ammonium nitrate produces a 47% increase in the conversion of halogen acid to amino acid, while an equivalent amount of ammonium carbonate produces an increase of 160%. Since the *p*H of both ammonolytic solutions is practically the same, the conclusion is that the presence of one of the ions from ammonium carbonate exerts a decided effect on the direction of the reaction. It is assumed that the carbamate ion, and to a lesser degree the bicarbonate, reacts with the amino group to form the carbamate of the amino acid, thus inhibiting the reaction between the unchanged halogen acid and the primary amino compound. The carbamate of the amino acid is unstable and at temperatues above 70° it decomposes to the amino acid. The formation of the carbamino derivative of the amino acid takes place according to the following equations:

$$H_2NCH_2COO^- + H_2NCOO^- \rightleftarrows \begin{matrix} CH_2COO^- \\ | \\ HNCOO^- \end{matrix} + NH_3 \qquad (h)$$

$$H_2NCH_2COO^- + HCO_3^- \rightleftarrows \begin{matrix} CH_2COO^- \\ | \\ HNCOO^- \end{matrix} + H_2O \qquad (i)$$

$$H_2NCH_2COO^- + CO_2 \rightleftarrows \begin{matrix} CH_2COO^- \\ | \\ +NCOO^- \\ H_2 \end{matrix} \rightleftarrows \begin{matrix} CH_2COOH \\ | \\ NCOO^- \\ H \end{matrix} \qquad (j)$$

The reaction represented by equation (h) is assumed to be involved to a greater extent in the formation of the carbamino compound under the condition of ammonolysis; the reactions represented by equations (i) and (j) are assumed to take place to a smaller extent.

The effect of ammonium carbonate on the conversion of chloroacetic acid is summarized in Figure 2. The amount of carbon dioxide combined with twelve moles of ammonia is varied from 0.1 to 6.0 moles, a quantity sufficient to combine completely with ammonia in the form of bicarbonate-carbamate, $NH_4HCO_3 \cdot NH_2CO_2NH_4$. Increase in the amount of carbon dioxide results in a steady rise of conversion of chloroacetic acid to glycine until the mole ratio of ammonia to carbon dioxide is three to one.

The composition of ammonia-carbon dioxide compounds in equilibrium with their aqueous solutions has been extensively investigated by Terres and Weiser (20) and also by Yanecke (21). Carbon dioxide and ammonia

are assumed to form a number of compounds: 2 $NH_4HCO_3 \cdot (NH_4)_2CO_3 \cdot H_2O$, $(NH_4)_2CO_3 \cdot H_2O$, NH_4HCO_3, $NH_4CO_2NH_2$, and $NH_4CO_2NH_2 \cdot NH_4HCO_3$. Of these, the first two are stable around 35° while the bicarbonate and carbamate exist at temperatures of 20–80°. The composition of the solid commercial carbonate is given either as a mixture of the carbamate-bicarbonate or as a definite double salt of the two: $NH_2CO_2NH_4 \cdot NH_4HCO_3$.

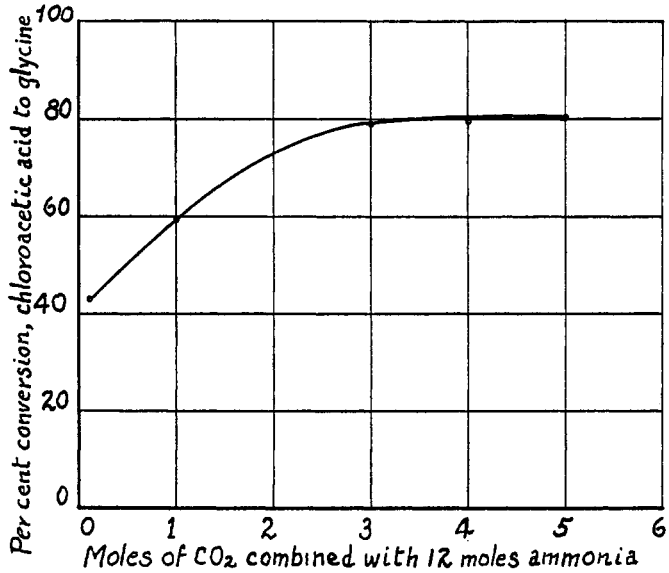

FIG. 2. CARBAMATE EFFECT ON THE AMMONOLYSIS OF ONE MOLE OF CHLOROACETIC ACID WITH TWELVE MOLES OF AMMONIA AT 60°

When ammonium carbonate or bicarbonate is dissolved in water, the following equilibria are assumed to exist:

$$NH_3 + HOH \rightleftarrows NH_4^+ + OH^-$$

$$CO_2 + 2NH_3 \rightleftarrows NH_4^- + NH_2CO_2^-$$

$$NH_2CO_2^- + H_2O \rightleftarrows NH_3 + HCO_3^- \text{ or } NH_4^- + CO_3^-$$

The relative amount of carbamate and carbonate in aqueous solutions containing carbon dioxide and ammonia can be determined (22), and Table IV summarizes the composition of various solutions which were used in the ammonolysis of halogen acids. In saturated solutions of ammonium carbonate, decomposition begins at 56–58° and becomes vigorous at 60°, carbon dioxide being given off in greater amounts than ammonia. At this temperature the amount of carbamate ion is about the same as that of a saturated solution of pure ammonium carbamate at 25°. Saturated solu-

tions of ammonium bicarbonate decompose at 44–45°; the amount of carbamate ion at the decomposition temperature is less than that present in the saturated solutions of carbonate or carbamate. Generally, aqueous solutions of ammonia which contain an appreciable amount of carbon dioxide, contain at temperatures below 60° considerable carbamate ion, the amount increasing near the decomposition temperature of the solution.

The reaction between amino acids and carbon dioxide or alkaline carbonates to give the carbamino derivatives has been reported in the literature (23). The crystalline calcium salt of glycine carbamate and the

TABLE IV

COMPOSITIONS OF SOLUTIONS OF VARIOUS AMMONIA-CARBON DIOXIDE COMPOUNDS

SALT	TEMP., °C.	CONCENTRATION	PER CENT TOTAL SALT AS	
			Carbonate	Carbamate
Ammonium carbamate[a] ($NH_2CO_2NH_4$)	25	0.050 molal	90.3	9.7
		0.195 molal	80.8	19.2
		1 g. salt to 1.5 g. water	39.20	60.8
Ammonium carbonate[b] ($NH_2CO_2NH_4 \cdot NH_4HCO_3$)	25	25.2 g. salt in 100 g. solution	54.40	45.60
	59[c]	55 g. salt in 100 g. solution	37.09	62.91
	60[d]	55 g. salt in 100 g. solution	33.92	66.18
	60[e]	55 g. salt in 100 g. solution	34.20	65.80
Ammonium bicarbonate (NH_4HCO_3)	25	19 g. salt in 100 g. solution	94.50	5.50
	46[c]	22.8 g. salt in 100 g. solution	78.80	21.22

[a] Data from Burrows and Lewis (22).

[b] Ammonium carbonate, reagent grade.

[c] Sample taken fifteen minutes after temperature was reached.

[d] Sample taken five minutes after temperature was reached.

[e] Sample taken fifteen minutes after temperature was reached.

glycine carbamate ethyl ester have been isolated. The assumption of some writers, however, that the velocity of the carbamate formation depends on the existence of free carbon dioxide, and that neither the carbonate nor the bicarbonate ion could react extensively with the amino acid, is not borne out by the present investigation. Rate studies in the reaction between chloroacetic acid and glycine show that the addition of sodium carbonate diminishes the rate to one-half; when the reaction is complete the amount of reacted glycine is less than with phosphate buffers which have the same *p*H. Further, ammonium carbonate, bicarbonate, or carbamate exerts an inhibitive effect on the formation of secondary and tertiary amino compounds at 20° and 25°; at these temperatures the amount of free carbon dioxide in such ammonolytic solutions is negligible.

Aqueous solutions of ammonia which contain an appreciable amount of ammonium carbonate combine both the *p*H and the carbamate effects for the ammonolysis of halogen acids.

The influence of halogen. In the ammonolysis of an α-halogen acid, RCHXCOOH, the nature of the halogen atom and of the radical R should be taken into consideration. Both influence the rate at which the α-halogen acid reacts and the extent to which other side reactions, such as hydrolysis and formation of unsaturated acids, take place. In table V appears a comparison of the ammonolysis of 0.8 mole of various halogen acids at 60° with 4 moles of ammonium carbonate. These data indicate that for the ammonolysis of α-halogen acids with more than three carbon atoms at temperatures above 40° and atmospheric pressure, the bromo compound must be used. The chloro acids react too slowly, and unless

TABLE V

COMPARISON OF AMMONOLYSIS OF SEVERAL α-HALOGEN ACIDS AT 60° WITH FOUR MOLES OF AMMONIUM CARBONATE

HALOGEN ACID	TIME REQUIRED FOR REACTION OF 0.8 MOLES OF ACID (MINUTES)	AMINO ACID PRODUCED (MOLES)
$CH_2BrCOOH$	1	0.64
$CH_2ClCOOH$	54	.66
$CH_3CHClCOOH$	540	.61
$CH_3CHBrCOOH$	21	.61
$CH_3CH_2CHBrCOOH$	33	.57
$(CH_3)_2CBrCOOH$	2	.05
$CH_3CH_2CH_2CHBrCOOH$	180	.57
$(CH_3)_2CHCHBrCOOH$	1080	.50
$CH_3(CH_2)_3CHBrCOOH$	210	.62

pressure is used loss of ammonia results in increase of hydrolytic reactions; branching on the carbon atom which holds the halogen increases the rate of reaction tremendously, but at the same time causes a reduction in the amount of the amino compound and an increase in the amount of unsaturated acid.

Influence of other factors. Many catalysts will accelerate the rate of ammonolysis. Copper, cuprous and cupric salts, charcoal, bentonite, sodium iodide, etc., have been found to increase the rate of halide ion formation without increasing the conversion of the primary amino compound. The use of cuprous salts may be of advantage with the higher α-chloro acids.

The effect of solvent was investigated with chloroacetic acid. Solutions of ammonia in absolute methanol, ethanol, 90% methanol, and chloroform do not offer any advantage over the aqueous system. Similar results

were obtained with the use of anhydrous ammonia. At the boiling point of liquid ammonia even the most reactive halogen acids do not show any appreciable change. Complete reaction takes place when the halogen acid is sealed in a bomb with anhydrous ammonia and allowed to stand overnight at room temperature or heated for one hour at 60°. Table VI summarizes the extent of conversion of chloroacetic acid to glycine when ammonolyzed with anhydrous ammonia.

Optimum conditions for ammonolysis. On the basis of the foregoing discussion the optimum conditions for the ammonolysis of α-halogen acids may be formulated. Aqueous solutions of ammonia which contain a considerable amount of carbon dioxide are more efficient ammonolytic media than solutions of ammonia buffered by other ammonium salts. In addition to the *p*H effect, the compounds of carbon dioxide and ammonia

TABLE VI

AMMONOLYSIS OF CHLOROACETIC ACID WITH ANHYDROUS AMMONIA AT VARIOUS TEMPERATURES

MOLES ACID	MOLES AMMONIA	RATIO OF ACID:NH_3	TEMP.,[a] °C.	TIME, HRS.	PER CENT YIELD	
					Cl^-	RNH_2
0.05	0.2	1:4	30	5	99	38.8
.05	.7	1:14	30	5	100	40.2
.05	.4	1:8	60	2	100	40.9
.05	.4	1:8	60	0.5	92.5	39.8
.01	.4	1:40	65	0.25	99.2	48.0
.01	.6	1:60	65	1.0	99	50.5
.05	.6	1:60	b.p. NH_3	24	1.4	0.0

[a] Heated in a 125 cc. metal bomb.

produce a blocking on the amino group through the formation of the unstable carbamate of the amino acid and thus inhibit the formation of the secondary and tertiary amino compounds. In addition, ions of the compounds of carbon dioxide and ammonia can be removed easily by heating, which is not the case with other ammonium salts. Temperatures between 40° and 60° and solutions which contain ten to twelve moles of ammonia with four to five moles of carbon dioxide for each mole of halogen acid have been found best for the formation of the lower α-amino acids (two to six carbon atoms). For the branched α-halogen acids such as α-bromoisovaleric and the higher α-halogen acids, which have a low reactivity, the reaction mixture is kept at 40° for 24 to 48 hours. The time may be considerably shortened by heating at 60–70° under pressure.

The application of the *p*H and carbamate effects to the ammonolysis of other halogen compounds will be discussed in future papers.

EXPERIMENTAL

α-Halogen acids. Chloroacetic and α-chloropropionic acids were prepared from the corresponding fatty acids by passing in finely dispersed chlorine at 105–110°, in the presence of red phosphorus (3% of the weight of the fatty acid). Chlorination was stopped when 85–90% of the required amount of chlorine had been absorbed. The crude halogen acid was fractionated at 30–40 mm. pressure. The middle fraction was of sufficient purity (95–96% α-halogen acid) for the usual preparation of amino acids. For determination of rates, the halogen acid was refractionated three times, until the halogen content and the equivalent neutralization number were within 0.2% of the theoretical.

The α-bromo acids were prepared by a modified Hell-Volhard-Zelinsky method, using thionyl chloride or phosphorus trichloride as a catalyst. The method of purification was similar to that used for the chloro acids. The purity of the acid was checked by determination of halogen, and of the equivalent neutralization number. α-Bromoisovaleric acid, after two fractionations, was further purified by recrystallization from hexane.

Ammonium carbonate and ammonium carbamate. Ammonium carbonate, reagent grade, was used; every lot was analyzed for ammonia and carbon dioxide. The material obtained commercially as reagent grade contained from 29.75–30.5% ammonia and 53.5–55% carbon dioxide; calculated for $C_2H_{11}N_3O_5$, 32.4% ammonia and 56% carbon dioxide. The carbamate was made by dropping small pieces of solid carbon dioxide into excess of liquid ammonia. The solid, after evaporation of ammonia was purified by recrys allization from alcohol. The saturated solution of ammonium carbonate used for ammonolysis contained 25.2 g. at 25° of the salt ($C_2H_{11}N_3O_5$) per 100 g. of solution; at 60° the saturated solution contained 55 g. of salt per 100 g. of solution. The solutions at 25° were prepared by warming solid ammonium carbonate with three times its weight of water at 40°, cooling to 25°, and allowing to stand overnight. The solutions at 60° were prepared by heating gradually solid ammonium carbonate with an amount of water equal to one-fourth of its weight.

The relative amounts of carbamate and carbonate ions in solutions containing ammonia and carbon dioxide were determined by addition of barium ion to the ice-cold sample; only the barium carbonate is precipitated (22), while the carbamate remains in solution. After the filtration of barium carbonate, the filtrate is boiled, thereby converting the carbamate to carbonate. For convenience the ammonia combined with carbon dioxide is expressed as ammonium carbonate, $(NH_4)_2CO_3$.

Analysis of the reaction mixture. The ionic halogen was determined by the Volhard volumetric method, using the Caldwell-Meyer modification for the chloro acids. For the bromo acids certain precautions were found necessary to minimize the error introduced due to the reaction between silver nitrate and the halogen acid. The solution containing the ionic halogen with unchanged halogen acid was cooled to 0°, then after the addition of silver nitrate titrated immediately with thiocyanate, keeping the flask immersed in an ice-water mixture.

The amount of amino nitrogen was determined by the Koch (24) modification of the micro form of the Van Slyke (25) apparatus. The accuracy of the method was extensively investigated and it was found necessary to introduce the following procedure: Pure samples of amino acids were prepared by five recrystallizations from water. The dried sample was then analyzed for nitrogen by the Kjeldahl method. From the pure samples, solutions containing 5 g. of the amino acid per liter of solution were prepared. By means of these solutions the apparatus was

standardized. Table VII lists the results obtained with the standard solutions of α-amino acids in the apparatus used throughout this investigation. The values in column 3 of the table were used in the calculations. The apparatus was always checked with standard amino acid solution before each series of runs. Experience with several hundred determinations indicates an accuracy of one per cent or less in the direct determination of amino nitrogen of a relatively pure amino acid. In the determination of amino nitrogen from reaction mixtures which contain ammonia and unchanged halogen acid, the limits of accuracy are within two to three per cent. Large errors are introduced unless the following precautions are taken. The solution to be analyzed must be free from ammonia and should give a white coloration with Nessler's solution. It is stated that ammonium salts do not interfere seriously in that they required 1.5 to 2 hours for completion of reaction at 20°; it has been found, however, that the presence of even small amounts of ammonium salts introduces errors. Another precaution is to check the amount of "blank" due to nitrogen in the reagents, air leaks, etc., at least once every six consecutive determinations. The temperature should be kept as near 20° as possible, though no serious error is introduced at temperatures between 20–25°, provided the blank is redetermined and the

TABLE VII

MILLIGRAMS OF AMINO ACID PER CC. AMINO NITROGEN (S.T.P.)

α-AMINO ACID	THEORY	FOUND	PER CENT DIFFERENCE
Aminoacetic	3.35	3.10	−7.5
α-Aminopropionic	3.97	3.94	−0.7
α-Aminobutyric	4.59	4.50	−1.9
α-Aminocaproic	5.84	5.60	−4.1
α-Aminoisovaleric	5.22	5.18	−0.8

apparatus checked with the standard solution of amino acid to be determined, if the temperature changes.

Ammonolysis of chloroacetic acid at various temperatures. Reaction tubes were prepared from 20 mm. Pyrex tubing closed at one end. The required amount of aqueous ammonia or other ammonolytic solution was placed in the tube, which was then immersed in an ice-salt mixture. The required amount of chloroacetic acid, usually 0.01 mole, was weighed in a smaller tube, and then immersed in the ammonolytic solution in such a manner that the upper level of the solution did not reach the top of the tube containing the halogen acid. The reaction tube afterwards was sealed and clamped upright in the thermostat. After fifteen minutes, the reaction tube was carefully tilted so that the halogen acid mixed with the ammonolytic solution. At the end of the reaction period, each tube was again cooled, the seal broken, and the mixture diluted to volume. Aliquot portions were then analyzed for ionic halogen, total halogen, and amino nitrogen as previously described.

To avoid the difficulty and danger due to breakage of the glass bombs at temperatures of 100°, the following procedure was used: The reaction tube was placed in an iron bomb made of one-inch pipe with caps at both ends. The glass bomb was then surrounded by the same solution as contained within. The iron pipe was fitted with the cap and placed upright in the bath for 0.5 hour before shaking to start the reaction. Table VIII lists the results of typical runs. The production of halide ion

was quantitative and hence it is omitted from the table. The production of amino acid listed represents the mean values of two to ten runs. The maximum variation for temperatures below 50° is less than 3%. At temperatures of 60–100° the variation is higher, particularly in the runs with a mole ratio of acid to ammonia of 1:60. At these temperatures the reaction is extremely rapid; at 100° with a mole ratio of 1:60

TABLE VIII

AMMONOLYSIS OF CHLOROACETIC ACID AT VARIOUS TEMPERATURES

ACID MOLES	AMMONIA[a] MOLES	MOLE RATIO ACID:NH_3	TEMP., °C.	TIME HEATED, HRS.	PRODUCTION OF RNH_2, %
0.01	0.04	1:4	25	48	27.8
.01	.08	1:8	25	48	38.1
.01	.12	1:12	25	48	48.1
.01	.30	1:30	25	48	66.1
.01	.60	1:60	25	48	81.0
.01	.04	1:4	40	24	28.0
.01	.12	1:12	40	24	49.5
.01	.12	1:12	40	24	49.0
.01	.30	1:30	40	24	67.1
.01	.60	1:60	40	24	82.9
.01	.04	1:4	50	6	37.6
.01	.08	1:8	50	6	47.3
.01	.12	1:12	50	6	54.2
.005	.10	1:20	50	4	67.0
.003	.09	1:30	50	4	70.0
.003	.18	1:60	50	4	84.5
.01	.04	1:4	60	4	36.0
.01	.08	1:8	60	4	45.5
.01	.12	1:12	60	4	55.1
.003	.09	1:30	60	2	69.0
.003	.18	1:60	60	2	74.1
.01	.04	1:4	100	1.5	36.4
.01	.08	1:8	100	1.5	55.0
.01	.12	1:12	100	1.5	59.3
.003	.09	1:30	100	1.0	60.0
.003	.18	1:60	100	1.0	60.5

[a] Strength of aqueous ammonia, 27.7%.

the reaction is complete within one minute after mixing, and therefore the mode of mixing enters as a variable.

pH of ammonolytic media. The *p*H of concentrated ammonium hydroxide at 25°, 60°, or 100° is difficult to measure. The glass electrode does not give consistent values even when standardized at *p*H 12.0. Similarly, the hydrogen electrode gives erratic values. Consequently, for *p*H above 10 the colorimetric method was used. Deter-

minations were made by use of: *o*-cresolphthalein and phenolphthalein for *p*H 8.2 to 10.0; thymolphthalein for values of 9.3 to 10.5; resorcin yellow and sodium indigotin disulfonate for values of *p*H 11.0 to 13. Trinitrobenzene fades rapidly in presence of ammonia. For determination at 25°, 10 cc. of the solution with the proper amount of indicator was compared with standard buffer solutions containing the same indicator. The values below *p*H 10.0 were checked by determinations with a glass electrode. The *p*H of ammonolytic solutions at 60° was similarly determined by sealing ampules containing the solution and indicator, and heating to 60° for one-half hour, then comparing with standard buffer solutions. Above *p*H 10.0 at 25°, the accuracy is not better than 0.4 *p*H, while below 10.0 the colorimetric and glass electrode determinations checked within 0.1 *p*H. Table IX lists the *p*H of various aqueous solutions of ammonia and ammonium salts which were used in the ammonolysis of halogen acids.

Effects of salts on the ammonolysis of chloroacetic acid. Reaction tubes were prepared, containing 0.01 mole of chloroacetic acid and the required amount of ammonia

TABLE IX

*p*H OF VARIOUS SOLUTIONS USED IN AMMONOLYSIS

COMPOSITION OF SOLUTION	OBSERVED *p*H	
	25°	60°
Concentrated aqueous ammonia (27.7%)	12.1	11.7
Saturated solution of ammonium carbonate	8.7	8.2
Concentrated aqueous ammonia: 6 moles; Ammonium carbonate: 1 mole	9.3	8.8
Concentrated aqueous ammonia: 6 moles; Ammonium carbonate: 2 moles	8.8	8.3
Concentrated aqueous ammonia: 6 moles; Ammonium carbonate: 3 moles	8.8	8.3
Concentrated aqueous ammonia saturated with ammonium chloride	9.0	8.8
Concentrated aqueous ammonia saturated with ammonium nitrate	8.8	8.6

and salt (finely pulverized). The method of sealing and mixing was the same as described above. Where chlorides were used, the salt was weighed in an analytical balance in order to make the proper allowance in the determination of ionic halogen from chloroacetic acid. The effect of salts at 60° under atmospheric pressure was carried out in small flasks provided with a rod for stirring. The acid was added after the ammonolytic solution reached 60°. Table X lists the results of representative runs. The production of halide ion was quantitative and hence is not reported. The production of amino acid listed represents the mean values of 2–4 runs. The maximum variation was less than 3%.

Carbamate effect on ammonolysis. Carbon dioxide was passed into a well-chilled solution containing twelve molar equivalents of ammonia until the required amount of carbon dioxide was absorbed, as determined by analysis for carbonate ion. The solution was then placed in a thermostat and one mole of chloroacetic acid was added. When the reaction was complete samples were withdrawn and analyzed for total halogen, ionic halogen, and amino nitrogen. The extent of conversion was checked by isolation of the glycine. The reaction mixture was heated to 80° to distill off the

ammonia and carbon dioxide, then boiled over a free flame until the temperature of the solution reached 112°. The solution was decolorized and precipitated with three volumes of methanol. After 24 hours the crude glycine was filtered and suspended

TABLE X

EFFECT OF SALTS ON THE AMMONOLYSIS OF CHLOROACETIC ACID AT 60°

ACID MOLES	AQUEOUS AMMONIA MOLES	MOLES OF SALT	MOLE RATIO ACID:NH_3	CONVERSION TO RNH_2[a]	
				Heated at atmospheric pressure	Heated under pressure
0.01	0.12	0.0	1:12	42.0	55.0
.01	.12	.03 Na_2CO_3	1:12	47.9	64.5
.01	.12	.06 $NaHCO_3$	1:12	61.8	65.0
.01	.06	.06 NH_4Cl	1:12	59.6	61.2
.01	.06	.06 NH_4NO_3	1:12	60.5	66.5
.01	.06	.06 $NH_4C_2H_3O_2$	1:12	63.4	61.7
.01	.12	.06 NaCl	1:12	45.0	59.0
.01	.06	.03 $(NH_4)_2SO_3$	1:12	43.5	56.5
.01	.06	.06 $(NH_4)_2CO_3$	1:12	78.5	81.5

[a] The reaction tubes were heated 4 hours in all runs.

TABLE XI

CARBAMATE EFFECT IN THE AMMONOLYSIS OF CHLOROACETIC ACID AT 60°C[a]

$ClCH_2COOH$ MOLES	AMMONIA (27.7 %) MOLES	CARBON DIOXIDE MOLES	TEMP., °C.	TIME, HRS.	AMOUNT OF H_2NCH_2COOH	
					Produced	Recovered[c]
1	12.04	0.1	25	48	41.5	30.6
1	12.04	1.0	25	48	65.8	53.5
1	12.0	3.0	25	48	79.5	71.0
1	12.0	5.0	25	48	70.1	59.5
1	12.0	6.0	25	48	71.1	60.0
1	12.0[b]	0.1	60	4	43.2	34.8
1	12.0	1.0	60	4	59.3	46.0
1	12.0	3.0	60	4	79.0	70.6
1	12.0	4.0	60	4	78.5	70.6
1	12.0	5.0	60	4	80.5	71.0
1	12.0	6.0	60	4	77.5	68.0

[a] Atmospheric pressure.

[b] Strength of ammonia: 21.5%.

[c] Crude glycine precipitated with methanol; filtered and extracted with 95% methanol until chloride content was less than 02.%.

twice in 150 cc. of methanol. The dry glycine was analyzed for chloride, ammonia, and amino nitrogen. A sample from the combined filtrates was analyzed for amino nitrogen. The amount of glycine which remains dissolved in the filtrates is from 10–12 g. The amount of amino acid indicated by the analysis of the reaction mixture

and that recovered, plus the amount in the filtrates, agree within 2-3%. When the conversion of halogen acid to amino acid is low, the ammonium salts of secondary and tertiary amino compounds increase the solubility of glycine in the water-methanol mixture, and hence the amount recovered is further lowered. Table XI lists the results obtained from typical runs. The values for the amino acid produced and recovered represent the mean of 3–5 runs. The maximum variation is less than 3%.

RATE STUDIES

The rates of the ammonolysis of halogen acids were determined at 25° and 60°. The ammonolytic medium at 25° was sixty moles of aqueous concentrated ammonia for one mole of acid. At 60° four moles of ammonium carbonate were used for each mole of halogen acid.

Ammonolysis of chloroacetic acid. A two-liter flask provided with a wired stopper and containing 1640 cc. of aqueous ammonia (equivalent to 15 moles) was placed in a thermostat at 25° ± .05°. When the solution acquired the temperature of the bath, 37.8 g. (0.4 moles) of chloroacetic acid was added over a period of one minute while the flask was shaken to prevent heating. At regular intervals 10 cc. samples were withdrawn and analyzed. The sample for halide ion was acidified with cold, dilute sulfuric acid to stop the reaction. The sample for determination of the amino nitrogen was prepared according to the following procedure: After removal from the reaction flask, the sample was placed in a 250 cc. Erlenmeyer flask and the ammonia removed by suction. The evaporation of ammonia reduces the temperature so that there is no appreciable reaction during this interval. When practically all the ammonia was removed, 5 cc. of 5 *N* sodium hydroxide was added and the solution boiled rapidly until ammonia ceased to be evolved. The solution then was diluted to standard volume and aliquot portions were analyzed for amino nitrogen in the micro apparatus. Dilutions and size of samples taken were so adjusted that the amount of amino nitrogen obtained in each analysis was not less than 0.5 cc. The amount of total halogen contained in the volume of samples withdrawn for analyses (usually 10 cc.) was determined by digesting the sample with alcoholic sodium hydroxide for several hours, and then proceeding according to standard methods.

The ammonium carbonate solution was prepared by heating gradually to 60° ammonium carbonate (cubes) containing 8 molar equivalents of ammonia with 200 cc. of water. When the temperature within the flask reached 57–58°, the flask was transferred to a thermostat at 60° ± .05°. One mole of acid dissolved in 50 cc. of water was allowed to come to the same temperature and then added to the solution of ammonium carbonate over a period of one minute. The evolution of carbon dioxide prevents any appreciable rise in temperature in the initial stages of the reaction. At regular intervals 5 cc. samples were withdrawn and diluted to 50 cc. to stop the reaction. Aliquot portions of this were analyzed for ionic halogen, total halogen, and amino nitrogen according to the method described. The results obtained are shown graphically in Figure 3. The effect of catalysts which accelerate the rate of reaction between chloroacetic acid and ammonia is shown in Figure 4. Run I shows the effect of cuprous oxide, (0.05 mole of oxide per mole of acid); run II shows the effect of 0.1 mole of potassium iodide per mole of acid, while run III is a run without catalyst for comparison.

Ammonolysis of other halogen acids. The same general procedure, with slight modifications was used for the determination of rates of the other halogen acids. In each case 0.2 mole of acid was used. Figures 5-11 show graphically the rates of ammonolysis of: bromoacetic acid; α-chloropropionic acid; α-bromopropionic acid;

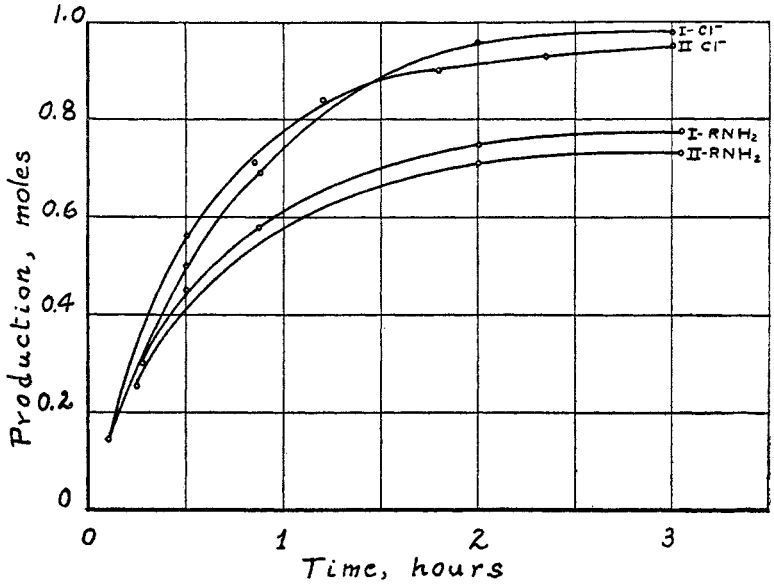

FIG. 3. AMMONOLYSIS OF ONE MOLE OF CHLOROACETIC ACID

I = Sixty moles of aqueous ammonia at 25°. II = Four moles of ammonium carbonate at 60°.

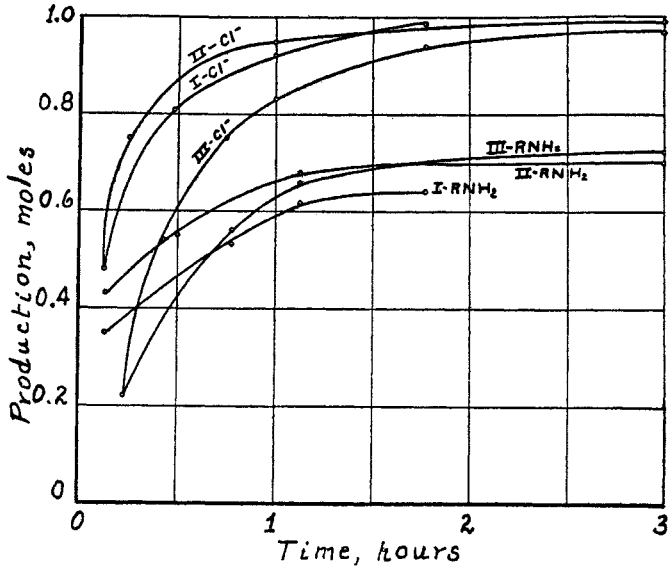

FIG. 4. EFFECT OF CATALYSTS ON THE AMMONOLYSIS OF ONE MOLE OF CHLOROACETIC ACID WITH FOUR MOLES OF AMMONIUM CARBONATE AT 60°

I = Copper catalyst; II = 0.1 mole of potassium iodide; III = no catalyst.

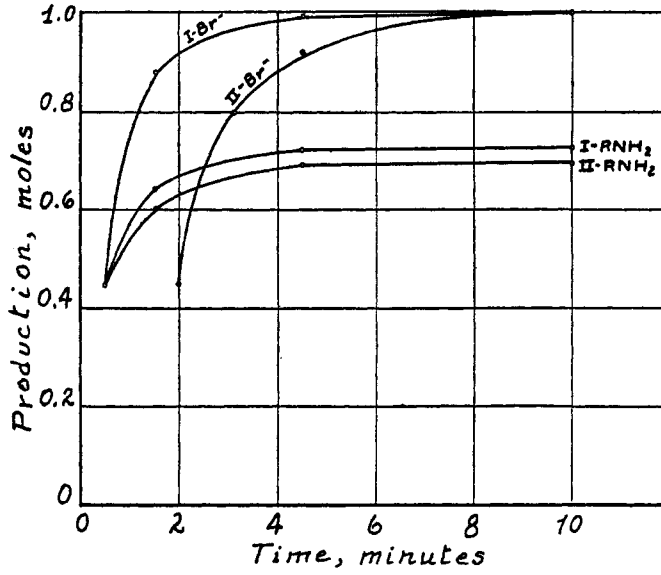

FIG. 5. AMMONOLYSIS OF ONE MOLE OF BROMOACETIC ACID

I = Four moles of ammonium carbonate at 60°. II = Sixty moles of aqueous ammonia at 25°.

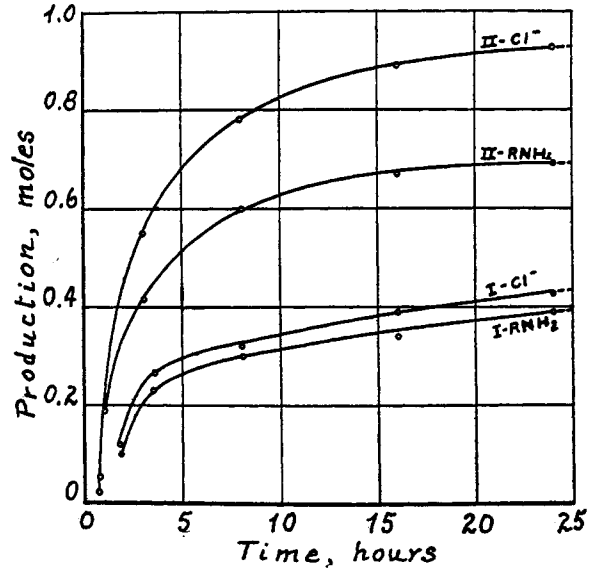

FIG. 6. AMMONOLYSIS OF α-CHLOROPROPIONIC ACID

I = Sixty moles of aqueous ammonia at 25°. II = Four moles of ammonium carbonate at 60°.

Curve I, continued from graph

Time, hrs.	Cl, moles	RNH_2, moles
65	0.60	0.47
137	.80	.62
252	.94	.77
348	.98	.81

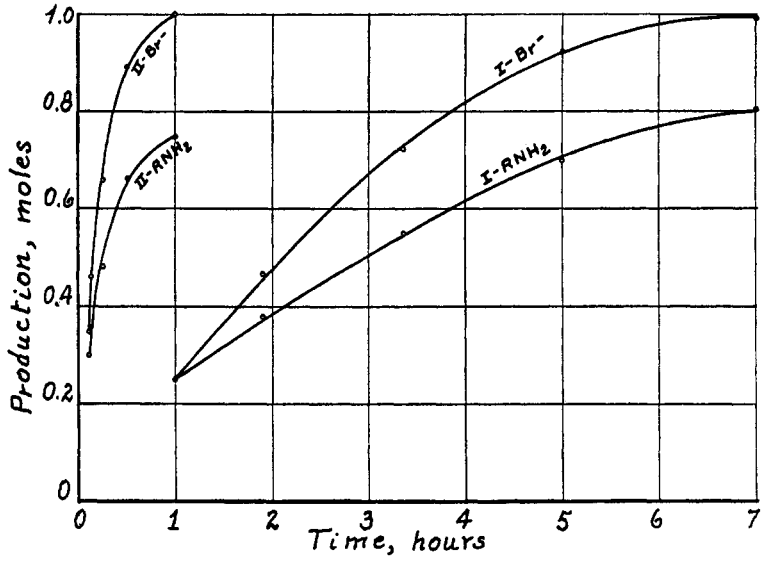

FIG. 7. AMMONOLYSIS OF ONE MOLE OF α-BROMOPROPIONIC ACID

I = Sixty moles of aqueous ammonia at 25°. II = Four moles of ammonium carbonate at 60°.

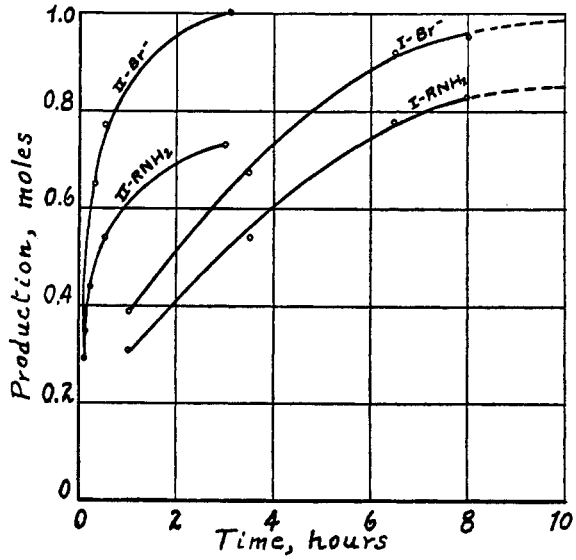

FIG. 8. AMMONOLYSIS OF ONE MOLE OF α-BROMO-n-BUTYRIC ACID

I = Sixty moles of ammonia at 25°. II = Four moles of ammonium carbonate at 60°.

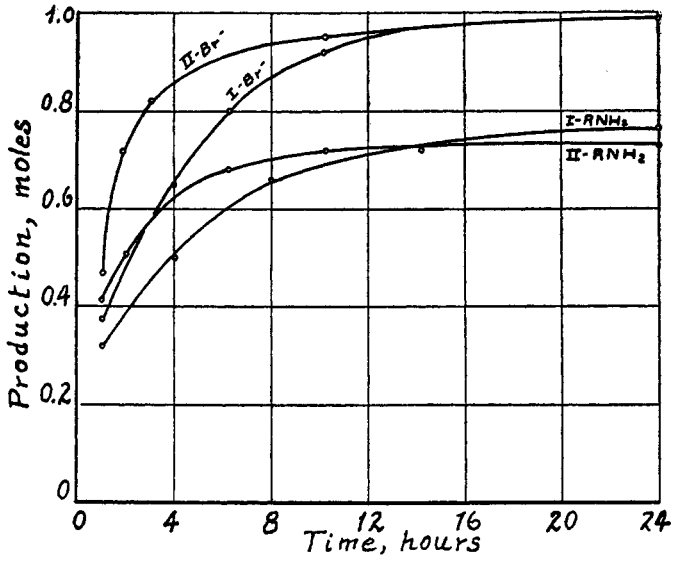

FIG. 9. AMMONOLYSIS OF ONE MOLE OF α-BROMO-*n*-VALERIC ACID

I = Sixty moles of ammonia at 25°. II = Four moles of ammonium carbonate at 60°.

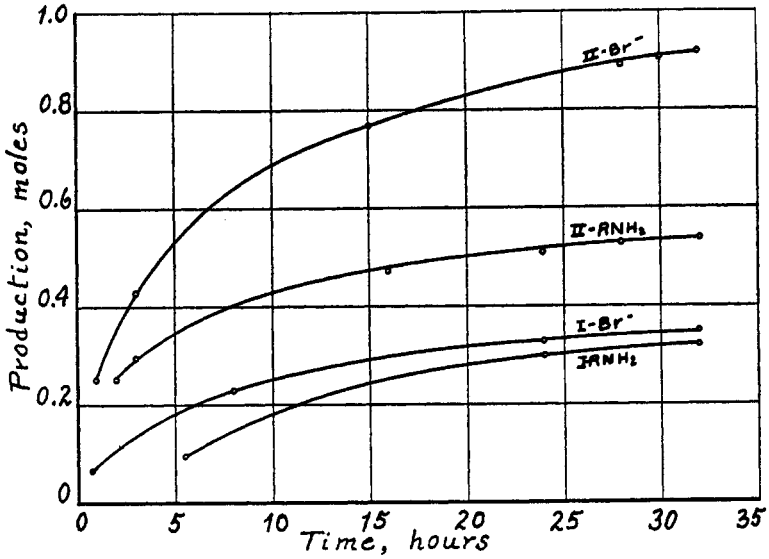

FIG. 10. AMMONOLYSIS OF α-BROMOISOVALERIC ACID

I = Sixty moles of aqueous ammonia at 25°. II = Four moles of ammonium carbonate at 60°.

Curve I, continued from graph

Time, hrs.	Br, moles	RNH_2, moles
75	0.46	0.41
120	.65	.53
264	.92	.76
312	1.00	.82

α-bromobutyric acid; α-bromo-*n*-valeric acid; α-bromoisovaleric acid; and α-bromo-*n*-caproic acid.

Reaction of chloroacetic acid and glycine. A molar solution of chloroacetic acid has a *p*H of 1.55; when it is mixed with an equivalent amount of a molar solution of glycine the extent of the reaction (at 25°) as measured through formation of halide ion and disappearance of glycine is about one per cent, over a period of 360 hours. The *p*H of the mixture is 2.55. When 2.5 moles of sodium hydroxide are added to the mixture, the *p*H changes to 13.6 and the reaction proceeds rapidly. After 24 hours over ninety per cent of the halide ion has been produced and 62–64% of the glycine has reacted.

For rate studies, a molar solution of glycine containing 1.5 moles of sodium hydroxide was placed in a glass-stoppered bottle and immersed in a thermostat at 25° ±

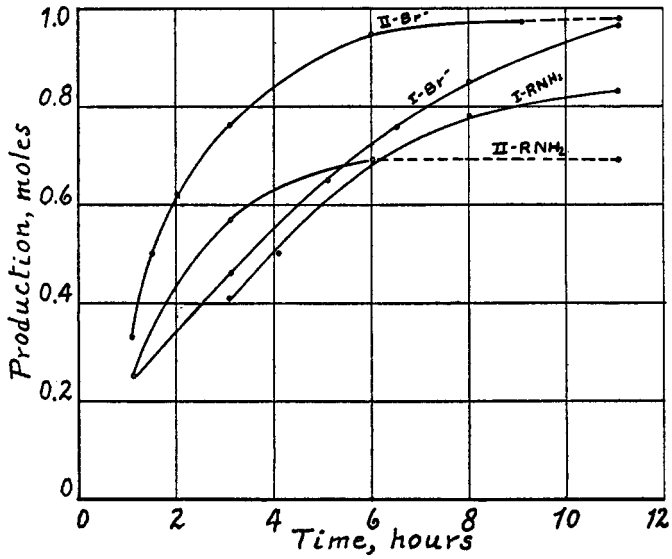

FIG. 11. AMMONOLYSIS OF α-BROMO-*n*-CAPROIC ACID

I = Sixty moles of aqueous ammonia at 25°. II = Four moles of ammonium carbonate at 60°.

.05°. One mole of chloroacetic acid dissolved in water was exactly neutralized at a temperature of 0–5° in order to minimize the hydrolysis of the halogen acid, and then diluted to one liter, and placed in the thermostat. When both solutions reached 25° the chloroacetic acid solution was added rapidly into the bottle containing the amino acid solution, mixed, and samples withdrawn immediately for total halogen, ionic halogen, amino nitrogen, and *p*H determination. At regular intervals samples were withdrawn. Each sample was analyzed for ionic halogen and amino nitrogen as previously described; since there was no ammonia present, the solution was used directly after dilution for amino nitrogen determination. To stop the reaction in the samples withdrawn for analysis, dilute sulfuric acid was added to *p*H 2. Samples for the determination of *p*H were withdrawn at regular intervals and tested directly. For *p*H above 10, the colorimetric method was used exclusively; at *p*H below 10,

determinations were made both by the colorimetric method and a glass electrode. Table XII lists the reaction of glycine and chloroacetic acid in the presence of 2.5 moles of sodium hydroxide at 25°.

In several runs a total of two moles of sodium hydroxide was used, and the solution buffered by the addition of salts. The salt was added to the solution of amino acid and the bottle shaken until the contents were dissolved. In the runs with trisodium phosphate and sodium bicarbonate, a small amount of the salt remained undissolved.

TABLE XII

REACTION OF ONE MOLE OF GLYCINE WITH ONE MOLE OF CHLOROACETIC ACID IN THE PRESENCE OF 2.5 MOLES OF SODIUM HYDROXIDE AT 25°C.

TIME, HRS.	*p*H[a]	HALIDE ION FORMED	GLYCINE REACTED
0.0	13.8	0.1	0.0
0.5	13.8	6.7	2.0
4.0	13.6	35.8	36.0
9.0	13.6	63.0	47.0
16	13.6	80.1	58.0
74	13.6	91.6	64.0
96	13.6	96.3	65.1

[a] Indicator used: sodium indigo sulfonate.

TABLE XIII

REACTION OF ONE MOLE OF GLYCINE WITH ONE MOLE OF CHLOROACETIC ACID IN PRESENCE OF TWO MOLES OF SODIUM HYDROXIDE AND 0.6 MOLES TRISODIUM PHOSPHATE AT 25°C.

TIME, HRS.	*p*H	CHLORIDE ION PRODUCED %	GLYCINE REACTED %
0.0	12.7[a]	0.06	0.00
1.6	12.5[a]	16.80	10.4
3.91	12.2[a]	36.2	28.4
5.91		48.9	38.2
9.0	11.2[a]	62.5	46.6
14.2	10.2[b]	76.5	55.0
23.95	9.8[b]	85.0	60.1
36.5		94.0	62.5
175	9.3[c]	99.5	63.0

[a] Determined by resorcin yellow.
[b] Determined by thymolphthalein.
[c] Determined by phenolphthalein.

Table XIII shows the rate when the solution was buffered by 0.4 mole of trisodium phosphate; table XIV the effect of 1.0 mole of sodium carbonate; table XV the effect of 2.0 moles of sodium bicarbonate; and table XVI the effect of 0.5 mole of sodium dihydrogen phosphate.

The reaction of chloroacetic acid and glycine at *p*H 13.8 to 13.6 and at *p*H 12.7 to 9.3 shows no appreciable difference either in speed or in the total amount of glycine that reacts with the halogen acid. The amino acid is present in the anion form and

TABLE XIV

REACTION OF ONE MOLE OF GLYCINE WITH ONE MOLE OF CHLOROACETIC ACID IN PRESENCE OF TWO MOLES OF SODIUM HYDROXIDE AND ONE MOLE OF SODIUM CARBONATE AT 25°C.

TIME, HRS.	*p*H	CHLORIDE ION PRODUCED %	GLYCINE REACTED %
0.0	12.5[a]	0.05	0.0
2.2	12.3[a]	10.0	4.9
5.67		22.9	15.9
10.01	11.2[b]	38.1	24.8
15.37	10.2[b]	52.0	34.0
24.0	9.8[b]	70.5	46.0
37.5		82.0	50.5
46.25		87.0	53.0
87.5		91.5	53.5
200.0	9.3[c]	99.0	57.0

[a] Determined by resorcin yellow.
[b] Determined by thymolphthalein.
[c] Determined by phenolphthalein.

TABLE XV

REACTION OF ONE MOLE OF GLYCINE WITH ONE MOLE OF CHLOROACETIC ACID IN PRESENCE OF TWO MOLES OF SODIUM HYDROXIDE AND TWO MOLES OF SODIUM BICARBONATE AT 25°C.

TIME, HRS.	*p*H	CHLORIDE ION PRODUCED %	GLYCINE REACTED %
0	9.2	0.0	0.0
24	8.5	5.5	2.5
45	8.5	11.0	6.7
92	8.5	20.5	11.4
188	8.5	34.2	22.9
252	8.4	43.2	26.8
353	8.3	53.2	31.3

TABLE XVI

REACTION OF ONE MOLE OF GLYCINE WITH ONE MOLE OF CHLOROACETIC ACID IN PRESENCE OF TWO MOLES OF SODIUM HYDROXIDE AND 0.5 MOLE OF SODIUM DIHYDROGEN PHOSPHATE AT 25°C.

TIME, HRS.	*p*H	CHLORIDE ION PRODUCED %	GLYCINE REACTED %
0	8.5	0.0	0.0
24	8.3	4.25	3.5
92	7.8	6.7	5.2
188	7.6	11.7	8.7
252	7.2	13.2	9.9
353	7.2	18.0	11.75

reacts fairly rapidly in the initial stage; for each mole of halogen acid 0.64 mole of the total amino acid is used in the reaction. The halogen acid, in addition to the reaction with glycine, reacts partly with the secondary amino compound formed in the reaction, and with hydroxyl ion. The rate at which glycine is used in the reaction follows generally the rate of halide ion formation until about the half-reaction point, when the amino acid reacting drops off sharply. The rate of reaction between chloroacetic acid and glycine in very alkaline solutions can be somewhat diminished by the introduction of carbonate ions into the solution. When sodium carbonate is used in place of trisodium phosphate and the *p*H of the solution is kept about the same value (10 to 12), the rate of reaction drops to about one-half the values obtained with the phosphate buffer. This is assumed to be due to the effect of the carbonate or other ions which unite with the amino group. Increase in the hydrogen ion concentration of the solution, by the addition of sodium bicarbonate or sodium dihydrogen phosphate greatly diminishes the rate of reaction. Between *p*H 8 and 9 the amount of amino acid used in the reaction is about 1×10^{-3} moles per hour and at *p*H 7, 1×10^{-4} moles per hour; these rates are considered negligible. Thus, as the *p*H of the solution approaches the isoelectric point of the amino acid the reaction of the amino group diminishes and finally stops.

PREPARATION OF AMINO ACIDS

Preparation of glycine. Twenty-two hundred grams of ammonium carbonate (30% ammonia), one liter of concentrated aqueous ammonia, and 500 cc. of water are placed in a flask and heated slowly in a water-bath until the temperature reaches 58°. A solution of 500 g. of chloroacetic acid (95%) in 400 cc. of water is added slowly to the ammonia mixture over a period of ten minutes. The temperature of the bath is adjusted so that the reaction mixture does not rise much above 60°, and heated for four hours. The temperature is then raised gradually to 80°, and the ammonia and carbon dioxide are distilled into an absorption flask containing water. The reaction mixture is finally heated over a free flame until the temperature of the solution reaches 112°. Ten grams of charcoal is added and after a few minutes of boiling, the hot solution is filtered with suction. The filtrate (about one liter) is allowed to cool to 70°, then mixed with 3.5 liters of methanol. After 12–24 hours the crude glycine is filtered. The impurities are ammonium chloride and the ammonium salts of the secondary and teritary amino compounds; these are removed by twice suspending the crude glycine for two hours in 1500 cc. of 90% methanol. The solubility of glycine in 99.5% methanol is 0.3%; in 80% methanol, 0.6%; in 80% methanol and in presence of an equivalent amount of ammonium chloride the solubility is increased to 1.38%. The filtered crude glycine contains about 0.2% of ammonium chloride. The yield is 250 to 260 g., or 66 to 69%.

The crude glycine containing about 0.2% of ammonium chloride is easily purified. The amount of glycine obtained above is dissolved in 500 cc. of water by heating nearly to boiling. Ten grams of charcoal is added and the solution is filtered while hot; the glycine is precipitated by addition of 1.2 liters of methanol. After 4 hours the pure amino acid is filtered with suction and washed with three 100-cc. portions of methanol. The dry material is free from chloride and ammonia. The yield is 220–230 g. or 59–61%.

Preparation of glycine at 25°. Ammonium carbonate (350 g.) and 300 cc. of water are warmed to 40–50° for 0.5 hour, then cooled to room temperature and mixed with 400 cc. of concentrated aqueous ammonia. One mole of chloroacetic acid (100 g. of 95%) is added directly over a period of five minutes. The flask is stoppered and

placed aside. After twenty-four hours the mixture is gradually heated to distill the ammonia and carbon dioxide, and then the procedure described is followed. About the same yield is obtained as at 60°.

Preparation of higher amino acids. The higher amino acids are conveniently prepared from the bromo acids by the same general method described for glycine. For alanine, chloropropionic acid may be used, but the reaction requires 36–40 hours for completion at 55–60°; the ratio of halogen acid to ammonia is raised to 1:16. The presence of dihalogen compounds in the higher halogen acids should be avoided as they give rise to impurities which are difficult to eliminate. To illustrate the general method the preparation of α-aminobutyric acid is described.

Ammonium carbonate, 450 g. (8 moles of ammonia) is heated gradually with 140 cc. of water until the temperature reaches 55°. The mixture is shaken and cooled to 40°, and 410 cc. of aqueous ammonia (6 moles) is added. The mixture is allowed to stand for 0.5 hour at 40°, when 167 g. of α-bromobutyric acid is added gradually. The flask is allowed to stand at a temperature of 40–50° for 24 hours, then the ammonia and carbon dioxide are distilled from the water-bath. The solution is then placed in an evaporating dish and concentrated until the amino acid separates out. The mixture is chilled and the crystals of the amino compound are filtered and washed twice with small amounts of methanol. The filtrate is evaporated to about 125 cc. and mixed with 250 cc. of methanol. The second crop of crystals is filtered and purified. The yield of the pure amino acid is 59–62 g. or 57–60%.

SUMMARY

1. The rates of ammonolysis of chloroacetic, bromoacetic, α-chloropropionic, α-bromopropionic, α-bromobutyric, α-bromo-*n*-valeric, α-bromoisovaleric, and α-bromo-*n*-caproic acid were studied at 25° in aqueous ammonia and at 60° in saturated solutions of ammonium carbonate.

2. It has been shown that the ammonolysis of α-halogen acids at 60° with four to six moles of ammonium carbonate yields about the same amount of amino acids as sixty moles of aqueous ammonia at 25°.

3. Studies in the ammonolysis of chloroacetic acid at various temperatures with varying mole ratios of acid to ammonia show that at 25°, 40°, and 50° increase in the concentration of ammonia produces an increase in the formation of glycine; at 60°, 70°, and 100° the effect of increased concentration drops abruptly after a one-to-twelve mole ratio of acid to ammonia has been reached.

4. Studies of the ammonolysis of chloroacetic acid at 25° and a t60° in the presence of various salts show that ammonium salts increase the conversion of the halogen acid to the primary amino compound. Ammonium carbonate gives the maximum effect.

5. Studies of the *p*H of various ammonolytic media, of the composition of ammonium carbonate solutions and of rates between chloroacetic acid and glycine show that the formation of the secondary and tertiary amino compound can be inhibited by lowering the *p*H of the ammonolytic medium and by the formation of an unstable amino acid carbamate.

6. The *p*H and carbamate effects are of general application in ammonolytic reactions; the optimum conditions of the ammonolysis of halogen acids for the preparation of amino acids have been described.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

THE IDENTIFICATION OF SULFONIC ACIDS

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Of the numerous methods which have been suggested for use in the identification of sulfonic acids, none has proved to be generally applicable. Undoubtedly, the method most commonly employed is that involving formation of the sulfonyl chloride followed, where necessary, by conversion to the corresponding amide or anilide (1–4). Aside from the fact that this procedure is somewhat time-consuming, the only serious objection to it is the fact that the formation of the sulfonyl chloride is frequently complicated by the presence of substituent groups which react with phosphorus pentachloride.

Another method to which one finds frequent reference, but which apparently has not been used extensively, involves the formation of aliphatic (5) or aromatic (5–22) amine salts. The success attendant upon the use of this method seems to depend largely upon the purity of the sulfonic acid to be identified. With impure acids, and in some cases with mixtures, oils which are difficult if not impossible to crystallize are commonly encountered.

The microscopic examination of crystalline derivatives has been suggested as a means of identifying certain sulfonic acids. Such properties as index of refraction, crystal habit, etc. have been examined using metal salts (10) as well as amine salts (10, 23), and benzoyl (24) and thiuronium (25) derivatives.

Other possible procedures include the hydrolysis of the acids to the corresponding hydrocarbons or substituted hydrocarbons (1, 2, 26, 27); the replacement of the sulfonic acid group by halogen when the familiar bromine water test is used with phenolsulfonic or aminosulfonic acids (26); and the ebullioscopic method (28).

In 1935 one of us had occasion to make use of the so-called "S-benzylthiuronium chloride" in the formation of solid derivatives of certain xanthates (29), dithio acids (29, 30), and mercaptans (31). At that time, the need for a more satisfactory method for use in the characterization of sulfonic acids was recognized and, since the earlier work of R. F. Chambers and Scherer (32) indicated that the thiuronium chloride might prove to be a reagent of general applicability, a number of derivatives of sulfonic

acids were prepared, purified, and analyzed. While this work was in progress, however, there appeared a paper by Donleavy (33) in which the thiuronium derivatives of thirty-six carboxylic acids and three sulfonic acids were described. Since Donleavy had established priority (34) and had indicated that further work designed to extend the use of this method was planned, the preliminary studies referred to above were discontinued.

In view of the fact that no further reports have been published by Donleavy, and since there have appeared recently from other laboratories a number of publications (35, 36, 37) bearing on the subject, it seemed permissible to resume the study of the original problem. This seemed worth while also in consideration of the fact that published data indicate a lack of agreement in the melting points of a number of these derivatives. The desirability of so doing is further indicated by recent evidence of interest in the use of the thiuronium chloride reagent (38, 39, 40).

An examination of the data published by earlier workers shows that the analytical data frequently fail to agree with calculated values unless it is assumed that the thiuronium derivatives are hydrated. Since the same situation was encountered in the present work, an effort was made to determine whether the presence of water of crystallization could be demonstrated by dehydration. There was also made a preliminary study of the possibility of separating, on the basis of differences in the solubility of their thiuronium derivatives, sulfonic acids (isomeric and otherwise) which appear as products of various sulfonation processes.

EXPERIMENTAL

Preparation of S-benzylthiuronium chloride. The chloride was prepared in substantially quantitative yield by a modification of the method described by Donleavy (33).

One-half mole each of benzyl chloride (63.3 g.) and thiourea (38.0 g.) in 75 cc. of 95% alcohol were warmed under reflux on a steam-bath. An exothermic reaction resulted in complete solution of the thiourea. The pale yellow solution was refluxed for one-half hour, after which the reaction-mixture was cooled in ice-water. The white crystalline solid product was washed onto a Büchner funnel with three 25-cc. portions of cold ethyl acetate, filtered by suction, and dried. Additional crops were obtained from the mother liquor by concentration followed by cooling. In the course of a number of preparations, both the low-melting (140–145°) and high-melting (172–174°) forms (41) were obtained. The former was converted to the high-melting variety upon recrystallization from water, and melted sharply at 174°.[1] In reaction with samples of a particular sulfonic acid, the two forms of the thiuronium chloride lead to derivatives which are identical.

[1] All melting points recorded for purified substances are corrected. Mixed melting point determinations were made in all cases in which the melting point of a sulfonic acid derivative approximated that of either of the two forms of S-benzylthiuronium chloride.

TABLE I

THIURONIUM DERIVATIVES OF SULFONIC ACIDS

ACID	THIURONIUM DERIVATIVE		
	M.P., °C.	Nitrogen	
		Calc'd (%)[a]	Found (%)
Ethylsulfonic	114.7	8.97	8.80
Thymolsulfonic	212.4	6.76 (1 H_2O)	6.57
d-Camphorsulfonic	209.7	6.72 (1 H_2O)	6.67
α-Bromocamphor-α-sulfonic	133.7	5.88	5.84
Benzenesulfonic[b]	147.5–148.5	8.64	8.57
p-Toluenesulfonic[c]	181–182	8.28	8.15
o-Xylenesulfonic	207.6–208.1	7.92	7.98
m-Xylenesulfonic	145.6–146.1	7.92	7.83
p-Xylenesulfonic	183.7	7.92	7.76
m-Nitrobenzenesulfonic	146.1	10.84 (1 H_2O)	10.83
Sulfanilic	184.5–185.0	12.35	12.16
m-Diethylaminobenzenesulfonic	182.4	10.69	10.67
Phenol-*p*-sulfonic	168.7	7.82 (1 H_2O)	7.76
p-Chlorobenzenesulfonic	174.9–175.4	7.45 (1 H_2O)	7.57
m-Benzenedisulfonic	214.3	9.51 (1 H_2O)	9.51
Diphenyl-*p*,*p*'-disulfonic	171.0	7.25 (7 H_2O)	7.25
Anthraquinone-β-sulfonic	211.1	5.94 (1 H_2O)	5.81
α-Naphthalenesulfonic	136.8	7.14 (1 H_2O)	7.23
β-Naphthalenesulfonic	190.5–190.8	7.00 (2 H_2O)	7.01
Naphthalene-2,7-disulfonic	205 (decomp.)	8.53 (2 H_2O)	8.51
1-Naphthylamine-4-sulfonic	195.1 (decomp.)	5.62 (20 H_2O)	5.52
1-Naphthylamine-5-sulfonic	179.4	10.79	10.93
1-Naphthylamine-8-sulfonic[d]	300 (decomp.)	5.62 (20 H_2O)	5.43
N-Phenyl-1-naphthylamine-8-sulfonic	182–189 (decomp.)	7.70 (8 H_2O)	7.58
1-Amino-8-naphthol-3,6-disulfonic[e]	312 (decomp.)	8.08 (2 H_2O)	8.00
2-Naphthylamine-6-sulfonic	330 (decomp.)	7.38 (10 H_2O)	7.27
2-Naphthylamine-4,8-disulfonic	209–211 (decomp.)	10.71 (1 H_2O)	10.62
2-Naphthylamine-6,8-disulfonic	276 (decomp.)	8.98 (8 H_2O)	8.89
1-Naphthol-2-sulfonic	169.4	7.18	7.21
1-Naphthol-4-sulfonic	103.4	8.23 (7 H_2O)[f]	8.25
1-Naphthol-4,8-disulfonic	205.2	8.80	8.70
2-Naphthol-6-sulfonic	206.7	7.18	7.31
2-Naphthol-3,6-disulfonic	233.2	8.80	8.69
Benzothiazole-2-sulfonic[g]	170.5–171.0	11.02	11.01

[a] Unless otherwise indicated the values listed in this column relate to the products to be anticipated as the result of elimination of alkali halide between one or more molecules of S-benzylthiuronium chloride and the alkali salts of acids containing one or more sulfonic acid groups.

[b] Sulfur: Calc'd for $C_{14}H_{16}N_2O_3S_2$, 19.75. Found, 19.87.

[c] Sulfur: Calc'd for $C_{15}H_{18}N_2O_3S_2$, 18.93. Found, 18.60.

[d] The high melting point, low yield obtained, and the analytical value for nitrogen

Preparation of derivatives. In general, the procedure for the preparation of derivatives consisted in dissolving the sulfonic acid in 2 *N* sodium hydroxide solution and neutralizing any excess base with dilute hydrochloric acid. In case the sodium or potassium salt of the acid was available, the salt was dissolved directly in water. In some few cases it was necessary to apply heat in order to effect complete solution. Where the solubility of the alkali salt permitted, the solution was cooled in an ice-bath before addition of the thiuronium chloride.

A quantity of S-benzylthiuronium chloride sufficient to react with the sodium salts formed by all acidic groups present in the molecule of the sulfonic acid was dissolved in water and the resulting solution was cooled in an ice-bath. In the majority of cases, the cold solution of the alkali salt of the acid was added, with stirring, to the thiuronium chloride solution. When, however, no solid product was obtained in this manner, a reversal of the order of addition sometimes resulted in the appearance of a crystalline derivative.

The solid derivatives so prepared were filtered, washed with water, recrystallized (from 50% alcohol) to constant melting point, and analyzed for nitrogen by the Kjeldahl method. Several derivatives were analyzed for sulfur by the Carius method. The data relevant to the derivatives prepared are given in Table I.

In addition to the acids listed in Table I, the following were also used in attempts to prepare satisfactory solid derivatives: *o*-aminophenol-*p*-sulfonic; phenylhydrazine-*p*-sulfonic; 2-amino-8-naphthol-6-sulfonic; 2-naphthylamine-5,7-disulfonic; 1-naphthylamine-3,6,8-trisulfonic; 2-naphthol-8-sulfonic; 1-naphthol-3,8-disulfonic; 2-naphthol-6,8-disulfonic; and 1,8-dihydroxynaphthalene-3,6-disulfonic. In these cases, the products were oils, resinous materials, or substances which decomposed so rapidly that purification of the derivatives was impossible.

Dehydration studies. Small samples of derivatives believed to contain water of crystallization were dried *in vacuo* over sulfuric acid, transferred to small glass-stoppered weighing bottles which had been dried *in vacuo* to constant weight, and subsequently heated in a vacuum oven at 125° and 28–30 mm. Derivatives, the analysis of which indicated no hydration, were heated concurrently as controls. Representative data are given in Table II.

Solubility measurements. The solubilities of a number of derivatives were estimated by determining the quantities of the thiuronium derivatives dissolved by

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all suggest that the unchanged sodium salt of the acid might have been recovered. However, qualitative and fusion tests demonstrated the absence of sodium.

[e] For reasons similar to those given in the preceding footnote, together with the fact that some excess hydrochloric acid was present, there is suggested the possibility that the product obtained might be the hydrochloride of the original aminosulfonic acid. That such is not the case was shown by failure to secure a positive qualitative test for halogen and by the analytical data for sulfur. Sulfur: Calc'd for $C_{13}H_{19}N_3O_7S_3 \cdot 2H_2O$, 18.84. Found, 18.91. Both the analyses for nitrogen and sulfur correspond to the dihydrate of the product which would result from reaction involving only one of the two sulfonic acid groups.

[f] This calculated value assumes the heptahydrate of the product obtained if reaction occurred at both the $-ONa$ and $-SO_3Na$ groups. The analytical data for sulfur, however, do not check with this formulation and the analyses for sulfur and nitrogen do not correspond to any other product which might reasonably be expected. Sulfur: Found, 17.37.

[g] Sulfur: Calc'd for $C_{15}H_{15}N_3O_3S_3$, 25.20. Found, 25.72.

measured volumes of various solvents. Such measurements were made both at room temperature and at temperatures near the boiling points of the solvents. Among the solvents employed were: water, methyl alcohol, ethyl alcohol, diethyl ether, chloroform, carbon tetrachloride, carbon disulfide, dioxane, benzene, toluene, and xylene. The experimental data are too extensive and not sufficiently conclusive to warrant inclusion in this paper.

DISCUSSION

Of the forty-three sulfonic acids used in this study, thirty-four formed crystalline derivatives with S-benzylthiuronium chloride. The physical characteristics of these derivatives are such as to render them useful for purposes of identification.

A careful examination of the data of Table I points to considerable uncertainty as to the composition of certain of these products. For both

TABLE II

RESULTS OF ATTEMPTS TO DEHYDRATE THE THIURONIUM DERIVATIVES OF CERTAIN SULFONIC ACIDS

PARENT ACID	DURATION OF HEATING (HRS.)	APPARENT WATER CONTENT (MOLES)	WATER REMOVED (MOLES)
m-Xylenesulfonic	96	0	0.07
1-Naphthol-4,8-disulfonic	72	0	0.03
m-Benzenedisulfonic	72	1	0.30
Naphthalene-2,7-disulfonic	48	2	0.55
Diphenyl-p,p'-disulfonic	96	7	0.89
1-Naphthol-4-sulfonic	96	10	0.20
2-Naphthylamine-6-sulfonic	96	20	0.66

metal and amine salts of sulfonic acids, earlier workers have demonstrated (10, 13) the presence of water of crystallization to the extent indicated by analyses for nitrogen, while with but two exceptions (32, 35), those who have reported on the thiuronium derivatives have merely assumed the presence of water. In the present work, the behavior of the derivatives during melting point determinations failed to suggest that these compounds were hydrated. Hydration is indicated, however, by the analytical data, since it seems unlikely that, for a considerable number of these substances, good agreement between the experimental values and those calculated assuming hydration is coincidental. On the other hand, it is indeed difficult to believe that there should be formed hydrates of sufficient stability to resist the rather extreme conditions used in the dehydration experiments. Accordingly, it is felt that where the analytical data suggest an abnormally high degree of hydration, there exists a reasonable doubt as to the nature of the solid derivative obtained. It should be recognized,

however, that a reproducible solid derivative may be useful for analytical purposes even though its composition and structure may be unknown.

Also questionable is the composition of the derivative of 1-naphthol-4-sulfonic acid. Analytical data for nitrogen and sulfur are incompatible and there is no ready explanation why in this case alone a reaction should occur between the sodium naphtholate and the thiuronium chloride. Nevertheless, this derivative is reproducible.

Several of the derivatives reported in this paper have been prepared by earlier workers and there has been some duplication among previously published data. In order to compare results published thus far, certain sulfonic acids and the reported melting points of their thiuronium deriva-

TABLE III

COMPARISON OF MELTING POINTS REPORTED FOR CERTAIN THIURONIUM DERIVATIVES

PARENT ACID	M.P., °C.
α-Naphthalenesulfonic	136–137* (32), 136.8, 138 (25)
m-Nitrobenzenesulfonic	140 (33), 146.1
Benzenesulfonic	144 (33), 147.5–148.5, 148–149* (35)
p-Toluenesulfonic	170 (33), 181–182, 182–183* (35)
p-Aminobenzenesulfonic	184.5–185, 187–188* (35)
β-Naphthalenesulfonic	188–189* (32), 190.5–190.8, 193 (25)
Naphthalene-2,7-disulfonic	199–200* (decomp.) (32), 205 (decomp.), 211–212 (decomp.) (25)
Naphthalene-1,6-disulfonic	234–235* (decomp.) (32), decomp. above 81 (25)
Naphthalene-1,5-disulfonic	244–245* (32), 251 (25)
Naphthalene-2,6-disulfonic	256 (25), 258* (32)

tives are assembled in Table III. Where no literature reference is given, the value reported is that found in the present investigation. Melting points marked with an asterisk are uncorrected.

While otherwise in fairly good agreement, these data show that the melting points reported by Donleavy (33) are uniformly several degrees low. Veibel and co-workers (35, 36) found the same to be true for melting points recorded by Donleavy for thiuronium derivatives of carboxylic acids. In general, the data recorded in this paper are in good agreement with those of Veibel and Lillelund (35).

The advantages peculiar to this method for the identification of sulfonic acids have been outlined elsewhere (33, 35) in a wholly adequate manner and need not be repeated here. Our experience indicates that the method is satisfactory for mono- and di-sulfonic acids if other functional groups are absent. The presence of phenolic or amino groups reduces, but does

not preclude, the possibility of securing a satisfactory solid derivative. The presence of the amino group is particularly disadvantageous in the naphthalene sulfonic acids. An advantage not common to the formation of amine salts lies in the fact that satisfactory thiuronium derivatives may be formed using relatively impure sulfonic acids. The frequent production of the decidedly offensive odor of benzylmercaptan resulting from the decomposition of the thiuronium chloride may, to some, constitute a serious objection to the method. Although Veibel and Lillelund (35) claim that the formation of benzylmercaptan can be prevented, we would prefer to state that the technique employed by them tends to, but does not wholly, overcome the difficulty.

Finally, it should be pointed out that the studies on the relative solubilities of these derivatives were of an exploratory character. It was found, however, that certain separations may be made. For example, it appears that the isomeric xylenesulfonic acids may be separated by use of appropriate organic solvents. Similar separations seem possible with the α- and β-naphthalenesulfonic acids and with the products obtained upon sulfonation of β-naphthol.

SUMMARY

1. The use of S-benzylthiuronium chloride in the identification of sulfonic acids has been investigated, and the melting points of solid derivatives of thirty-four sulfonic acids have been recorded.

2. The results of this study have been compared with those of earlier workers, and certain limitations on the usefulness of the method have been discussed.

AUSTIN, TEX.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

PREPARATION OF SOME AMINO KETONES AND AMINO ALCOHOLS CONTAINING THE ac-TETRAHYDRO-β-NAPHTHYLAMINE, TETRAHYDROISOQUINOLINE, OR β-PHENYLETHYLAMINE NUCLEUS

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Among the general conclusions which have been drawn from the published work on adrenaline, ephedrine, and related compounds (1), is the fact that substitution on the side chain nitrogen atom markedly affects the vasopressor activity of the resulting compound. Thus, the substitution of alkyl radicals larger than the methyl group definitely has been shown to reduce or even destroy pressor action. The same may be said for the substitution of aryl radicals. In spite of the large volume of published work in this field, there appeared to be ample reasons for continuing research along these lines. For example, no one has attempted to substitute a radical on the side chain nitrogen which in itself might, when attached to nitrogen, exert a definite pressor activity. Such a substituent might be expected to augment rather than decrease pressor activity. To test this possibility α-bromoacetophenone, α-bromopropiophenone, α-chloro-*p*-hydroxyacetophenone, α-bromo-β-acetonaphthone, phenylethyl bromide, and phenoxyethyl bromide were condensed with ac-tetrahydro-β-naphthylamine, tetrahydroisoquinoline, and phenylethylamine. The amino ketones were then reduced to the corresponding amino alcohols. ac-Tetrahydro-β-naphthylamine and phenylethylamine are known to exert pressor action. The same cannot be said for tetrahydroisoquinoline. It was included, however, for structural reasons, for like the naphthylamine derivative it may be regarded as a derivative of phenylethylamine. The phenoxyethyl derivatives were prepared not so much expecting potent pressor compounds as to test a generalization. It has often been stated that in the series of pressor compounds it is necessary that the nitrogen atom be attached to the second carbon atom in the side chain, relative to the aromatic ring. Fourneau (2) has shown recently that N-phenylethylenediamine was as active as β-phenylethylamine. This appeared to indicate that a third atom in the side chain, between the ring and the nitrogen atom, did not necessarily reduce pressor activity, providing it was some element other than carbon.

Another aspect of this work also appeared to be of interest. Many attempts have been made to prepare compounds possessing both pressor action and local anesthetic action (1). This has been done in most cases by preparing O-benzoates of amino alcohols of the type $ArCHOHCH_2NH_2 \cdot HCl$. In general, benzoylation did produce local anesthetics, but the pressor activity was either greatly diminished or entirely destroyed. It appeared obvious therefore that anesthetic activity must be introduced in some other manner. Kanao (3) has shown that alcohols of the above type acquire local anesthetic activity when alkyl radicals of higher molecular weight are attached to the nitrogen atom. This suggested that the amino alcohols prepared in the course of this work might possess a similar activity.

The pharmacological tests on these compounds have not been completed. However the tests that have been made indicate that the purposes of this work have been realized to some extent. Both 1-phenyl-2-ac-tetrahydro-β-naphthylaminoethanol hydrochloride (II) and 1-phenyl-2-ac-tetrahydro-β-naphthylaminopropanol hydrochloride (V) in 0.5% solution produced anesthesia of longer duration than did 1% cocaine solution on rabbit's cornea. 1-*p*-Hydroxyphenyl-2-ac-tetrahydro-β-naphthylaminoethanol hydrochloride (XII) and 1-phenyl-2-tetrahydroisoquinolinoethanol hydrochloride (XV) were somewhat less efficient than cocaine. 1-Phenyl-2-tetrahydroisoquinolinoethane hydrochloride (XXII) and 1-*p*-hydroxyphenyl-2-tetrahydroisoquinolinoethanol hydrochloride (XXIV) showed no anesthetic activity.

Compounds II, V, XV, and XXII are reported as being slightly irritating, XXIV as irritating, and XII as producing severe irritation. Since only six compounds have been tested it was not possible to draw any general conclusions, but certain facts are indicated. The presence of a phenolic hydroxyl group decreased the activity in one case (XII) and in another case (XXIV) completely destroyed it. The presence of this group also increased the irritating action of the compounds XII and XXIV. It is also significant that compound XXII, which showed no anesthetic activity, differs from XV only in the absence of the side chain hydroxyl group.

Only two of the compounds have been tested for toxicity. Compound II was more toxic to mice than cocaine while V was less toxic than cocaine. Only one compound has been tested for pressor activity. Compound II in doses of 3–5 mg. (injection in cats) produced a rise in pressure of 30 mm. of mercury. Repeated dosages produced the same rise.

These tests were made possible through the courtesy of the Merck Therapeutic Institute.

EXPERIMENTAL

Analysis. The semi-micro Kjeldahl and the semi-micro Dumas methods were used for the determination of nitrogen. The distillate in the Kjeldahl method was absorbed in 4% boric acid solution and titrated to a methyl red end-point (4). The Volhard and gravimetric methods were used for the determination of chlorine.

α-Bromoacetophenone. The product used was prepared according to the method of Rubin and Day (5).

α-Bromopropiophenone. This was prepared by a method similar to that employed by Schmidt (6). [See also Rubin and Day (5).]

α-Chloro-p-*hydroxyacetophenone.* This was prepared according to Tutin, Caton, and Hann (7) using ligroin, however, instead of carbon disulfide as the solvent. The successful preparation of this compound depended upon careful attention to details of the method used. Hence its preparation is described in detail. Thirty grams (0.277 mole) of anisole and 36 g. (0.318 mole) of chloroacetyl chloride were dissolved in 500 cc. of ligroin. To the rapidly stirred solution, 45 g. (0.336 mole) of anhydrous aluminum chloride was added in small portions at 2–3 minute intervals over a period of 35 minutes. The mixture was heated at 35° for one hour and then 45 g. (0.336 mole) more of aluminum chloride was added in approximately 30 minutes. The resulting mixture was heated for two and one-half hours. The mixture gradually became so viscous that it could no longer be stirred. At the end of the heating period the remaining solvent was removed by distillation. The resulting mass was cooled and decomposed by the addition of ice over a period of thirty minutes. The solid was broken up as much as possible during the addition of the ice and then complete decomposition of the complex was accomplished by slowly adding 200 cc. of concentrated hydrochloric acid. The resulting dark violet solution was cooled and extracted with three 250-cc. portions of ether. The ether extracts were combined and treated with a 200-cc. portion of 5% ammonium carbonate solution to eliminate the excess acid. After removal of the aqueous layer, the ether layer was extracted with five 250-cc. portions of 10% sodium carbonate solution. Acidification of the sodium carbonate extracts, after treatment with charcoal, yielded a crude product which was rather darkly colored. This, upon crystallization from 75% alcohol, yielded 21 g. (44%) of a light yellow product, melting at 148° (corr.).

α-Bromo-β-acetonaphthone. This was prepared according to the method of Immediata and Day (8).

β-Phenoxyethyl bromide. This was prepared essentially according to Bentley, Haworth, and Perkins (9). The product used boiled at 144° (40 mm.) and melted at 35° (corr.).

ac-Tetrahydro-β-naphthylamine hydrochloride. This was prepared according to the method of Organic Syntheses (10) with a slight modification. It was found that the crude hydrochloride from this method could be obtained almost colorless by shaking with 150–200 cc. of ether in the cold.

1,2,3,4-Tetrahydroisoquinoline hydrochloride. This was prepared similarly to the method of Bamberger and Dieckmann (11). This consisted in treating a solution of isoquinoline in absolute alcohol with sodium. The product was isolated as the hydrochloride. The yields were 70–72%, m.p. 195–196° (corr.). Due to the nature of the source of the isoquinoline, it seemed altogether probable that the product might be contaminated with its isomer, tetrahydroquinoline hydrochloride. To determine this, the following method of purification was adopted. The hydrochloride from above was dissolved in water, the free base liberated by an excess of sodium hydroxide solution, and then extracted with ether. After drying the ether solution over sodium

hydroxide pellets, it was chilled and a rapid stream of moist carbon dioxide was passed through it. This process precipitated the carbonate of the more basic tetrahydroisoquinoline. This was removed by filtration, washed with ether, dissolved in 10% acetic acid, and the free base was liberated by an excess of sodium hydroxide solution. It was extracted with ether, dried over sodium hydroxide pellets, and then dry hydrogen chloride gas was passed over the surface of the ether solution. The tetrahydroisoquinoline hydrochloride was filtered, washed with ether, and dried. The melting point of this product compared favorably with that of the first product 195–196° (corr.).

β-Phenylethylamine hydrochloride. This was prepared by the sodium-ethyl alcohol reduction of phenylacetonitrile according to the method of Johnson and Guest (12).

Preparation of the amino ketones. These compounds were prepared from the α-halogen substituted ketones and the amines just described. Two equivalents of the amine were allowed to react with one equivalent of the halogenated compound in dry alcohol or ether solution. The reaction-mixtures were allowed to stand for a definite period of time. Ether was added and the amine salts which settled out were removed by filtration and washed with dry ether. A stream of dry hydrogen chloride was then passed over the surface of the cold ether filtrates. An excess of the gas must be avoided and the solutions should be stirred or shaken during the treatment. The precipitated hydrochlorides were washed with ether and recrystallized from alcohol and ether.

The free bases were prepared by treating solutions of the hydrochlorides in dilute alcohol with a 5% solution of sodium bicarbonate. The mixtures were stirred and allowed to stand in the cold overnight. The filtered products were then recrystallized from dilute alcohol.

The oximes were prepared from the amino ketone hydrochlorides in the usual manner and recrystallized from dilute alcohol.

Preparation of the amino-alcohols. They were prepared from the corresponding amino ketone hydrochlorides by catalytic hydrogenation, usually employing a ten per cent palladium on charcoal catalyst. Solutions of the hydrochlorides in 95% alcohol were shaken in an atmosphere of hydrogen, in an apparatus similar to that of Shaefer (13), until the calculated volume of hydrogen had been absorbed. The mixtures were then heated to boiling and the catalyst removed by filtration. In some cases it was necessary to extract the catalyst with hot alcohol to remove the adsorbed product. The alcoholic filtrates were concentrated to 50–100 cc., ether added and the mixtures were allowed to stand in the cold for several hours to complete the precipitation of the amino alcohol hydrochlorides. The latter were usually recrystallized from alcohol and ether. The free bases, in most cases, were prepared by the method used to obtain the free bases of the amino ketones.

Preparation of the esters. Suspensions of the amino alcohol hydrochlorides in excess benzoyl chloride were heated in an oil-bath. The temperature and time of heating were important factors and varied considerably depending on the amino alcohol used. After cooling to room temperature, the residues were shaken with 100 cc. of dry ether and allowed to stand overnight in the cold. The ether layer was decanted and another 100 cc. of dry ether was added to the residue. When this mixture was allowed to stand overnight in the cold the ester hydrochlorides usually crystallized. The crude products were recrystallized from dry alcohol by the addition of small amounts of ether. The free bases were prepared by the method previously described.

Preparation of β-phenoxyethylamine and β-phenylethylamine derivatives. Solutions

containing two equivalents of the amine and one equivalent of β-phenoxyethyl bromide or β-phenylethyl bromide in absolute alcohol were heated at 65-80°. The solutions were cooled to 10° and 50–100 cc. of dry ether added. After standing for several hours in the cold the amine hydrochlorides were removed by filtration and the filtrates were treated with dry hydrogen chloride. The crude hydrochlorides were then recrystallized from alcohol and ether. The free bases were obtained by the method previously described.

The analytical results and melting points for the new compounds are included in Tables I, II and III.

I. *α-ac-Tetrahydro-β-naphthylaminoacetophenone hydrochloride.* ac-Tetrahydro-β-naphthylamine (7.94 g., 0.054 mole) was dissolved in 150 cc. of dry ether. To this solution of the amine, 5.4 g. (0.027 mole) of α-bromoacetophenone was added in small portions, shaking after each addition until all went into solution. The reaction-mixture was allowed to stand at room temperature for three hours. If allowed to stand longer than five hours the solution became red and the product was hard to purify. After separating the ac-tetrahydro-β-naphthylamine hydrobromide, the hydrochloride of the condensation product was isolated from the filtrate and recrystallized from alcohol. If any red coloration was apparent, the hydrochloride was first washed with 50 cc. of acetone and then recrystallized from alcohol; yield 42%.

The free base of this compound, which was obtained only as an impure oil, was identified as its oxime. The latter was obtained as white prisms by recrystallization from 50% alcohol, m.p. 120° (corr.).

Anal. Calc'd for $C_{18}H_{20}N_2O$:N, 10.37. Found: N, 10.17.

II. *1-Phenyl-2-ac-tetrahydro-β-naphthylaminoethanol-1 hydrochloride.* Five grams (0.016 mole) of the amino ketone hydrochloride (I) was dissolved in 175 cc. of warm alcohol and reduced according to the general method; yield 90%. The product was recrystallized from alcohol and ether. The free base was obtained by the general procedure.

III. *1-Phenyl-2-ac-tetrahydro-β-naphthylaminoethanol-1 benzoate hydrochloride.* Three grams (0.0099 mole) of compound II and 10 cc. (0.072 mole) of benzoyl chloride were heated in an oil-bath for three hours at 105°; yield 67%. The free base was prepared by the general method.

IV. *α-ac-Tetrahydro-β-naphthylaminopropiophenone hydrochloride.* To a dry ether solution containing 7.94 g. (0.054 mole) of ac-tetrahydro-β-naphthylamine was added 5.8 g. (0.027 mole) of α-bromopropiophenone. The reaction-mixture was allowed to stand for twelve days at room temperature during which time crystals of ac-tetrahydro-β-naphthylamine hydrobromide separated. When the theoretical amount of the amine hydrobromide was recovered, the chilled ether filtrate was treated with dry hydrogen chloride. During the passage of this gas over the surface of the solution, the contents of the flask were shaken constantly to retard the formation of a gummy material. The hydrochloride which separated was treated with 30 cc. of warm acetone to remove the greater part of the red color from the product. After two recrystallizations from alcohol and ether, a white crystalline product was obtained; yield 43%.

The free base, prepared by the general method, was removed by filtration as soon as possible and dried in a vacuum desiccator. The product was a white, hygroscopic material which turned dark very quickly in the air.

The oxime was prepared from the hydrochloride in the usual manner and recrystallized from 50% alcohol; colorless prisms, m.p. 137° (corr.).

Anal. Calc'd for $C_{19}H_{22}N_2O$: N, 9.52. Found: N, 9.39.

V. *1-Phenyl-2-ac-tetrahydro-β-naphthylaminopropanol-1 hydrochloride.* This compound was prepared from the corresponding amino ketone hydrochloride by the procedure used for compound II, except that 20% palladium on charcoal was used as the catalyst. The time of the reduction was seven hours. After filtration, the catalyst was extracted with 50 cc. of boiling alcohol. The extract was added to the main alcoholic filtrate and concentrated to about 75 cc. Careful addition of 35 cc. of ether caused the product to precipitate in crystalline form; yield 96%. The free base was obtained by the general procedure.

VI. *1-Phenyl-2-ac-tetrahydro-β-naphthylaminopropanol-1 benzoate hydrochloride.* The ester hydrochloride was prepared by the method described for compound III, except that the mixture was heated at 105° for six hours. The mixture was cooled to 15° and 100 cc. of dry ether slowly added. After standing overnight in the ice-box, the ether layer was decanted and another portion (100 cc.) of dry ether was added and shaken vigorously. The ether was again decanted and a third portion of ether was added. This was allowed to stand for two weeks in the ice-box before the oily residue finally crystallized. The crude product was recrystallized from absolute alcohol by the addition of dry ether; yield 23%. The free base was obtained in the usual manner.

VII. *α-ac-Tetrahydro-β-naphthylamino-β-acetonaphthone hydrochloride.* This compound was prepared from ac-tetrahydro-β-naphthylamine and α-bromo-β-acetonaphthone by the method described for compound I. The crude hydrochloride was washed with dry ether and recrystallized from 65% alcohol; yield 38%.

The free base was obtained by the general method except that the reaction-mixture was allowed to stand at room temperature for one hour. Longer standing resulted in the formation of a gummy material. The compound was obtained as light yellow needles by recrystallization from warm 95% alcohol.

The oxime, prepared as before, was recrystallized from 60% alcohol, m.p. 145° (corr.).

Anal. Calc'd for $C_{22}H_{22}N_2O$: N, 8.48. Found: N, 8.50.

VIII. *1-β-Naphthyl-2-ac-tetrahydro-β-naphthylaminoethanol-1 hydrochloride.* Due to the insolubility of the corresponding amino ketone hydrochloride, only small quantities of it were reduced at one time. Two grams (0.008 mole) was dissolved in 250 cc. of boiling 80% alcohol. This solution was poured into a previously warmed reduction flask and the catalyst, 10% palladium on charcoal, added. The reduction was carried out at 60°, otherwise the procedure was the same as that used for compound II. The product was recrystallized from alcohol and ether; yield 86%.

The free base was prepared by adding the minimum amount of 50% sodium hydroxide solution to a solution of the hydrochloride in 50% alcohol and the mixture allowed to stand in the ice-box overnight. The base was recrystallized from absolute alcohol by the very slow addition of water.

IX. *1-β-Naphthyl-2-ac-tetrahydro-β-naphthylaminoethanol-1 benzoate hydrochloride.* The general method was used with the exception that the reaction-mixture, consisting of 0.0056 mole of the amino alcohol hydrochloride and 0.123 mole of benzoyl chloride, was heated at 114° for two hours. After cooling, 100 cc. of dry ether was added and the reaction-mixture allowed to stand cold overnight. The ether layer was decanted and the gummy residue washed with 50 cc. of dry ether, and then dissolved in 25 cc. of boiling alcohol. When cold, 25 cc. of dry ether was added, and after standing overnight in the ice-box, the desired product crystallized. It was recrystallized from alcohol and ether; yield 40%. The free base, obtained in the usual manner, was recrystallized from alcohol.

TABLE I

DERIVATIVES OF ac-TETRAHYDRO-β-NAPHTHYLAMINE

NO.	FORMULA	M.P. °C (CORR.)	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
				Calc'd	Found	Calc'd	Found
I	$C_6H_5COCH_2NHC_{10}H_{11}\cdot HCl$	197–199	$C_{18}H_{20}ClNO$	4.64	4.60	11.75	11.69
II	$C_6H_5CHOHCH_2NHC_{10}H_{11}\cdot HCl$	212–213	$C_{18}H_{22}ClNO$	4.61	4.52	11.67	11.75
	$C_6H_5CHOHCH_2NHC_{10}H_{11}$	78.5	$C_{18}H_{21}NO$	5.24	5.16		
III	$C_6H_5CHCH_2NHC_{10}H_{11}\cdot HCl$ (OCOC$_6$H$_5$)	174–175	$C_{25}H_{26}ClNO_2$	3.43	3.36	8.70	8.65
	$C_6H_5CHCH_2NHC_{10}H_{11}$ (OCOC$_6$H$_5$)	68.5	$C_{25}H_{25}NO_2$	3.77	3.67		
IV	$C_6H_5COCH(CH_3)NHC_{10}H_{11}\cdot HCl$	199–200 decomp.	$C_{19}H_{22}ClNO$	4.44	4.37	11.23	11.36
	$C_6H_5COCH(CH_3)HNC_{10}H_{11}$	40–41	$C_{19}H_{21}NO$	5.01	4.86		
V	$C_6H_5CHOHCH(CH_3)NHC_{10}H_{11}\cdot HCl$	206–208	$C_{19}H_{24}ClNO$	4.41	4.27	11.16	11.03
	$C_6H_5CHOHCH(CH_3)NHC_{10}H_{11}$	69.5–70	$C_{19}H_{23}NO$	4.98	4.89		
VI	$C_6H_5CHCH(CH_3)NHC_{10}H_{11}\cdot HCl$ (OCOC$_6$H$_5$)	139.5–141	$C_{26}H_{28}ClNO_2$	3.21	3.25	8.14	8.20
	$C_6H_5CHCH(CH_3)NHC_{10}H_{11}$ (OCOC$_6$H$_5$)	58.5–59.5	$C_{26}H_{27}NO_2$	3.51	3.49		

VII	$C_{10}H_7COCH_2NHC_{10}H_{11}\cdot HCl$	170 decomp.	$C_{22}H_{22}ClNO$	3.98	3.81	10.08	9.98
	$C_{10}H_7COCH_2NHC_{10}H_{11}$	84.5–85.5	$C_{22}H_{21}NO$	4.44	4.32		
VIII	$C_{10}H_7CHOHCH_2NHC_{10}H_{11}\cdot HCl$	211–12	$C_{22}H_{24}ClNO$	3.96	3.91	10.03	9.93
	$C_{10}H_7CHOHCH_2NHC_{10}H_{11}$	93.5	$C_{22}H_{23}NO$	4.42	4.31		
IX	$C_{10}H_7CHCH_2NHC_{10}H_{11}\cdot HCl$ $\quad\quad\vert$ $\quad OCOC_6H_5$	201.5–203	$C_{29}H_{28}ClNO_2$	3.06	3.09	7.75	7.59
	$C_{10}H_7CHCH_2NHC_{10}H_{11}$ $\quad\quad\vert$ $\quad OCOC_6H_5$	101.5	$C_{29}H_{27}NO_2$	3.32	3.23		
X	$C_6H_5CH_2CH_2NHC_{10}H_{11}\cdot HCl$	245–246.5	$C_{18}H_{22}ClN$	4.87	4.69	12.33	12.26
XI	p-$HOC_6H_4COCH_2NHC_{10}H_{11}\cdot HCl$	221	$C_{18}H_{20}ClNO_2$	4.41	4.27	11.17	11.29
	p-$HOC_6H_4COCH_2NHC_{10}H_{11}$	117–118	$C_{18}H_{19}NO_2$	4.98	4.90		
XII	p-$HOC_6H_4CHOHCH_2NHC_{10}H_{11}\cdot HCl$	198–199.5	$C_{18}H_{22}ClNO_2$	4.38	4.26	11.09	11.01
	p-$HOC_6H_4CHOHCH_2NHC_{10}H_{11}$	173–175	$C_{18}H_{21}NO_2$	4.95	4.79		
XIII	$C_6H_5OCH_2CH_2NHC_{10}H_{11}\cdot HCl$	226–8	$C_{18}H_{22}ClNO$	4.62	4.61	11.68	11.75

X. *1-Phenyl-2-ac-tetrahydro-β-naphthylaminoethane hydrochloride.* A solution of 4.12 g. (0.028 mole) of ac-tetrahydro-β-naphthylamine and 2.5 g. (0.014 mole) of phenylethyl bromide in 25 cc. of absolute alcohol was refluxed for four hours; yield 65%. Attempts to prepare the free base resulted only in the isolation of an oil, which could not be purified.

XI. *α-ac-Tetrahydro-β-naphthylamino-*p*-hydroxyacetophenone hydrochloride.* To a suspension of 4.8 g. (0.027 mole) of α-chloro-*p*-hydroxyacetophenone in 10 cc. of absolute alcohol, was added 7.94 g. (0.054 mole) of ac-tetrahydro-β-naphthylamine. The mixture was stirred until all went into solution. A small amount of heat was evolved and the solution became red. The reaction-mixture was allowed to stand for six hours at room temperature. Seventy-five cubic centimeters of ether was added with stirring, and after cooling for one hour, the precipitated amine salt was removed by filtration. The slightly red hydrochloride isolated from the filtrate was washed with ether and recrystallized from 125 cc. of alcohol and a small amount of ether; yield 15%. The free base, obtained in the usual manner, was recrystallized from 95% alcohol.

Although several methods were used to obtain the oxime, none of the trials were successful. In each case the free base was isolated. Attempts to obtain the semicarbazone were also unsuccessful.

XII. *1-*p*-Hydroxyphenyl-2-ac-tetrahydro-β-naphthylaminoethanol-1 hydrochloride.* The amino ketone hydrochloride, XI, was reduced in the usual manner, in the presence of a 10% palladium-charcoal catalyst. The product was recrystallized from alcohol; yield almost quantitative. The free base was prepared in the same way as the free base of the corresponding ketone. It crystallized as white cubic crystals.

XIII. *1-Phenoxy-2-ac-tetrahydro-β-naphthylaminoethane hydrochloride.* A solution of 4.9 g. (0.023 mole) of β-phenoxyethyl bromide in 10 cc. of absolute alcohol was added to 0.048 mole of ac-tetrahydro-β-naphthylamine. This reaction-mixture was heated for two and one-half hours at 70°, after which it was cooled to 15° and 100 cc. of ether added. The product was washed with ether and recrystallized from alcohol; yield 54%. The free base could be obtained only as an impure oil.

XIV. *α-Tetrahydroisoquinolinoacetophenone hydrochloride.* Tetrahydroisoquinoline (7.85 g., 0.059 mole) was dissolved in 150 cc. of dry ether. To the cold ether solution 5.8 g. (0.028 mole) of α-bromoacetophenone was slowly added with shaking. A precipitate began to form almost immediately, and the reaction proceeded with the evolution of heat. The reaction-mixture was allowed to stand at room temperature for one hour with occasional shaking, and the tetrahydroisoquinoline hydrobromide was removed by filtration. The ether filtrate was cooled and a slow current of dry hydrogen chloride gas was passed over the surface of the solution. A mixture of oil and solid was precipitated. The ether was decanted and the residual mass was washed with two 35-cc. portions of dry ether. Fifty cubic centimeters of dry ether was added and the mixture allowed to stand overnight in the ice-box to crystallize. The crude product was washed with ether and purified by dissolving in warm alcohol, cooling, and adding a small amount of ether; colorless leaflets, yield 75%.

The free base was obtained by adding 5% sodium bicarbonate solution to a solution of the hydrochloride in 50% alcohol. After standing in the cold for one hour, the product was filtered and recrystallized from alcohol. The pure product turned yellow in the air, m.p. 63.5-64.5° (corr.). This compound has been previously prepared and reported as melting at 100–101° (14).

The oxime was prepared from the hydrochloride in the usual manner. The crude product was recrystallized from 50% alcohol, m.p. 136.5° (corr.).

Anal. Calc'd for $C_{17}H_{18}N_2O$: N, 10.53. Found: N, 10.47.

XV. *1-Phenyl-2-tetrahydroisoquinolinoethanol-1 hydrochloride.* This compound was prepared by the hydrogenation of the amino ketone hydrochloride, in 95% alcohol, in the presence of a 10% palladium on charcoal catalyst. The reaction was slow, fifty hours being required for the reduction of 0.0417 mole; colorless plates, yield 91%. The free base was obtained by the general procedure.

XVI. *1-Phenyl-2-tetrahydroisoquinolinoethanol-1 benzoate hydrochloride.* Three grams (0.008 mole) of the amino alcohol hydrochloride was suspended in 10 cc. (0.072 mole) of benzoyl chloride and heated under reflux, gradually raising the temperature over a period of three hours to 118°, and then heating three additional hours at this temperature. The product was isolated and purified according to the general method; colorless needles, yield 88%. The free base was prepared in the usual manner.

XVII. *α-Tetrahydroisoquinolinopropiophenone hydrochloride.* To a dry ether solution containing 7.85 g. (0.059 mole) of tetrahydroisoquinoline was added 6.2 g. (0.0287 mole) of α-bromopropiophenone, and the solution was refluxed for fifteen hours. The product was recrystallized by adding dry ether to its solution in cold absolute alcohol and allowing the mixture to stand in the cold for twenty-four hours; yield 89%.

The free base was obtained by the same procedure used for the base of compound XIV. It was recrystallized from alcohol and water and obtained as white prisms which turned yellow in the air.

The oxime, prepared from the hydrochloride, was recrystallized from 65% alcohol, by dissolving the crude product at 40–50° and allowing the solution to stand for three days at 10°; colorless needles, m.p. 63° (corr.).

Anal. Calc'd for $C_{18}H_{20}N_2O$: N, 10.00. Found: N, 10.18.

XVIII. *1-Phenyl-2-tetrahydroisoquinolinopropanol-1 hydrochloride.* The amino ketone hydrochloride (XVII) in 95% alcohol was hydrogenated in the Adams reduction apparatus (15), using 10% palladium on charcoal as the catalyst, under an initial pressure of 38 pounds. The solution was heated to boiling and the catalyst was removed. The catalyst was then extracted twice with 150-cc. portions of boiling alcohol. The combined alcohol filtrates were concentrated, cooled, and the crystallization of the hydrochloride completed by the addition of a little ether. It was recrystallized from alcohol.

The free base was prepared in a manner similar to that used for the preparation of the amino ketone free base. It was recrystallized from alcohol and water. Attempts to benzoylate this alcohol were unsuccessful, although several methods were tried.

XIX. *α-Tetrahydroisoquinolino-β-acetonaphthone hydrochloride.* To a cold, dry ether solution containing 7.85 g. (0.059 mole) of tetrahydroisoquinoline, 7.4 g. (0.0295 mole) of α-bromo-β-acetonaphthone was slowly added. After shaking thoroughly for fifteen minutes, the reaction-mixture was allowed to stand for one-half hour at room temperature, after which the precipitated tetrahydroisoquinoline hydrobromide was removed by filtration and washed with ether. It was noted that if the reaction-mixture was allowed to stand too long before filtering, the yields of condensation product were decreased. The cold ether filtrate was treated with dry hydrogen chloride and the precipitated hydrochloride was recrystallized from alcohol; white hygroscopic plates, yield 50%.

The free base was obtained by adding an excess of 20% sodium hydroxide solution to a solution of the hydrochloride in 50% alcohol. After standing cold, the base was removed by filtration and recrystallized from warm alcohol by the careful addition of water. The white crystalline product turned pink in the air.

TABLE II

DERIVATIVES OF 1,2,3,4-TETRAHYDROISOQUINOLINE

NO.	FORMULA	M.P. °C. (CORR.)	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
				Calc'd	Found	Calc'd	Found
XIV	$C_6H_5COCH_2NC_9H_{10}\cdot HCl$ $C_6H_5COCH_2NC_9H_{10}$	168–169 63.5–*64.5	$C_{17}H_{18}ClNO$ $C_{17}H_{17}NO$	4.87 5.57	4.77 5.40	12.33	12.19
XV	$C_6H_5CHOHCH_2NC_9H_{10}\cdot HCl$ $C_6H_5CHOHCH_2NC_9H_{10}$	206–207 56.5–57.0	$C_{17}H_{20}ClNO$ $C_{17}H_{19}NO$	4.83 5.53	4.68 5.38	12.24	12.07
XVI	$C_6H_5CHCH_2NC_9H_{10}\cdot HCl$ $OCOC_6H_5$ $C_6H_5CHCH_2NC_9H_{10}$ $OCOC_6H_5$	169.5–170.5 98.5	$C_{24}H_{24}ClNO_2$ $C_{24}H_{23}NO_2$	3.56 3.92	3.58 3.81	9.01	8.90
XVII	$C_6H_5COCH(CH_3)NC_9H_{10}\cdot HCl$ $C_6H_5COCH(CH_3)NC_9H_{10}$	173–175 38	$C_{18}H_{20}ClNO$ $C_{18}H_{19}NO$	4.64 5.28	4.77 5.40	11.75	11.90
XVIII	$C_6H_5CHOHCH(CH_3)NC_9H_{10}\cdot HCl$ $C_6H_5CHOHCH(CH_3)NC_9H_{10}$	235 96.8–97.5	$C_{18}H_{22}ClNO$ $C_{18}H_{21}NO$	4.61 5.24	4.69 5.30	11.68	11.75
XIX	$C_{10}H_7COCH_2NC_9H_{10}\cdot HCl$ $C_{10}H_7COCH_2NC_9H_{10}$	188–189.5 71.5	$C_{21}H_{20}ClNO$ $C_{21}H_{19}NO$	4.18 4.65	4.24 4.71	10.50	10.41
XX	$C_{10}H_7CHOHCH_2NC_9H_{10}\cdot HCl$ $C_{10}H_7CHOHCH_2NC_9H_{10}$	219–221 91	$C_{21}H_{22}ClNO$ $C_{21}H_{21}NO$	4.12 4.62	4.07 4.59	10.44	10.32

XXI	$C_{10}H_7CHCH_2NC_9H_{10}\cdot HCl$ $\vert$ $OCOC_6H_5$	164.5–165	$C_{28}H_{26}ClNO_2$	3.16	3.14	7.99	8.03
	$C_{10}H_7CHCH_2NC_9H_{10}$ $\vert$ $OCOC_6H_5$	112	$C_{28}H_{25}NO_2$	3.44	3.40		
XXII	$C_6H_5CH_2CH_2NC_9H_{10}\cdot HCl$	216–218	$C_{17}H_{20}ClN$	5.12	5.07	12.96	13.09
	$C_6H_5CH_2CH_2NC_9H_{10}$	43	$C_{17}H_{19}N$	5.90	5.95		
XXIII	p-$HOC_6H_4COCH_2NC_9H_{10}\cdot HCl$	216–217	$C_{17}H_{18}ClNO_2$	4.61	4.50	11.68	11.75
	p-$HOC_6H_4COCH_2NC_9H_{10}$	154	$C_{17}H_{17}NO_2$	5.24	5.30		
XXIV	p-$HOC_6H_4CHOHCH_2NC_9H_{10}\cdot HCl$	217–219	$C_{17}H_{20}ClNO_2$	4.58	4.61	11.60	11.69
	p-$HOC_6H_4CHOHCH_2NC_9H_{10}$	156	$C_{17}H_{19}NO_2$	5.20	5.12		
XXV	$C_6H_5OCH_2CH_2NC_9H_{10}\cdot HCl$	180.5–182	$C_{17}H_{20}ClNO$	4.84	4.90	12.24	12.31
	$C_6H_5OCH_2CH_2NC_9H_{10}$	35	$C_{17}H_{19}NO$	5.53	5.60		

* Previously reported by Wedekind (14) as melting at 100–101°.

The oxime obtained from the hydrochloride, by the usual method, was recrystallized from 65% alcohol, m.p. 128° (corr.).

Anal. Calc'd for $C_{21}H_{20}N_2O$: N, 8.86. Found: N, 8.71.

XX. *1-β-Naphthyl-2-tetrahydroisoquinolinoethanol-1 hydrochloride.* The amino ketone hydrochloride (XIX) was dissolved in 85% alcohol and hydrogenated at 60° in the presence of a 10% palladium on charcoal catalyst. Under these conditions the reduction required eleven hours; colorless prisms, yield 82%.

The free base was prepared by the method used for the base of the corresponding amino ketone hydrochloride (XIX). The product was recrystallized from alcohol and water.

XXI. *1-β-Naphthyl-2-tetrahydroisoquinolinoethanol-1 benzoate hydrochloride.* A mixture of 3 g. (0.009 mole) of the amino alcohol hydrochloride (XX) and 12 cc. (0.0417 mole) of benzoyl chloride was gradually heated to 115° and kept at this temperature for three hours. The cooled reaction-mixture was washed several times with dry ether and then dissolved in absolute alcohol. Dry ether was added and the mixture allowed to stand cold for several days or until crystallization occurred. The product was finally recrystallized from a small amount of absolute alcohol; colorless plates, yield 34%. The free base, obtained by the general procedure, was recrystallized from absolute alcohol.

XXII. *1-Phenyl-2-tetrahydroisoquinolinoethane hydrochloride.* Five cubic centimeters (0.028 mole) of phenylethyl bromide was added to a solution of 10 g. (0.059 mole) of tetrahydroisoquinoline in 10 cc. of absolute alcohol. The solution was heated for seven hours; colorless plates, yield 40%. The free base was prepared in the usual manner.

XXIII. *α-Tetrahydroisoquinolino*-p-*hydroxyacetophenone hydrochloride.* A suspension of 5.1 g. (0.028 mole) of α-chloro-*p*-hydroxyacetophenone in 12 cc. of absolute alcohol was added slowly to 7.85 g. (0.059 mole) of tetrahydroisoquinoline, keeping the temperature below 20°. Ten cubic centimeters of dry ether was added and the mixture allowed to stand for one hour. One hundred cubic centimeters of ether was then added and the tetrahydroisoquinoline hydrochloride removed by filtration after fifteen minutes. It was not entirely composed of the amine salt but contained a small amount of dark red material insoluble in water. The cold ether filtrate was then treated very slowly with dry hydrogen chloride. An excess of hydrogen chloride must be avoided, otherwise the product becomes very red. The crude product was dissolved in alcohol and reprecipitated by the addition of ether; white plates, yield 40%. The free base, prepared in the usual manner, was dissolved in 80% alcohol, diluted with water slowly, and cooled. The base crystallized as slightly yellow plates. Repeated trials to obtain the oxime of this compound were unsuccessful.

XXIV. *1*-p-*Hydroxyphenyl-2-tetrahydroisoquinolinoethanol-1 hydrochloride.* This compound was prepared by the general method from XXIII; colorless needles, yield 91%. The free base was obtained in the usual manner.

XXV. *1-Phenoxy-2-tetrahydroisoquinolinoethane hydrochloride.* To a solution of 3.08 g. (0.023 mole) of tetrahydroisoquinoline in 10 cc. of absolute alcohol was added 2.4 g. (0.011 mole) of β-phenoxyethyl bromide. The solution was heated for three hours at 70°; yield 60%. The free base was prepared by the general method.

XXVI. *α-Phenylethylaminoacetophenone hydrochloride.* To a dry ether solution containing 7.6 g. (0.0628 mole) of β-phenylethylamine, 6.3 g. (0.0314 mole) of α-bromoacetophenone was added. The reaction-mixture was allowed to stand at room temperature for forty-five minutes. The precipitated amine hydrobromide was removed by filtration and washed with dry ether. The filtrate was cooled to 15° and treated with dry hydrogen chloride. The crude amino ketone hydrochloride

was washed with ether and recrystallized from 95% alcohol and a small amount of ether; colorless prisms, yield 30%.

All attempts to prepare the free base failed. The oxime was prepared from the hydrochloride in the usual manner and recrystallized from alcohol, m.p. 123° (corr.).

Anal. Calc'd for $C_{16}H_{18}N_2O$: N, 10.36. Found: N, 10.30.

XXVII. *1-Phenyl-2-phenylethylaminoethanol-1 hydrochloride.* The amino ketone hydrochloride (XXVI) was reduced in 95% alcohol at 60° by the regular procedure. The crude product was recrystallized from alcohol; white prisms, yield 90%. The free base was obtained in the usual manner.

XXVIII. *1-Phenyl-2-phenylethylaminoethanol-1 benzoate hydrochloride.* A suspension of 2 g. (0.0072 mole) of the amino alcohol hydrochloride (XXVII) in 14 g. (0.10 mole) of benzoyl chloride was heated for three hours at 90°. After washing the oily reaction-mixture with several portions of ether, it was allowed to stand cold overnight in contact with ether. The product so obtained was recrystallized from hot alcohol and ether; yield 88%.

The free base was obtained by the addition of sodium hydroxide pellets to a solution of the hydrochloride in 85% alcohol. The mixture was warmed to 50° for ten minutes, then cooled for several hours in an ice-bath. The crude product was recrystallized from alcohol and water.

XXIX. *α-Phenylethylaminopropiophenone hydrochloride.* A solution of 6.7 g. (0.0314 mole) of α-bromopropiophenone in 10 cc. of absolute alcohol was added to 0.0628 mole of β-phenylethylamine. The mixture was allowed to stand at room temperature for one hour, after which time 75 cc. of ether was slowly added. After standing one hour cold, the precipitated amine salt was removed by filtration and the amino ketone hydrochloride was precipitated from the filtrate by treatment with dry hydrogen chloride. Recrystallization from alcohol and ether yielded colorless prisms; yield 63%. The free base was obtained only as an impure oil.

The oxime, prepared from the hydrochloride, was recrystallized from alcohol, m.p. 152.5° (corr.).

Anal. Calc'd for $C_{17}H_{20}N_2O$: N, 10.41. Found: N, 10.28.

XXX. *1-Phenyl-2-phenylethylaminopropanol-1 hydrochloride.* This compound was prepared from compound XXIX by the usual procedure. It was recrystallized from a mixture of alcohol and ether; colorless prisms, yield 83%.

The base was prepared by adding sodium hydroxide pellets to the amino alcohol hydrochloride dissolved in 60% alcohol. This solution was heated for five minutes, then cooled, and water was added to turbidity. This was allowed to stand in the ice-box overnight and the crude product was recrystallized from alcohol and water.

XXXI. *1-Phenyl-2-phenylethylaminopropanol-1 benzoate hydrochloride.* Two grams (0.0007 mole) of the amino alcohol hydrochloride (XXX) was suspended in 14 g. (0.010 mole) of benzoyl chloride and the mixture was heated for six hours at 110°. The solution was cooled, 100 cc. of dry ether was added, and the mixture allowed to stand for several hours in the cold. Since no oily residue separated, the ether was evaporated to a small volume to recover the ester hydrochloride. Recrystallization from 15 cc. of absolute alcohol and 75 cc. of dry ether gave a white hygroscopic powder; yield 50%. The free base was prepared by the procedure used for the base of the corresponding alcohol (XXX).

XXXII. *α-Phenylethylamino-β-acetonaphthone hydrochloride.* To a dry ether solution containing 6.9 g. (0.057 mole) of β-phenylethylamine, was added 7.1 g. (0.028 mole) of α-bromo-β-acetonaphthone. The reaction-mixture was allowed to stand for thirty minutes at room temperature; colorless prisms, yield 30%. The free base was obtained only as an impure oil.

TABLE III

DERIVATIVES OF β-PHENYLETHYLAMINE

NO.	FORMULA	M.P. °C. (CORR.)	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
				Calc'd	Found	Calc'd	Found
XXVI	$C_6H_5COCH_2NHCH_2CH_2C_6H_5 \cdot HCl$	175–177 decomp.	$C_{16}H_{18}ClNO$	5.08	4.92	12.86	12.98
XXVII	$C_6H_5CHOHCH_2NHCH_2CH_2C_6H_5 \cdot HCl$	205–206	$C_{16}H_{20}ClNO$	5.05	4.98	12.41	12.58
	$C_6H_5CHOHCH_2NHCH_2CH_2C_6H_5$	89.5–90.0	$C_{16}H_{19}NO$	6.22	6.15		
XXVIII	$C_6H_5CH(OCOC_6H_5)CH_2NHCH_2CH_2C_6H_5 \cdot HCl$	146.5–148	$C_{23}H_{24}ClNO_2$	3.67	3.61	9.30	9.39
	$C_6H_5CH(OCOC_6H_5)CH_2NHCH_2CH_2C_6H_5$	101	$C_{23}H_{23}NO_2$	4.35	4.24		
XXIX	$C_6H_5COCH(CH_3)NHCH_2CH_2C_6H_5 \cdot HCl$	175–177 decomp.	$C_{17}H_{20}ClNO$	4.84	4.77	12.24	12.41
XXX	$C_6H_5CHOHCH(CH_3)NHCH_2CH_2C_6H_5 \cdot HCl$	208–209	$C_{17}H_{22}ClNO$	4.80	4.71	12.16	12.27
	$C_6H_5CHOHCH(CH_3)NHCH_2CH_2C_6H_5$	101.5–102	$C_{17}H_{21}NO$	5.49	5.40		
XXXI	$C_6H_5CH(OCOC_6H_5)CH(CH_3)NHCH_2CH_2C_6H_5 \cdot HCl$	185	$C_{24}H_{26}ClNO_2$	3.54	3.59	8.96	9.07
	$C_6H_5CH(OCOC_6H_5)CH(CH_3)NHCH_2CH_2C_6H_5$	93.5	$C_{24}H_{25}NO_2$	3.90	3.83		

XXXII	$C_{10}H_7COCH_2NHCH_2CH_2C_6H_5 \cdot HCl$	174–177 decomp.	$C_{20}H_{20}ClNO$	4.32	4.15	10.88	10.99
XXXIII	$C_{10}H_7CHOHCH_2NHCH_2CH_2C_6H_5 \cdot HCl$	194–196	$C_{20}H_{22}ClNO$	4.28	4.21	10.82	10.98
	$C_{10}H_7CHOHCH_2NHCH_2CH_2C_6H_5$	59.5–60	$C_{20}H_{21}NO$	4.81	4.70		
XXXIV	$C_{10}H_7CH(OCOC_6H_5)CH_2NHCH_2CH_2C_6H_5 \cdot HCl$	180.5–181.5	$C_{27}H_{26}ClNO_2$	3.24	3.19	8.21	8.33
	$C_{10}H_7CH(OCOC_6H_5)CH_2NHCH_2CH_2C_6H_5$	111.5–112	$C_{27}H_{25}NO_2$	3.54	3.50		
XXXV	$C_6H_5OCH_2CH_2NHCH_2CH_2C_6H_5 \cdot HCl$	230–231	$C_{16}H_{20}ClNO$	5.05	5.04	12.77	12.79

The oxime prepared in the usual way was recrystallized from alcohol, m.p. 123° (corr.).

Anal. Calc'd for $C_{20}H_{20}N_2O$: N, 9.21. Found: N, 9.05.

XXXIII. *1-β-Naphthyl-2-phenylethylaminoethanol-1 hydrochloride.* Four grams (0.0491 mole) of the corresponding amino ketone hydrochloride (XXXII) was dissolved in 250 cc. of 95% alcohol and hydrogenated at 60° by the regular procedure. The crude product was recrystallized from dry alcohol and ether; colorless prisms, yield 95%. The free base was prepared by the general procedure and recrystallized from alcohol and water.

XXXIV. *1-β-Naphthyl-2-phenylethylaminoethanol-1 benzoate hydrochloride.* This ester was prepared by suspending 2 g. (0.006 mole) of the amino alcohol hydrochloride (XXXIII) in 14 g. (0.10 mole) of benzoyl chloride. The mixture was heated for two hours at 100°. The general procedure was then used to obtain the product in crystalline form. It was recrystallized from alcohol and ether; colorless needles, yield 60%. The free base was prepared and crystallized by the general procedure.

XXXV. *1-Phenoxy-2-phenylethylaminoethane hydrochloride.* A solution of 3.91 g. (0.0152 mole) of β-phenoxyethyl bromide was added to 3.8 g. (0.0314 mole) of β-phenylethylamine. The reaction-mixture was heated for two hours at 70°; colorless needles, yield 60%. The free base was obtained only as an impure oil.

SUMMARY

1. A series of ten new amino ketones, derivatives of ac-tetrahydro-β-naphthylamine, tetrahydroisoquinoline, and phenylethylamine, have been prepared.

2. The corresponding amino alcohols have been prepared by catalytic reduction, employing palladium on charcoal as the catalyst.

3. The benzoates of eight of the amino alcohols have been prepared.

4. The preliminary pharmacological report that has been included for six of the above compounds showed them to have anesthetic activity as well as vasopressor activity.

PHILADELPHIA, PA.

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[CONTRIBUTION FROM THE DIVISION OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

THE REACTION OF ETHYL GLYCINATE HYDROCHLORIDE WITH PRIMARY, SECONDARY, AND TERTIARY GRIGNARD REAGENTS[1]

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INTRODUCTION

The study of the reaction between amino acid derivatives and the Grignard reagent began when, in 1905, Paal and Weidenkaff (1) reported on the reaction between glycine ester and phenylmagnesium bromide. They later (2, 3) published on the reaction of phenyl- and ethyl- magnesium bromides on ethyl diethylaminoacetate and of the aryl Grignard reagent on ethyl aspartate. In each instance the corresponding tertiary alcohol was obtained. In 1923 McKenzie, becoming interested in the mechanism of the elimination of the amino group of amino tertiary alcohols, used the reaction as a preparative method.

McKenzie and co-workers (4) treated a variety of amino acid esters, and in some instances the ester hydrochlorides, with several Grignard reagents. Phenylmagnesium bromide (4a, b, c) was usually employed, but benzyl (4c, d), *p*-tolyl (4f), ethyl (4e), and *n*-propyl (4e) Grignard reagents were also used. To obtain satisfactory yields of the amino tertiary alcohols large excesses of the Grignard reagent were required.

The most comprehensive work has been carried out by Fritz Bettzieche and coworkers (5). Bettzieche (5a) ran a series of comparative reactions with the amino acid ester and with its hydrochloride. An excess of the Grignard reagent was always employed, and it was found that the hydrochloride gave a better yield than the free ester. This fact, along with the absence of resinous by-products in most cases, led Bettzieche to conclude that the presence of the hydrochloride offered no complications. The benzoyl (5b) and *p*-toluenesulfonyl (5d) groups protected the amino group from the Grignard reagent and the amide linkage was not attacked under the conditions of the experiment. Dipeptide ester hydrochlorides and

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their benzoyl derivatives (5d) were also studied, but the only linkage attacked was the ester group.

Kanao and Shinozuka (6) report that the corresponding amino tertiary alcohols are obtained by the action of *n*-propyl- and of isoamyl- magnesium iodides on ethyl glycinate. Kapfhammer and Matthes (7) in addition to treating *l*-proline and *l*-oxyproline esters with the Grignard reagent used the diketopiperazine of the former. Barrow and Ferguson (8) proposed a more satisfactory method of isolating the amino tertiary alcohol resulting from the action of an alkyl Grignard reagent on an amino acid derivative.

DISCUSSION

As noted above Bettzieche (5) reported that the conversion of the amino acid esters to their hydrochlorides adequately protected the amino group from the Grignard reagent. McKenzie (4), likewise, did not report the evolution of any gas in reactions of this type. However, both groups of workers were forced to use large excesses of the Grignard reagent in order to obtain satisfactory yields of products. Tiffeneau, Lévy, and Ditz (9) also reported that the action of the Grignard reagent on the hydrochlorides of amino ketones presented no peculiarities. No experimental details are given, so one does not know how well the reactions proceeded. It would seem rather odd if the hydrogen atoms of an amine hydrochloride were not active toward the Grignard reagent since Houben, Boedler, and Fischer (10) have published evidence that somewhat similar hydrogen atoms are active toward the Grignard reagent. They found that all the hydrogen and ammonium halides brought about the decomposition of the Grignard reagent although some reacted more slowly than others. The hydrochloride of triethylamine was also found to effect the complete decomposition of the Grignard reagent.

Ivanoff and Spassoff (11) reported that various Grignard reagents with ethyl acetate gave rise to the hydrocarbon corresponding to the Grignard reagent. But only the secondary Grignard reagents were found to give an appreciable yield of hydrocarbon. The reaction, they said, must have involved enolization of the ester since the ester was completely recovered. They later (12) stated that the evolution of hydrocarbon is not necessarily due to enolization of the ester, and they reported the isolation of ketones from the reaction of ethyl acetate and isopropylmagnesium chloride. The hydrocarbon was now accounted for by reaction of the enolized ketone with the Grignard reagent.

From our study it seems quite definite that the conversion of amino acid esters to their hydrochlorides does not protect the amino group from the Grignard reagent. In all of the reactions studied large quan-

tities of gas were collected, and apparently all three hydrogen atoms attached to the nitrogen atom are active and completely displaced by the Grignard reagent if the reaction-mixture is warmed for a sufficient time. The only hydrocarbon found in the reactions was the one corresponding to the Grignard reagent used.

As in the earlier work, it was necessary to use large excesses of the Grignard reagent to get good yields of products. The ester hydrochloride with *n*-propylmagnesium chloride gave good yields of the corresponding amino tertiary alcohol. This compound has been reported by Kanao and Shinozuka (6), who obtained it from glycine ester and *n*-propylmagnesium iodide. They gave no experimental details but analysis of the product checked satisfactorily.

Ivanoff and Spassoff (12) studied the reaction of ethyl acetate and isopropylmagnesium chloride. If the reaction products were distilled *in vacuo* the chief product was the ketol of methyl isopropyl ketone, but if the distillation was carried out at atmospheric pressure the main product was methyl isopropyl ketone. No tertiary alcohol was found in the reaction-mixture. In contrast to this, our work shows that with ethyl glycinate hydrochloride and the same Grignard reagent the main product is the amino tertiary alcohol. In one reaction a small amount of amino-methyl isopropyl ketone was isolated. Kanao and Shinozuka (6) state that ethyl glycinate hydrochloride and isoamylmagnesium chloride gave rise to the corresponding amino tertiary alcohol, for which they reported a satisfactory analysis. Again no experimental details were given.

Under the conditions we employed there appeared to be no reaction between the ester hydrochloride and *t*-butylmagnesium chloride other than the displacement of the active hydrogen atoms. No products could be isolated and nearly all of the nitrogen of the starting material was accounted for.

EXPERIMENTAL

Preparation of ethyl glycinate hydrochloride. The ester hydrochloride,m. p. 143–143.3°, was prepared from methyleneaminoacetonitrile (13), m.p. 127–127.5°, according to the method of Marvel (14).

Preparation of Grignard reagents. The Grignard reagents were prepared in a flask which had been flushed with dry nitrogen. The resulting solution was allowed to stand several days and then filtered into a bottle which had been flushed with nitrogen. The solutions were titrated according to the method of Gilman *et al.* (15) to obtain the concentration of Grignard reagent in the solution.

Reaction of n-*propylmagnesium chloride with ethyl glycinate hydrochloride* (I). The procedure finally adopted for this reaction was as described in (III). In this particular reaction the 180 cc. (containing 68.7 g. of *n*-propylmagnesium chloride; 0.668 mole) of Grignard solution was placed in a 500 cc. flask. The 23.3 g. (0.167 mole) of ethyl glycinate hydrochloride was added over a period of three hours. The ester hydrochloride was introduced through the free neck of the flask which

was immediately stoppered, and a further addition not made until the reaction subsided. At the completion of the addition of the ester hydrochloride 150 cc. of dry ether was added, and the reaction-mixture stirred vigorously for one-half hour. The reaction-mixture was then stirred and refluxed for an additional hour. During the reaction 12.6 l. (24°/734 mm.) of gas was collected, but was not analyzed.

The reaction-mixture was decomposed and worked up as described in (III). The ether was distilled from the solution through column #2 (16) (a Fenske column of the total reflux type packed with single turn, one-eighth inch helices; 1.5 x 67 cm.; twelve theoretical plates). The residue was then distilled through column #1 (a column of the above-mentioned type; 1 x 45 cm.; nine theoretical plates). Sufficient material was not present to maintain a reflux but 1.8 g. of white solid, which was later shown to be 2-amino-1,1-di-*n*-propylethanol-1, was obtained.

From the aqueous layer was obtained 13.6 g. of amino tertiary alcohol hydrochloride, m.p. 105–107°. Total yield of the amino tertiary alcohol hydrochloride was 15.8 g. (52.1%).

Reaction of n-*propylmagnesium chloride with ethyl glycinate hydrochloride* (II). Since previous workers did not report any gas from this reaction it was thought that perhaps the gas might be due to reduction, and so a low-temperature reaction was carried out. The quantities of reactants were the same as used in (I). For the addition of the ester hydrochloride two concentric glass tubes were tapered and sealed at the bottom. They were ground in at the tapered portion and a hole drilled at the ground surfaces. Then by turning the hole of the inner tube to coincide with that of the other, solid was admitted to the flask.

The Grignard solution was cooled to −10°, and the temperature of the reaction-mixture was not allowed to rise above −5° during the addition of the ester hydrochloride, which was effected in one and one-half hours. The reaction-mixture was held at −10° for three hours and then warmed to 30° to drive out the dissolved gas. After warming the reaction-mixture, 10 l. (23°/738 mm.) of gas, which was not analyzed, had been collected.

The reaction-mixture was decomposed as before. The ether layer was extracted with water and the extracts added to the aqueous layer. The ether layer was then distilled through column #2, leaving practically no residue. Steam distillation of the aqueous layer was begun, but bumping became so violent that it became necessary to filter off and wash the magnesium hydroxide.[2] From the steam distillate was obtained 8.3 g. (27.3%) of amino tertiary alcohol hydrochloride, m.p. 108.2–108.7°.

Reaction of n-*propylmagnesium chloride with ethyl glycinate hydrochloride* (III). The procedure finally adopted was the following: A 1-l., three-necked flask was fitted with a mercury-seal stirrer and reflux condenser. In the other neck of the flask was placed a dropping-funnel fitted with a mercury-seal stirrer. A gas lead went from this funnel to the top of the condenser and thence to the gas-collecting carboys which were filled with saturated salt solution. The apparatus was flushed with nitrogen. In the 1-l. flask was placed 607 cc. (containing 137.3 g. of *n*-propylmagnesium chloride: 1.33 moles) of Grignard solution. Ethyl glycinate hydrochloride was forced through a #60 screen and 23.3 g. (0.167 mole) of this material placed in

[2] This magnesium hydroxide was kept moist and then suspended in water and steam distilled. Some 2 l. of distillate was collected which was just acidified to Congo red with hydrochloric acid and evaporated to dryness on the steam-bath. Practically no residue was obtained, indicating that very little, if any, material was adsorbed on the base.

the dropping-funnel with sufficient dry ether to form a suspension. The stirrers were started and the ester hydrochloride suspension added at such a rate that refluxing was maintained, the addition requiring one and one-quarter hours. Soon after the addition of the ester hydrochloride began, the reaction-mixture became cloudy and solid separated. After the completion of the addition of the ester hydrochloride the reaction-mixture was stirred at room temperature for four hours and then refluxed for an additional hour. After cooling, the reaction-mixture was decomposed by pouring into a solution of 110 g. of ammonium chloride and 5 cc. of concentrated ammonium hydroxide in 400 cc. of water. Sufficient ice was present so that ice remained at the completion of the decomposition. The mixture was allowed to stand overnight.

The layers of the decomposition-mixture were separated, the aqueous layer (2.2 l.) divided in half, and each half extracted with one 200-cc. and three 100-cc. portions of ether. The extracts were combined with the ether layer and the solution dried with freshly heated potassium carbonate. The ether was filtered from the carbonate, the carbonate washed with dry ether and the washings added to the main solution. The ether was distilled off through column #2, and the residue washed into a 50 cc. Claisen flask with a little dry ether. After the removal of the ether 9.7 g. of a white solid (b.p. 76° at 4 mm.; m.p. 41.5°) was obtained. Kanao and Shinozuka (6) report b.p. 94.5–95° at 10 mm. and m.p. 58°. A residue of only a few drops remained in the flask. A benzenesulfonyl derivative of this material was prepared, which was soluble in alkali but insoluble in acid. A benzoyl derivative was also prepared and after recrystallization from 30% ethanol melted at 91–91.2°.

Anal. Calc'd for $C_{15}H_{23}NO_2$: C, 72.29; H, 9.24; N, 5.62.
Found: C, 72.89; H, 9.43; N (Dumas), 5.83.

To the aqueous layer was added 190 g. of sodium hydroxide dissolved in a small amount of water. This mixture was allowed to stand overnight. The supernatant liquid was then drawn off and the magnesium hydroxide centrifuged from the remainder of the solution. The precipitate was washed several times with water and the washings combined with the aqueous layer. This aqueous solution was now steam distilled until the distillate was no longer alkaline to litmus and only a few drops of acid required to acidify some 1500 cc. of distillate. The first 2 l. of distillate was aerated with a stream of nitrogen, the gas passing out through a condenser, to remove some of the ammonia. The steam distillate was just acidified to Congo red with hydrochloric acid and each 1700-cc. portion extracted with one 200-cc. and three 100-cc. portions of ether. The ether extracts (A) were combined and placed over 100 g. of freshly heated potassium carbonate.

The acidified steam distillate was evaporated to a small volume on a hot plate, the temperature of the solution during the evaporation being 50–60°. The small liquid residue was transferred to a beaker and dried in a forced draft oven at 55–60°. The solid residue was well ground in a mortar and extracted with a 200-cc., a 150-cc., and two 100-cc. portions of *n*-butyl alcohol (b.p. 117° at 742 mm.) and the residue finally washed with 100 cc. of boiling *n*-butyl alcohol. The extracts and washing were combined and 100 cc. of dry ether added to the solution. This solution was allowed to stand overnight in the cold room and then centrifuged from the ammonium chloride which separated. The resulting clear solution was vacuum distilled (bath temperature never above 55°) to a rather small volume and this poured into ether. After standing overnight in the cold room the solid was filtered off. The ether was distilled from the filtrate and the residue of *n*-butyl alcohol vacuum distilled practically to dryness. The distilling flask was rinsed with dry ether and the resultant

solid combined with that obtained earlier.[3] Yield of 2-amino-1,1-di-*n*-propylethanol-1 hydrochloride: 10.7 g.; m.p., 106.5–107.5°. Total yield as amino alcohol hydrochloride: 22.8 g. (75.2%).

This hydrochloride, when isolated, is anhydrous, but on keeping in a corked vial it absorbs moisture, which brings about a lowering of the melting point. But on drying in an oven at 100° the melting point is restored to its original value. When the hydrochloride is freed of the last traces of ammonium chloride by recrystallization from dry benzene it melts at 108.7–109°.

Anal. Calc'd for $C_8H_{20}ClNO$: C, 52.89; H, 11.02; N, 7.71.
Found: C, 52.32; H, 11.12; N (Dumas), 7.58.

Amino nitrogen was determined on the hydrochloride by the Van Slyke method.
Theory: 14.8 cc. N and 15.3 cc. N.
Found: 14.3 cc. N and 14.8 cc. N.

Ether extract (A) was filtered, the carbonate washed with dry ether, the washings added to the filtrate, and the ether distilled off through column #2. The small residue was transferred to a distilling flask and 0.9 g. of liquid boiling at 77–80° and having the odor of ethyl alcohol was collected.

The alkaline aqueous residue remaining after the steam distillation was extracted with one 200-cc. and two 100-cc. portions of ether. The extracts were dried over potassium carbonate and the ether distilled through column #2, all the material distilling below 35° and leaving no residue.

The alkaline aqueous solution was just acidified with hydrochloric acid to Congo red. A solid separated, which was collected. This solid would not char in the hottest Bunsen flame. The filtrate was extracted with four 200-cc. and four 100-cc. portions of ether. The combined extracts were dried over calcium chloride and then distilled through column #2. From the residue a small amount of material (b.p. 75–80°; 3,5-dinitrobenzoate, m.p. 90–90.5°) with the odor and behavior of ethyl alcohol was obtained.

The acidified aqueous filtrate was analyzed for nitrogen (Kjeldahl) and found to contain nitrogen equivalent to 0.41 g. of ethyl glycinate hydrochloride.

During the addition of the ester hydrochloride to the Grignard solution, 12.61 l. (24°, 742 mm.) of gas was collected. This gas was analyzed with an Orsat apparatus, and carbon dioxide, carbon monoxide, oxygen, and olefins were found to be absent. For the absorption of olefins the percentages of sulfuric acid suggested by Matuszak (17) were used. Slow combustion of the gas remaining after absorption in the pipettes indicated propane, but the results were not absolutely conclusive. A sample of the gas was then liquefied with liquid oxygen and distilled through a Podbielniak column.[4] Distillation showed the gas to be composed of 38.8% non-condensables, 57.2% propane, and 4.0% ether. Thus, 12.73 g. of propane was obtained, which means that nearly two atoms of hydrogen were replaced by the Grignard reagent.

Reaction of isopropylmagnesium chloride with ethyl glycinate hydrochloride (IV). The reaction and treatment of the reaction-mixture were carried out as described

[3] In another experiment, using the same quantities of reactants as used in this case, it was found that ether did not precipitate out all the amino tertiary alcohol hydrochloride, and to obtain all the product it was necessary to remove the solvent. In this experiment some material was accidentally lost but even so the yield of amino tertiary alcohol hydrochloride was 60.4%.

[4] We are indebted to M. C. Rogers for the distillation of the gas samples.

above (III). Ethyl glycinate hydrochloride (23.3 g.; 0.167 mole) and 614 cc. (containing 137.3 g. of isopropylmagnesium chloride; 1.33 moles) of Grignard solution were used. The addition of the ester hydrochloride suspension required one hour; the reaction-mixture was stirred for one and one-quarter hours more and then refluxed for an additional two and one-half hours.

From the combined ether layer and ether extracts (the aqueous layer was extracted with 3 l. of ether in 125-cc. portions) was obtained a residue which on distillation gave 6.2 g. of material boiling at 71–75° at 5 mm. The material remaining in the flask apparently condensed and 3.0 g. of a yellow, viscous liquid was collected at 75–175° at 5 mm. The material distilling at 71–75° at 5 mm. was not pure 2-amino-1,1-diisopropylethanol-1 but some of this material must have been present. A small amount of benzenesulfonyl derivative was obtained from this material, m.p. 103–103.8°. When mixed with the derivative (m.p. 103.9–104.5°) whose analysis is reported below (V), the melting point was 103–103.8°. A portion of the liquid boiling at 71–75° at 5 mm. was now dissolved in dry ether, and hydrogen chloride led into the cooled solution. To obtain a product, the solid must be filtered off after the addition of each small amount of hydrogen chloride. Otherwise, a dark, viscous oil results. Thus a white hydrochloride was obtained which after crystallization from dry benzene melted at 196–197°. This is apparently the hydrochloride of the amino tertiary alcohol.

Anal. Calc'd for $C_8H_{20}ClNO$: C, 52.89; H, 11.02; N, 7.71.
Found: C, 53.17; H, 11.44; N (Dumas), 7.39.

From the residue resulting from the evaporation of the acidified steam distillate 0.9 g. of material was extracted with *n*-butyl alcohol. This material could not be purified by solution in dry benzene, as it was insoluble in this solvent. However, extraction with acetone gave 0.68 g. of pure white flakes. This substance discolored at 145° and melted at 147–149° (decomp.). The material reacted with phenylhydrazine to give an oil which could not be crystallized. The substance is apparently the hydrochloride of aminomethyl isopropyl ketone.

Anal. Calc'd for $C_5H_{12}ClNO$: C, 43.64; H, 8.72; N, 10.18.
Found: C, 43.40; H, 9.04; N (Dumas), 10.31.

A benzenesulfonyl derivative, m.p. 81° (no range observable), was prepared.

Anal. Calc'd for $C_{11}H_{15}NO_3S$: C, 54.77; H, 6.22; N, 5.81.
Found: C, 54.18; H, 6.17; N (Dumas), 5.94.

No other products could be found. The final aqueous solution was found to contain nitrogen (Kjeldahl) equivalent to 1.94 g. of ethyl glycinate hydrochloride.

During the reaction 18.98 l. (24°, 742 mm.) of gas was collected. Analysis in the Orsat apparatus showed the absence of carbon dioxide, olefins, oxygen, and carbon monoxide. Combustion of the residue indicated propane, but again the data were not definitely conclusive. A portion of the gas was liquefied with liquid oxygen and distilled through a Podbielniak column. It was found to contain 37.4% non-condensables, 59.2% propane, and 3.4% ether. The 19.78 g. of propane liberated means that between two and three of the hydrogen atoms of the ester hydrochloride have been replaced.

Another reaction (V) between the ester hydrochloride and isopropylmagnesium chloride was carried out with the same quantities as described above (IV). The reaction-mixture was decomposed as soon as the solution could be cooled at the completion of the addition of the ester hydrochloride suspension. The layers of the decomposition-mixture were separated, the aqueous layer divided in half and each half extracted with one 250-cc., one 150-cc., and ten 125-cc. portions of ether. The

latter extracts left no odor when several drops were evaporated. The extracts were combined with the ether layer and dried over sodium sulfate. The ether was then distilled off through column #2 until a residue of some 200 cc. remained. Ten cubic centimeters of this residue was placed in a test tube immersed in an ice-bath. The ether was driven off with a stream of nitrogen and a benzenesulfonyl derivative, m.p. 103.9–104.5°, of the residue prepared. This is apparently the derivative of the amino tertiary alcohol.

Anal. Calc'd for $C_{14}H_{23}NO_3S$: C, 58.94; H, 8.07; N, 4.91.
Found: C, 58.57; H, 7.70; N (Dumas), 5.04.

The ether solution was freed of ether and the residue weighed 20.2 g.

Aliquots of the aqueous layer from the decomposition-mixture were made alkaline with sodium hydroxide, the magnesium hydroxide filtered off and washed with hot water, the washings being added to the filtrate. The filtrate was evaporated on the steam-bath to a small volume. The small aqueous residue was transferred to a Kjeldahl flask, acidified with sulfuric acid and evaporated to dryness with a stream of clean air. Kjeldahl determinations on the residue indicated the absence of nitrogen.

Reaction of t-butylmagnesium chloride with ethyl glycinate hydrochloride. The reaction and treatment of the reaction-mixture were carried out as described above (III). The addition of the ester hydrochloride suspension to the 1060 cc. (containing 156 g. of *t*-butylmagnesium chloride; 1.33 moles) of Grignard solution required forty minutes. The mixture was stirred for three hours and then refluxed for two and one-half hours more. The only material that could be isolated from the reaction-mixture was a small amount of hexamethylethane which was probably formed during the preparation of the Grignard solution. When the magnesium hydroxide was centrifuged off it could not be washed free of a lavender color, which indicates that it probably contained some glycine.

The final aqueous solution contained nitrogen (Kjeldahl) corresponding to 17.04 g. of ethyl glycinate hydrochloride.

During the reaction 23.1 l. (24°, 742 mm.) of gas was collected. A portion of this gas was liquefied with liquid oxygen and distilled through a Podbielniak column. The gas was found to be composed of 32.7% non-condensables, 57.9% isobutane, and 9.4% ether. The 31.06 g. of isobutane obtained indicates that all three hydrogen atoms of the amine hydrochloride group are active and can be replaced by the Grignard reagent if the reaction is allowed to proceed for a sufficient time.

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THE SYNTHESIS OF *d,l*-CITRULLINE FROM NON-BIOLOGICAL PRECURSORS[1]

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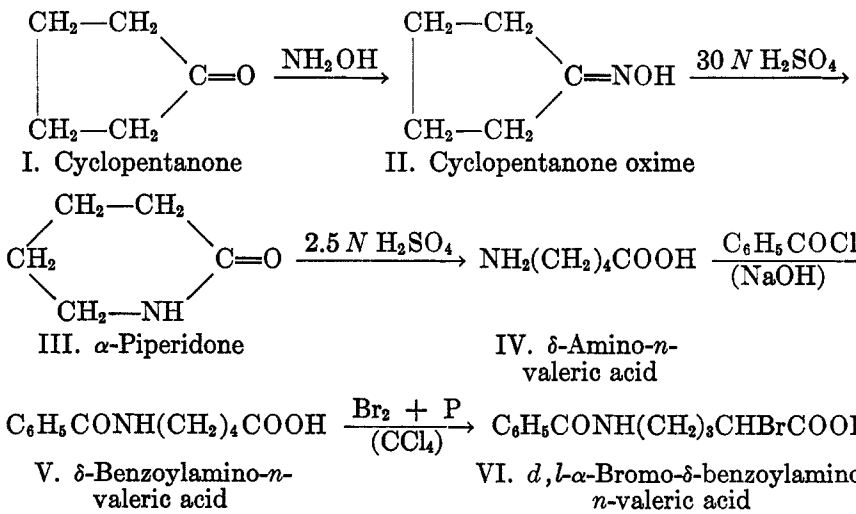
Citrulline has been prepared by the tryptic digestion of casein (1); the action of putrefied pancreas (2), bacteria (3), or alkali (4) on arginine; the hydrolysis of α-monobenzoyl-δ-carbamylornithine (5, 6); and the reaction of ornithine monosulfate with urea in the presence of cupric oxide (7, 8). The synthesis of dibenzoylcitrulline benzoylamide, α-monobenzoylcitrulline methyl ester, and α-monobenzoylcitrullineamide has also been described (9). The arginine which was utilized as starting material in these syntheses of citrulline was isolated from protein sources.

As has been pointed out by Marvel and Stoddard (10) and Rose (11) it is important that synthetic amino acids be used in determining the nutritional requirements of microorganisms, and for other metabolic purposes, in order that small amounts of naturally-occurring substances which might seriously affect the results of such studies may be excluded. For this reason a synthesis of *d,l*-citrulline has been devised by which this amino acid may be prepared in large amounts from substances of non-biological origin. The steps in this synthesis are shown below.



I. Cyclopentanone

II. Cyclopentanone oxime

III. α-Piperidone

IV. δ-Amino-*n*-valeric acid

V. δ-Benzoylamino-*n*-valeric acid

VI. *d,l*-α-Bromo-δ-benzoylamino-*n*-valeric acid

[1] Aided by grants from the Rockefeller Foundation and the University of California.

$$\xrightarrow{NH_3} C_6H_5CONH(CH_2)_3CH(NH_2)COOH \xrightarrow[(HCl)]{H_2O}$$

VII. *d,l*-α-Amino-δ-benzoylamino-*n*-valeric acid (*d,l*-δ-benzoylornithine)

$$NH_2(CH_2)_3CH(NH_2 \cdot HCl)COOH \xrightarrow{CuO + NH_2CONH_2}$$

VIII. *d,l*-α,δ-Diamino-*n*-valeric acid monohydrochloride (*d,l*-ornithine monohydrochloride)

$$[NH_2CONH(CH_2)_3CH(NH_2)COO]_2Cu \xrightarrow{H_2S}$$

IX. Copper salt of *d,l*-δ-carbamylornithine

$$NH_2CONH(CH_2)_3CH(NH_2)COOH$$

X. *d,l*-Citrulline

Experimental procedures thought to be of special interest in connection with the authors' synthesis are (a) the use of hydroxylamine sulfate to convert cyclopentanone (I) to the corresponding oxime (II) in place of sodium nitrite and sodium bisulfite employed by Eck and Marvel (12) for the synthesis of cyclohexanone oxime and (b) the preparation of δ-benzoylamino-*n*-valeric acid (V) from cyclopentanone oxime (II) in about 71% over-all yield. According to Schniepp and Marvel (13) the over-all yield is only 29% of the theoretical amount when the intermediate substances (III) and (IV) are isolated.

d,l-Ornithine monohydrochloride may be prepared by the described method somewhat more conveniently than from γ-phthalimidopropylmalonic ester (14), β-vinylacrylic acid (15), γ-phthalimidopropylthalimidomalonic ester (16), piperidine (17), acrolein (18), or α-aminoadipic acid and hydrazoic acid (19). According to the authors' preliminary experiments, as well as the investigations of Maeda and Nozoe (20), it seems probable that the synthesis of *d,l*-proline from *d,l*-α-bromo-δ-benzoylamino-*n*-valeric acid, prepared by the described series of reactions, is as convenient as any others (21) which have been reported.

EXPERIMENTAL

Cyclopentanone oxime (II). Three hundred thirty-six grams (4.0 moles) of cyclopentanone[2] (b.p. 126–128°/750 mm., uncorr.), 1000 ml. of water, and 720 g. (4.0 moles)

[2] Cyclopentanone may be obtained from commercial sources but that used for the present purpose was prepared from adipic acid essentially according to the method of Thorpe and Kon (22). The adipic acid was obtained from the E. I. du Pont de Nemours and Co., Wilmington, Delaware. Yields of cyclopentanone (b.p., 126–128°, uncorr.) averaging 81.5% were obtained from 1600 to 1800 g. quantities of adipic acid.

of technical (about 90%) hydroxylamine sulfate[3] are placed in a 5-l. round-bottomed flask. The mixture is brought to *p*H 6 by the addition of a saturated solution of technical sodium hydroxide (about 240 ml.) while it is being mechanically stirred. During the addition of the alkali, ice is added as necessary to keep the reaction-mixture at about 25°. The mixture is allowed to stand about thirty minutes. The precipitated cyclopentanone oxime and sodium sulfate, suspended in about 2.5 liters of liquid, are collected on a Büchner funnel and dried at room temperature.

The crude mixture is suspended in benzene (1 ml. per gram of solute), the suspension is heated to 40° and filtered, and the undissolved solid is washed twice with benzene. The filtrate, containing the cyclopentanone oxime, is distilled at atmospheric pressure in an oil-bath at about 125° to remove the benzene. The distillation is continued under reduced pressure using a water-pump. The yield of product, b.p. 93–97°/24 mm. (uncorr.) and m.p. 53.5–54.5° (uncorr.), from four runs averaged 368 g. (93% of the theoretical amount).

δ-Benzoylamino-n-*valeric acid*[4] (V). One hundred twenty grams (1.2 moles) of cyclopentanone oxime is dissolved cautiously in 240 ml. of cold approximately 30 *N* sulfuric acid solution. This solution is divided into twelve equal parts, each of which (about 30 ml.) is placed in a 500-ml. conical flask. Rearrangement of the oxime to α-piperidone is effected according to Wallach's (23) method by heating each flask with a free flame until a vigorous reaction occurs. The black solution is rinsed into a 5-liter round-bottomed flask using 250 ml. of water per flask. The combined solutions are refluxed with 10 g. of Norit "A" for two hours, after which the mixture is cooled and filtered.

The colorless filtrate is brought to *p*H 7 by the addition of a saturated solution of technical sodium hydroxide (about 400 ml.). This solution is made strongly alkaline by the addition of 150 ml. of a saturated solution of technical sodium hydroxide and is cooled and stirred vigorously with a mechanical stirrer while 120 ml. (1.0 mole) of technical benzoyl chloride is added over a period of thirty minutes. During this process a saturated solution of sodium hydroxide is added in 10-ml. portions as required to maintain the experimental solution basic to phenolphthalein. When the benzoyl chloride has been added, the solution is stirred for an additional thirty minutes. The suspended sodium sulfate is removed by filtration and washed twice with water.

The combined filtrate and washings are made strongly acid to Congo red by the slow addition of about 200 ml. of concentrated technical hydrochloric acid. The precipitated δ-benzoylamino-*n*-valeric acid is collected on a 6-inch Büchner funnel, washed twice with water to remove sodium sulfate, washed twice with 250-ml. portions of isopropyl ether to remove benzoic acid and other side-reaction products, and dried in air. The yield of product, m.p.[5] 90° ± 1° (uncorr.), from six runs averaged 190 g. (71%).

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[3] The hydroxylamine sulfate was obtained from the Commercial Solvents Co., Terre Haute, Indiana.

[4] This synthesis is a modification of the procedures reported by Schniepp and Marvel (13), Fischer and Zemplén (17), and Maeda and Nozoe (20).

[5] According to Schotten (24) and Gabriel (25) the melting point of δ-benzoylamino-*n*-valeric acid is 94°. Salkowski (26) and Wallach (23) found, however, that some samples liquefied at 94°, re-solidified, and then melted at 106–107°. A product melting at 105–106° was prepared by Schniepp and Marvel (13). The authors' product, precipitated from methanol by the addition of isopropyl ether, invariably melted

d,l-*δ-Benzoylornithine*[4] (VII). Four hundred grams (1.8 moles) of δ-benzoylamino-*n*-valeric acid, 20 g. of dry red phosphorus, and 1.5 liters of dry carbon tetrachloride are placed in a 3-l. three-necked flask equipped with a dropping-funnel, a mercury-sealed mechanical stirrer, and a one-meter water-cooled condenser connected to an efficient water-trap. Two hundred milliliters of dry bromine is placed in the dropping-funnel, the stirrer is started, and the bromine is added at a rate such that the hydrogen bromide is evolved rapidly and the heat of reaction causes the mixture to reflux vigorously. When all of the bromine has been added the flask is immersed in a water-bath, which is maintained at 70–85°, until the bromine has disappeared from the condenser (45–60 minutes). The mixture in the flask is cooled, the carbon tetrachloride is decanted, and a liter of water is added to the residual material in the flask. The mixture is stirred and powdered sodium bicarbonate (about 500 g.) is added slowly until the solid dissolves and further additions of bicarbonate cause no effervescence. The temperature of the reaction-mixture should be maintained at 25–30° with ice during the addition of the bicarbonate.

The mixture is filtered to remove excess bicarbonate and the alkali-insoluble side-reaction product, N-benzoyl-β,β-dibromo-α-piperidone.[6] The filtrate, containing the sodium salt of *d,l*-α-bromo-δ-benzoylamino-*n*-valeric acid in a volume of about 2.5 liters, is made strongly acid to Congo red by the addition of concentrated technical hydrochloric acid. The aqueous layer above the oily bromo acid is decanted and the residual oil is washed three times with water by decantation. The oily bromo acid is separated and four liters of 15 *N* ammonium hydroxide is added to the oil.

After amination has proceeded for three days the reaction-mixture is distilled under reduced pressure on a water-bath using a water-pump. The product is washed three times with ice-water to remove bromides and is dried at 40°. It melts with decomposition in 9–11 seconds when plunged into a bath at 274° (uncorr.).[7] The average yield of *d,l*-δ-benzoylornithine from six runs was 81 g. (19%).

d,l-*Ornithine monohydrochloride*[8] (VIII). One hundred seventy grams (0.72 mole) of *d,l*-δ-benzoylornithine and 3 liters of concentrated C. P. hydrochloric acid are placed in a 5-liter round-bottomed flask equipped with a water-cooled condenser which is connected to a water-trap. The solution is refluxed for twenty hours and then cooled for three hours in an ice-bath. The suspended benzoic acid is collected on a Büchner funnel and washed with ice-water to remove the mother liquor. The

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over the range, 94–105° (uncorr.). Recrystallization of this material from water gave a product which melted at 104–105° (uncorr.). The product obtained by precipitation of the latter material from methanol by isopropyl ether melted at 94–105° (uncorr.). These observations would appear to support the view of Salkowski (26) that δ-benzoylamino-*n*-valeric acid may exist in two crystalline forms.

[6] The yield of purified N-benzoyl-β,β-dibromo-α-piperidone from six runs averaged 96 g. (18%).

[7] The melting point bath, m.p. about 225°, consisted of an equal molar mixture of sodium nitrate and potassium nitrate. Soft glass melting point tubes of uniform bore, 0.6 mm. inside diameter and 0.8 mm. outside diameter, were used for the melting point determinations. Melting (or decomposition) temperatures of amino acids determined by this procedure, which is a modification of that described by Dunn and Brophy (27), are believed to be more significant than those obtained by other methods.

[8] A similar synthesis has been reported by Maeda and Nozoe (20).

combined filtrate and washings are distilled to dryness under reduced pressure on a water-bath using a water-pump. About 500 ml. of water is added and the distillation procedure is repeated to remove as much hydrochloric acid as possible.

The thick, yellowish residues from two runs, each starting with 170 g. of *d,l*-δ-benzoylornithine, are combined and dissolved in 800 ml. of hot 96% ethanol. The warm alcoholic solution is brought to *p*H 6-7, measured with wet nitrazine paper, by the slow addition of about 105 ml. of 15 *N* ammonium hydroxide solution. If the alkali is added slowly enough the *d,l*-ornithine monohydrochloride will separate as a finely divided solid. An oil tends to form when neutralization of the acid is too rapid. After all of the alkali has been added the mixture is allowed to stand for one hour. The suspended *d,l*-ornithine monohydrochloride is collected on a Büchner funnel and washed twice with 200-ml. portions of 96% ethanol. The yield of dry, crude product is about 250 g.

In order to remove the chief contaminant, ammonium chloride, the crude product is suspended for about ten minutes in 800 ml. of boiling 96% ethanol. The suspended *d,l*-ornithine monohydrochloride is collected immediately on a Büchner funnel, washed twice with 200-ml. portions of 96% ethanol and dried at 40°. The yield of product,[9] which melts with decomposition in 9 seconds when plunged into a bath at 233°, is 237 g. (97% of the theoretical amount).

Copper d,l-*citrullinate*[10] (IX). A mixture of 35 g. (0.21 mole) of *d,l*-ornithine monohydrochloride and 20 g. of cupric oxide in 200 ml. of water is boiled for thirty minutes. The mixture is filtered to remove excess cupric oxide. Fifty grams of urea is added to the filtrate and the mixture is evaporated on a steam-bath to a volume of about 175 ml. This solution is transferred to a 200-ml. round-bottomed flask, the stopper is wired in the flask, and the flask is immersed for three hours in a boiling water-bath. Within thirty minutes the copper salt begins to precipitate and after two hours it forms almost a solid mass. The flask is cooled overnight in a refrigerator. The copper salt is collected, washed three times with 100-ml. portions of water, and dried at 50°. It decomposes with effervescence in 25 seconds to give a reddish product when plunged into a bath at 260°. The average yield of copper *d,l*-citrullinate from five runs was 31 g.

d,l-*Citrulline*[10] (X). Two hundred eleven grams of copper *d,l*-citrullinate is suspended in 3.5 l. of water, the suspension is heated nearly to boiling while being stirred with a mechanical stirrer, and hydrogen sulfide is passed into the suspension for two hours. If the colloidal cupric sulfide does not coagulate sufficiently to filter well, stirring of the hot solution is continued for thirty to sixty minutes and, if necessary, an equal volume of 96% ethanol is added. The cupric sulfide is collected on a Büchner funnel and washed with water. If the filtrate is blue the treatment with hydrogen sulfide should be repeated. The filtrate is treated with 10 g. of Norit "A" to remove small amounts of colloidal cupric sulfide.

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[9] A solution containing 68.6 g. of the crude product dissolved in 50 ml. of hot water was decolorized with 1 g. of Norit "A." Three hundred milliliters of 96% ethanol was added to the filtrate and the mixture was allowed to stand overnight in the refrigerator. The precipitate was collected, washed with 100 ml. of 96% ethanol, and dried at 40°. The yield of product, which melted with effervescence in 9 seconds when plunged into a bath at 233°, was 58.6 g. (85% recovery). *Anal.* Less than 0.004% Fe, P_2O_5, and heavy metals; Cl^-, 100.0 and 100.0% of the theoretical amount.

[10] This synthesis is essentially that described by Kurtz (7) who prepared 1.51 g. of *d,l*-citrulline.

The volume of the colorless filtrate is reduced to about 400 ml. by distillation under reduced pressure on a water-bath using a water-pump. An equal volume of 96% ethanol is added to the hot residual solution and the mixture is allowed to stand three hours in an ice-bath. The crystalline *d,l*-citrulline is collected, washed with two 500-ml. portions of 96% ethanol, and dried at 40°. The yield of product, which melted with effervescence in nine seconds when plunged into a bath at 246°, was 136 g. A second crop of *d,l*-citrulline (16.7 g.) was isolated from the mother liquor which was reduced in volume and treated with ethanol as described. The total yield was 152.7 g. (62%, based on *d,l*-ornithine monohydrochloride).

The 136 g. of first crop *d,l*-citrulline was dissolved in 400 ml. of water and the solution was treated with 1 g. of Norit "A." The carbon suspension was filtered and washed. Twelve hundred milliliters of 96% ethanol was added to the hot solution and the mixture was cooled three hours in an ice-bath. The crystals were collected, washed with 350 ml. of 96% ethanol, and dried at 40°.

The yield of product, which melted with effervescence in 8 seconds when plunged into a bath at 246°, was 126.7 g. (93% recovery).

Anal. Less than 0.004% Cl^-, NH_3, Fe, P_2O_5, and heavy metals; formol titration with the glass electrode: m. eq. found, 2.264 (2.260 theor.) and 2.287 (2.281 theor.), average per cent of the theoretical, 100.2; moisture, 0.06%.

By recrystallization from water of 70.7 g. of *d,l*-citrulline, for which analyses are given above, 57.4 g. of first crop and 7.9 g. of second crop were obtained. The product (first crop) melted with effervescence in 9 seconds when plunged into a bath at 248°.

Anal. Moisture, 0.05%; and formol titration with the glass electrode: 100.3 average per cent of the theoretical amount.

SUMMARY

A synthesis of *d,l*-citrulline from substances of non-biological origin in seven main steps by which more than 100 grams of the analytically pure amino acid were prepared at one time is described.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

ALKYLATION OF PHENYLHYDRAZINE IN LIQUID AMMONIA

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Preliminary experiments had shown that phenylhydrazine is extremely soluble in liquid ammonia and that the resulting solutions react rapidly with alkali metals and alkali amides to give soluble alkali metal derivatives (equations I and II).

I. $$C_6H_5N_2H_3 + Na \rightarrow C_6H_5(Na)NNH_2 + \tfrac{1}{2}H_2$$

II. $$C_6H_5N_2H_3 + NaNH_2 \rightarrow C_6H_5(Na)NNH_2 + NH_3$$

This immediately suggested that the process of alkylation of phenylhydrazine in liquid ammonia might possess advantages over the conventional procedure which involves heterogeneous reaction between the alkali metal derivative and the alkyl halide in some inert solvent (1). The experimental work outlined in this paper is based upon the results of a study of the reactions of a typical aryl hydrazine, phenylhydrazine, with alkali metals and alkali amides in liquid ammonia, and the subsequent alkylation of these intermediates with alkyl halides to give the unsymmetrical disubstituted α-alkyl arylhydrazines (N,N-alkylphenylhydrazines).

EXPERIMENTAL

1. Reaction of phenylhydrazine with sodium in liquid ammonia. The principal reaction which occurs when sodium is added to a solution of phenylhydrazine is given in equation I. The addition of metallic sodium is accompanied by the rapid evolution of hydrogen and the formation of an orange-yellow solution. As the amount of sodium added approaches that required by the above equation the reaction slows down markedly, so that the blue color of metallic sodium persists for more than a few minutes. Quantities of sodium in excess of that required by the equation can then be added, inducing further reaction and involving reduction to aniline. Thus, if phenylhydrazine is added to a large excess of sodium dissolved in liquid ammonia complete reduction to aniline takes place.[1]

[1] That the preparation of sodium phenylhydrazine, using only one mole of sodium per mole of phenylhydrazine, involves some simultaneous reduction is furthermore indicated by the fact that the yields of N,N-alkylaryl hydrazine obtainable upon subsequent alkylation are always low, whereas yields approaching theoretical are obtained when the alkali metal compounds are prepared using the metal amides.

In a typical experiment 9.2 g. of sodium (0.4 mole) was dissolved in 500 cc. of liquid ammonia and 10.8 g. (0.1 mole) of phenylhydrazine was added. The solution was allowed to stand for one-half hour, after which the blue color of the excess sodium was discharged by the addition of 2.6 g. (0.0486 mole) of ammonium chloride. This indicates a ratio of approximately 3.5 moles of sodium per mole of phenylhydrazine, somewhat in excess of that required by equation III. The formation of aniline was

III. $$C_6H_5N_2H_3 + 3Na \rightarrow C_6H_5NNa_2 + NaNH_2$$

confirmed by isolation of the product and conversion into benzanilide, m.p. 159–160°.

2. Preparation of N,N-ethylphenylhydrazine. (a) Using the sodium-phenylhydrazine procedure. Twenty-seven grams of phenylhydrazine (0.25 mole) was dissolved in 400 cc. of liquid ammonia contained in a transparent one-liter Pyrex Dewar flask. Sodium metal was added in small pieces until the blue color no longer disappeared rapidly. Ethyl bromide (0.25 mole) was then added slowly with continuous agitation to the solution and the mixture allowed to stand until the ammonia had evaporated. The residue left after evaporation was extracted with chloroform and filtered to remove sodium bromide. The extract was dried over anhydrous sodium sulfate and then saturated with dry hydrogen chloride gas. A slight precipitate of phenylhydrazine hydrochloride was removed and the residual solution concentrated to a small volume, treated with ether, and cooled, thus facilitating the precipitation of N,N-ethylphenylhydrazine hydrochloride. After repeated crystallization of the product from chloroform-ether, 12 g. (28%) of the hydrochloride, m.p. 146–147° (2) was obtained.

In a duplicate run the crude hydrochloride was treated with aqueous sodium hydroxide and the N,N-ethylphenylhydrazine was extracted with ether. After removal of the ether, the residue was distilled under reduced pressure and the fraction boiling at 115–119° at 19–21 mm. was collected. For identification, a portion was treated with benzaldehyde yielding the crystalline benzylidene derivative, melting at 46–47°, as compared with the previously recorded melting point of 49° (3).

(b) Using the sodium amide-phenylhydrazine procedure. The method of Vaughn, Vogt, and Nieuwland (4) was used to convert 6.9 g. (0.3 mole) of sodium into sodium amide. To the dark gray suspension of finely divided iron (catalyst) and sodium amide in 500 cc. of liquid ammonia was added slowly 27 g. (0.25 mole) of phenylhydrazine. An excess of ethyl bromide (35 g., 0.32 mole) was then added dropwise. The solution was agitated during the addition of both phenylhydrazine and ethyl bromide. Afther the reaction was completed the ammonia was allowed to evaporate and the residue extracted with ether. The ether solution was washed with water and dried over sodium hydroxide. After removal of the ether the residue was distilled under reduced pressure. The fraction boiling at 120–127° at 25 mm. was redistilled, yielding 30 g. (88%) of pure N,N-ethylphenylhydrazine.

3. Preparation of N,N-benzylphenylhydrazine. (a) Using the sodium-phenylhydrazine method. Phenylhydrazine (27 g., 0.25 mole) was converted into the sodium derivative using metallic sodium. Benzyl chloride (35.4 g., 0.28 mole) was added slowly, after which the reaction mixture was treated as in 2a to give the hydrochloride. A total yield of 24 g. (41%) was obtained, melting at 164–169°. Michaelis and Philips (5) reported the melting poing 167° for this compound. Titration of the hydrochloride with standard base gave a neutral equivalent of 235, in agreement with the theory.

(b) Using the sodium amide-phenylhydrazine method. Sodium phenylhydrazine (0.334 mole), prepared as in 2b, was treated with a slight excess of benzyl chloride to

effect alkylation. After purification, 48 g. (73%) of N,N-benzylphenylhydrazine, distilling at 157-159° at 4 mm. was obtained. This material gave an acetyl derivative, m.p. 120–121°, agreeing with that reported previously (5).

4. Preparation of N,N-propylphenylhydrazine. (a) Using the sodium-phenylhydrazine method. Sodium phenylhydrazine, prepared by adding 6 g. (0.26 mole) of sodium to 27 g. (0.25 mole) of phenylhydrazine in 400 cc. of liquid ammonia, was allowed to react with 34 g. (0.27 mole) of propyl bromide. A yield of 13.3 g. (36%) of crude N,N-propylphenylhydrazine, boiling at 120–132° at 20 mm. was recovered from the reaction mixture.

(b) Using the potassium amide-phenylhydrazine method. A solution of 13 g. (0.33 mole) of potassium in liquid ammonia was converted to the amide using a rusty iron wire as the catalyst. Phenylhydrazine (0.25 mole) was added and the resulting orange-yellow solution was treated with 36 g. (0.29 mole) of propyl bromide. Extraction of the residue with ether, subsequent drying, and fractionation gave 35.4 g. (94%) of N,N-propylphenylhydrazine distilling at 122–130° at 20 mm. No lower-boiling fractions were obtained at in the previous case in which the sodium phenylhydrazine was prepared from metallic sodium. The product was characterized by conversion into the hydrochloride, m.p. 135° (6); the benzylidene derivative, m.p. 64°;

Anal. Calc'd for $C_{16}H_{18}N_2$: N, 11.77. Found: N, 11.69; and the *p*-nitrobenzoate, m.p. 153–154°;

Anal. Calc'd for $C_{16}H_{17}N_3O_3$: N, 14.05. Found: N, 14.09.

5. Reduction of N,N-propylphenylhydrazine with sodium in liquid ammonia. The absence of any N′-propyl-N-phenylhydrazine in the product obtained in 4b was confirmed by reduction with excess sodium in liquid ammonia. The N-propyl derivative should yield propylaniline, whereas the N′-propyl derivative should give aniline as one of the products.

Twelve and one-half grams of the product was dissolved in 400 cc. of liquid ammonia and 5 g. of sodium was added. After standing for one hour the solution was decolorized by adding ammonium chloride. The product was isolated in the usual manner and distilled *in vacuo* giving 7.5 g. (69%) of propylaniline boiling at 97–99° at 7 mm. The product was shown to consist exclusively of secondary amine by reaction with *p*-toluenesulfonyl chloride. It was identified by boiling point (micro) 221°, and by conversion (85% yield) to the acetyl derivative, melting at 48–49°.

These observations leave little doubt that alkylation of the alkali metal phenylhydrazine compounds under the given conditions yields only the unsymmetrical α-substituted phenylhydrazines (N,N-alkylphenylhydrazines).

SUMMARY

The alkylation of phenylhydrazine to give the unsymmetrical α-substituted phenylhydrazines (N,N-alkylphenylhydrazines) can be carried out conveniently in liquid ammonia as solvent. The following advantages may be gained by the use of this procedure: 1. The alkali metal phenylhydrazine compounds can be prepared readily by direct reaction of the primary hydrazine with the alkali metal or alkali amide. The latter is preferred in order to avoid reduction. 2. The alkali metal phenylhydrazine compounds and the alkyl halides are soluble in liquid ammonia, thus facilitating complete reaction. The preparation of N-ethyl-, N-benzyl-, N-propyl-, N-phenylhydrazines by this new technique is described.

Cleavage of the N—N bond in primary and unsymmetrical disubstituted hydrazines takes place in liquid ammonia upon treatment with an excess of sodium.

URBANA, ILL.

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DIPOLE MOMENT AND BOND CHARACTER IN ORGANOMETALLIC COMPOUNDS

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Determinations of the dipole moments of the molecules of organometallic compounds have been carried out usually with the object of investigating molecular configuration or of gaining information as to the polarities of the bonds within the molecules. The extensive investigations of Jensen (1) upon complex molecules containing alkyl or phenyl groups not directly linked to a metallic atom with cobalt, nickel, palladium, but, for the most part, platinum as the central atom have given positive evidence on the existence of the molecules in *cis* or *trans* configurations, and shown the incorrectness of the previously existing ideas as to the structures of some of the compounds. The moment values found for certain gold compounds aided in establishing the planar character of the molecules (2). In so far as the arrangements of the atoms in the molecules may be regarded as established, the dipole moments may be used to draw conclusions as to the moments associated with the individual valence bonds in the molecules, and thus of the relative amounts of covalent and ionic character of the bonds. Such determinations of approximate bond moment values form part of a program of research which has been carried on for some time in the Princeton laboratories with the object of gaining information on the electronegativities of the elements and the effects of these negativities and of the atomic polarizabilities upon dipole moments. In spite of the presence of numerous bonds with mutual inductive effects and with frequent uncertainties in bond angles, and of the fact that many of the molecular moments experimentally measured are merely the differences between moments not individually measurable, the approximate polarities of many bonds can be estimated.

Table I lists dipole moment values for germanium, mercury, and lead compounds determined by Dr. George L. Lewis and Mr. P. F. Oesper, some of which have been recently published (3), and for a number of other compounds taken from the literature. The five molecules with a central carbon atom are included for comparison with those containing a central fourth group metallic atom. The triphenyl compounds of the nitrogen

and the diphenyl compounds of the sulfur family elements are similarly listed in Table II, together with some compounds containing halogen or cyanide for purposes of comparison. All the values are the results of measurements made in solution and are, therefore, subject to solvent effects, which are, however, far too small to influence the conclusions to be drawn.

Perhaps, the simplest moment in Table I to interpret is that of the benzylmercuric chloride molecule. The zero moments of diethyl mercury (4) and of the mercuric halides (5) as well as the electron diffraction measurements on the latter (6) show that the two mercury valence bonds make

TABLE I

DIPOLE MOMENTS ($\times 10^{18}$) OF MOLECULES CONTAINING A CENTRAL METALLIC ATOM

$(CH_3)_3CCl$..... 2.15	$(C_6H_5)_3CCl$..... 1.95	$(CH_3)_2CCl_2$..... 1.99
$(CH_3)_3CBr$..... 2.21		
$(CH_3)_3CI$..... 2.13		
	$(C_6H_5)_3GeBr$..... 2.5	
$(C_2H_5)_3SnCl$..... 3.44	$(C_6H_5)_3SnCl$..... 3.30	$(C_2H_5)_2SnCl_2$..... 3.85
$(CH_3)_3PbCl$..... 4.47	$(C_6H_5)_3PbCl$..... 4.21	
$(C_2H_5)_3PbCl$..... 4.39		$(C_2H_5)_2PbCl_2$..... 4.70
$(C_2H_5)_3PbBr$..... 4.46	$(C_6H_5)_3PbBr$..... 4.21	
$C_6H_5CH_2HgCl$..... 3.0	$(C_6H_5)_3PbI$..... 3.73	

TABLE II

DIPOLE MOMENTS ($\times 10^{18}$) OF MOLECULES CONTAINING METHYL, ETHYL OR PHENYL GROUPS AND HALOGENS OR CYANIDES ATTACHED TO A FIFTH OR SIXTH GROUP ELEMENT

$(C_6H_5)_3N$..... 0	$(C_6H_5)_2AsCl$..... 2.70	$(C_6H_5)_2O$..... 1.14
$(C_6H_5)_3P$..... 1.45	$(C_2H_5)AsCl_2$..... 2.51	$(C_6H_5)_2S$..... 1.51
$(C_6H_5)_3As$..... 1.07	$(C_6H_5)_2AsCN$..... 4.19	$(C_6H_5)_2Se$..... 1.38
$(C_6H_5)_3Sb$..... 0.6	$(C_6H_5)_3SbCl_2$..... 1.35	$(C_6H_5)_2Te$..... 1.13
$(C_6H_5)_3Bi$..... 0		$(C_6H_5)_2SeCl_2$..... 3.47
		$(CH_3)_2TeI_2$..... 2.26

an angle of 180° with each other. As a rough approximation, the moment of the benzylmercuric chloride molecule may be regarded as the difference between the moments of the two opposed Hg—C and Hg—Cl bonds. The tetrahedral structures of the molecules, R_3MX and R_2MX_2, in which M is a fourth group element, R is an alkyl or phenyl group, and X is a halogen atom, require (7) that, in the absence of distortion, the moment of the R_3MX molecule should be the sum of the moments R—M and M—X and that of the molecule R_2MX_2 should be 1.15 times this sum. Subtraction of the rough value 0.3 for the H—C bond moment from the moment of the R_3MX molecule should, therefore, give the difference between the bond moments, (M—X) − (M—C). It has been pointed out (8)

that, if the moment of a bond depended simply on the difference between the electronegativities of the two bonded atoms, the moments of these tetrahedral molecules would be independent of the nature of the central atom, that is, the difference, (M—X) − (M—C), would be independent of M. In the case of a few chlorides of this type previously investigated, Brockway and Coop (9) attributed the increase in moment with increasing polarizability and electropositive character of the central atom to a greater absolute effect of these two factors upon the large M—Cl moment than upon the smaller M—C moment. This has been considered in more detail elsewhere, as has also the effect of increase in the size of M with consequent increase in the separation of the M—X dipoles in decreasing the lowering of the M—X moments in R_2MX_2 by mutual inductive effects. This effect is evidenced in the approach of the ratio between the R_2MX_2 and R_3MX moments to the theoretical value 1.15 as M increases, although it is uncertain in the lead compounds, where the experimental error is large.

It is reasonable to suppose that the M—X moment is larger than the M—C moment because the halogens are more electronegative than carbon. Evidence that the M—C moment values are not large is given by a somewhat uncertain moment value found by Mr. R. H. Wiswall for trimethylaluminum, and by the low moments of triphenylantimony and triphenylbismuth, in which the three metal-to-carbon bonds should make angles (10) of about 100° with one another unless the angles are widened beyond this value by repulsion between the phenyl groups. The uncertainty in the trimethylaluminum moment is due to molecular association, while additional uncertainty is introduced into the interpretation of the values for triphenylantimony and triphenylbismuth by the possibility of resonance effects. Unfortunately, association of triphenyl lead into double molecules of zero moment has prevented its use in determining a Pb—C bond moment. It seems fairly certain, however, that the moments of benzylmercuric chloride and the molecules with a fourth group atom in the center arise mainly from the considerable excess of the moments of the metal-halogen bonds over those of the metal-carbon bonds. The moments of these molecules minus 0.3, the value used for the H—C moment, plus the M—C moment gives the M—X moment. The observed molecular moments are so large that the M—C moments must be small, probably, between 0 and 2.0, in order that the M—X moments may not be larger than those found (11) by the molecular beam method for the molecules of the three salt vapors given in Table III. These small moment values for the metal-carbon bonds show them to be ordinary covalent bonds possessing no more ionic character than that possessed by many bonds in organic molecules.

If the metal-carbon bond moment is arbitrarily taken as zero, the moments of the molecules under consideration minus 0.3 give the lower limits

for the metal-halogen moments shown in Table III. This includes, for the sake of comparison, a value for the Ge—Cl bond calculated from the moment of monochlorogermane. Where values are available for a bond in both aliphatic and aromatic compounds, an average of the two slightly differing values is used. If these bonds had no covalent character but were 100% ionic, their moments would be calculated as the products of an electronic charge, 4.80×10^{-10}, times the distances between the ionic centers. If the lower limits of the bond moment values are divided by these calculated ionic moments, the quotients give (12) the lower limits for the amounts of ionic character in the bonds shown in Table III.

It is evident that the lower limit for the amount of ionic character in the Pb—Cl bond in these organometallic compounds is indistinguishable from the amount of ionic character of the sodium-iodine bond in the sodium iodide molecule. The germanium-halogen bond has less ionic character

TABLE III

AMOUNTS OF IONIC CHARACTER OF BONDS CALCULATED FROM DIPOLE MOMENTS

BOND	BOND MOMENT ($\times 10^{18}$)	% IONIC
Ge—Cl	>2.0	>19
Ge—Br	>2.2	>19
Sn—Cl	>3.1	>27
Pb—Cl	>4.1	>34
Pb—Br	>4.0	>31
Pb—I	>3.4	>25
Na—I	4.9	35
K—I	6.8	44
K—Cl	6.3	47

than the tin-halogen and, among the different lead-halogen bonds, the amount of ionic character decreases slightly on going from chlorine to bromine to iodine. It is evident that, although these metal-halogen bonds have usually been thought of as covalent, they actually possess amounts of ionic character comparable to those found in the bonds of many salt molecules.

The previously mentioned moments measured by Jensen (1) with the object of determining the configurations of planar molecules of the general formula $(R_3P)_2PtX_2$, in which P may be replaced by As or Sb, and X may be Cl, Br or I, may be examined with an eye to the bond moments involved, in order that these may be compared with the bond moments in molecules containing carbon directly linked to metal. The *trans* forms have zero moments because they have similar atoms or groups at diagonally opposite corners of the rectangle at the center of which lies the metal atom. The moments of these *cis* forms have values between 8.2 and 11.5, more than

double those listed in Table I. The angles between the four coplanar platinum valence bonds are so close to 90° that errors arising from the assumption that they are 90° will be unimportant. The molecular moment is thus seen to be 2 m *cos* 45°, where m is the sum of the R_3P moment, about 1.5, plus the P—Pt moment plus the Pt—X moment. The values of m calculated from the molecular moment values vary from 5.7 to 8.1. Subtraction of the R_3P moment 1.5 leaves values between 4.2 and 6.6 for the sums of the P—Pt and the Pt—X moments. The P—Pt bond should be semipolar with the phosphorus atom furnishing both electrons of the bond and thereby acquiring a positive charge. This bond might be expected (7) to have a moment not far from 3, which would leave a moment between 1.2 and 3.6 for the Pt—X bond. This rough treatment serves to show that the platinum-halogen bonds, probably, have moments comparable in magnitude to the moments of the metal-halogen bonds in the compounds in Table I, possessing, therefore, a good deal of ionic character, while the phosphorus-platinum bonds have the positive ends of their dipoles towards the phosphorus, as, otherwise, the platinum-halogen bond moments would have to be impossibly large to account for the observed moments.

Although there are uncertainties of detail, and accumulated errors bulk large in the differences obtained as in the compounds, $(R_3P)_2PtX_2$, the same general relations hold when platinum is replaced by cobalt or nickel, halogen by nitrite or nitrate, and phosphorus by arsenic or antimony. The same is true when R_3P is replaced by R_2S, R_2Se, or R_2Te, although, in these cases, the *trans* compound has a small moment, as the R_2S dipole does not lie in the diagonal of the molecular rectangle. The moment value 5–6 found (2) for mono-*n*-propyldibromogold indicates that the difference of the Au—C and Au—Br moments is about 4, which is practically the same as that indicated by the values in Table I for the Pb—C and Pb—Br difference.

The moments of the triphenyl compounds of the fifth group in Table II show, as previously mentioned, the low polarity of the bonds of these elements with carbon, little ionic character being possessed by these bonds. The larger moments of the arsenic compounds containing chlorine are due to the moment of the As—Cl bond, which has considerably less ionic character than have the metal-halogen bonds just discussed, but still possesses a moment larger than those of most so-called covalent bonds (13). The large moment observed when the chlorine of diphenylchloroarsine is replaced by cyanide arises mainly from the polarity of the bond between the carbon and nitrogen of the cyanide. The small size of the moment of triphenylantimony dichloride must be due to partial opposition of the various bond moments to one another, as the Sb—Cl bond has been found to have a moment of 2.6 (12).

The small moments of diphenyl selenide and telluride give evidence of the smallness of the amounts of ionic character in the selenium-carbon and tellurium-carbon bonds. As evidenced by the moments of diphenylselenium dichloride and dimethyltellurium diiodide, there is more ionic character in the selenium-chlorine and tellurium-iodine bonds, but still much less than has been found in the metal-halogen bonds just examined.

In conclusion, it may be stated that the dipole moments of the organometallic compounds which have been considered show a variation in the character of the valence bonds in the molecules from almost purely covalent to an amount of ionic character comparable to that found in some salt molecules. The order of magnitude deduced for the moments of the metal-carbon bonds shows them to be largely covalent in character, while a metal-halogen bond in an organometallic compound may be as ionic as in a salt molecule.

SUMMARY

The dipole moments of organic molecules containing mercury, germanium, tin, lead, or antimony, and chlorine, bromine, or iodine are examined and used to determine the approximate amounts of ionic character in the bonds linking the atoms to one another. Other dipole moments are collected from the literature for comparison. It is found that the bonds connecting carbon and metal atoms are essentially covalent, while the bonds connecting metal atoms to chlorine, bromine, or iodine atoms in the same compound are as ionic in character as the bonds in some typical salt molecules supposed to consist of a pair of oppositely charged ions.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE CHEMISTRY OF VITAMIN E. XXVIII. (1) SYNTHESIS OF THE THREE DIMETHYLETHYLQUINONES

LEE IRVIN SMITH AND J. W. OPIE

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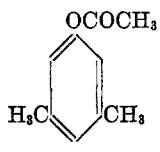
The three dimethylethylbenzoquinones were required in order to prepare a set of homologs of α-tocopherol. In preparing such trialkylbenzoquinones, it is not possible to start with benzene hydrocarbons having the three substituents in positions 1, 2, and 4, because the next substituent introduced practically always enters the 5 position. Consequently indirect methods must be used (2), and in a previous paper (2a) a general method has been described whereby quinones may be prepared readily and in good yields from the corresponding phenols. This method, when applied to the proper dimethylethylphenols, led to the dimethylethylquinones, but the synthesis of the phenols themselves in quantity from readily available material involved several steps.

Von Auwers (3) in a very complete study of the Fries rearrangement, found that the acetate of 3,5-dimethylphenol (I) and that of 2,3-dimethylphenol (III) rearranged to form the corresponding orthoacetophenols (II, IV) in good yields. He also found that these acetophenols could be



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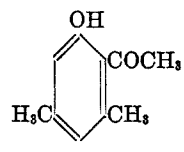

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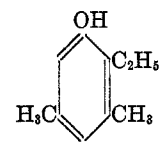

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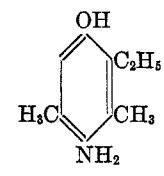

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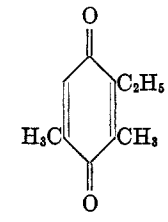

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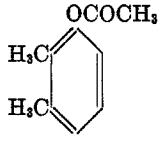

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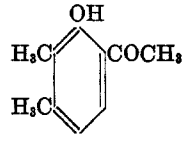

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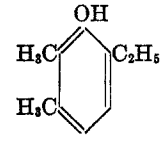

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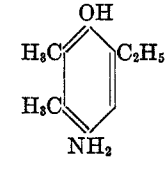

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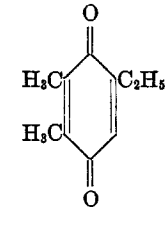

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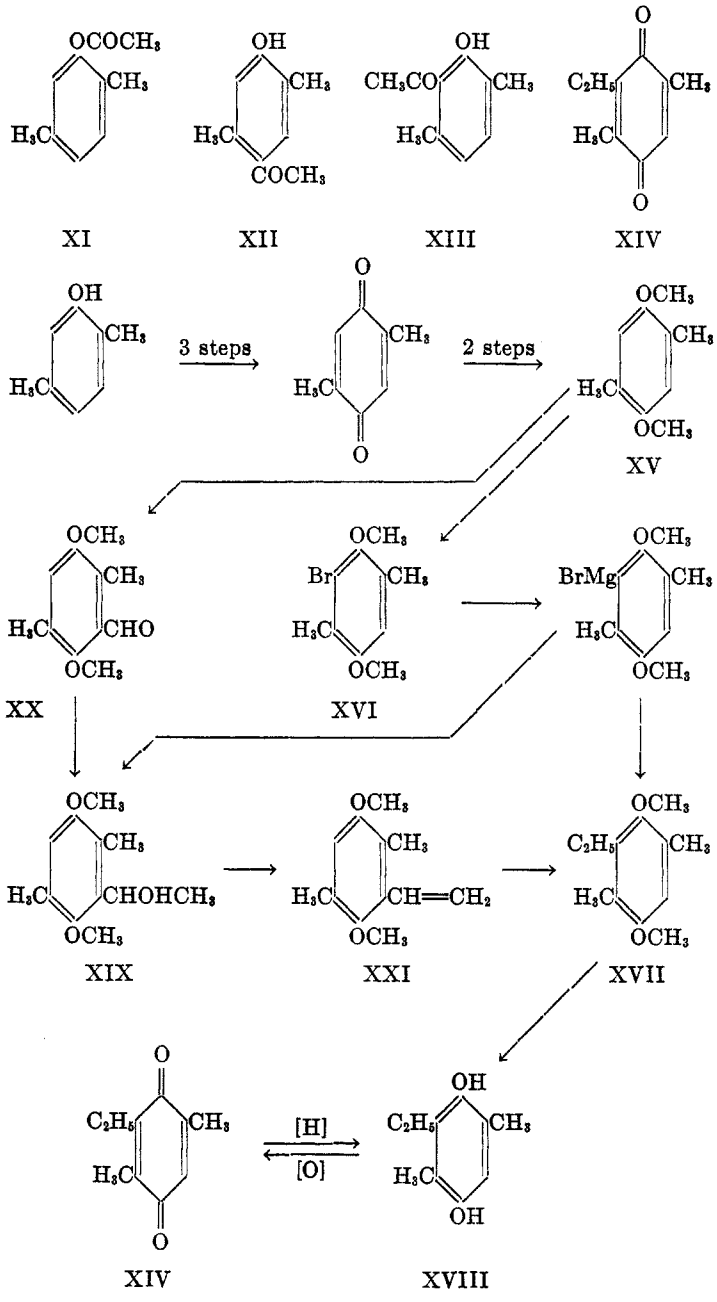
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CH3
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H3C
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XI
XII
XIII
XIV
OH
CH3
H3C
3 steps
O
CH3
H3C
O
2 steps
OCH3
CH3
H3C
OCH3
XV
OCH3
CH3
H3C
CHO
OCH3
XX
OCH3
Br
CH3
H3C
OCH3
XVI
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BrMg
CH3
H3C
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CHOHCH3
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H3C
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XXI
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XVII
O
C2H5
CH3
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XIV
[H]
[O]
OH
C2H5
CH3
H3C
OH
XVIII

reduced to the corresponding dimethylethylphenols (V and VI) by the Clemmensen method.

The methods of v. Auwers were used in preparing the phenols V and VI. Reduction of the aceto compounds II and IV was also carried out catalytically. No difficulty was experienced in preparing these two phenols in amounts sufficient for preparation of the quinones IX and X by the standard procedure, *viz.*, coupling the phenols with diazotized sulfanilic acid, cleaving the azo compounds to the amino phenols VII and VIII and oxidizing the latter to the quinones. Karrer and Hoffmann (2b) have prepared IX from the corresponding phenol by oxidative hydrolysis of the *p*-nitrosophenol.

However, the Fries rearrangement of the acetate of 2,5-dimethylphenol (XI) produces the para-aceto compound (XII) (3a, 4) instead of the ortho-aceto compound XIII and therefore it was necessary to prepare the third dimethylethylquinone, (XIV) from some other intermediate. The route to this quinone, starting with 2,5-dimethylphenol, is shown on page 428. In addition to the preparation of the three quinones, this paper also includes a description of improvements in the preparation of 2,3-dimethylaniline (5). The conversion of this amine into 2,3-dimethylphenol has been studied in some detail, and two procedures have been devised whereby this phenol is rendered much more readily accessible than heretofore. These are discussed in the experimental part.

EXPERIMENTAL PART[1]

2,6-Dimethyl-3-ethylbenzoquinone (IX)

3,5-Dimethylphenyl acetate (I) (249 g., 95% b.p. 118–120° under 19 mm.[2]) was prepared in the usual way from acetic anhydride (325 g.), and sulfuric acid (2 cc.).

2-Hydroxy-4,6-dimethylacetophenone (II) (3, 6). Aluminum chloride (100 g.) was carefully added to the cold (0°) acetate I (61 g.) and the mixture was then warmed for ten hours on the steam-bath, decomposed, and steam distilled. The product, isolated from the distillate, when fractionated under 13 mm., was separated into a forerun (12 g., 17%) boiling at 111–137°, and II (47 g., 67%), which boiled at 144°, and which solidified to a light yellow solid that melted at 57–58.5°.[3] The forerun, consisting of a mixture of the acetate I and 3,5-dimethylphenol, was used in a subsequent preparation of I. When corrected for the recovered starting material (considered to be entirely I), the yield of II was 80%.

3,5-Dimethyl-2-ethylphenol (V). A. Clemmensen reduction of the hydroxy ketone II (32.8 g.) gave a mixture which was extracted with ether, washed well with water, and then extracted with aqueous potassium hydroxide (20%, 125 cc.). The alkaline extract was saturated with carbon dioxide to precipitate the phenol, which weighed 15 g. (50%) and melted at 74–76°.[4]

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[1] Microanalyses by E. E. Renfrew, E. E. Hardy, and H. H. Hoehn. We wish to thank Dr. W. B. Renfrow, Jr., for checking certain of the experiments.

[2] Von Auwers and Borsche (6) give the b.p. as 120° (15 mm.).

[3] Von Auwers and Borsche (6) obtained 60–70% yield of material that melted at 57–58° and boiled at 140–141° (18 mm.).

[4] Von Auwers and Borsche (7) give the m.p. as 80–81°.

B. Catalytic reduction. The hydroxy ketone II (128 g.) was dissolved in alcohol (95%, 40 cc.), Raney nickel catalyst was added, and the ketone was shaken for three hours at 175° under hydrogen (initial pressure, 2000 lbs. at 25°). The contents of the bomb were poured into water and extracted with petroleum ether. The extract was filtered and shaken with Claisen's alkali. The alkaline solution was diluted with water, acidified, and extracted with ether. Removal of the solvent left a semi-solid residue which, when crystallized from petroleum ether gave 77.4 g. (67%) of the phenol melting at 79–80°.

4-Amino-3,5-dimethyl-2-ethylphenol (VII). The phenol V (77.4 g.) was coupled with diazotized sulfanilic acid (108 g.) according to the usual procedure (2). After the red solution had stood at room temperature for twenty-four hours, sodium hydrosulfite (250 g.) was added and the mixture was heated and stirred for two hours. The color suddenly faded, and the amino phenol began to separate. The cooled (0°) mixture was filtered. An analytical specimen of the amino phenol was prepared by recrystallizing a small portion twice from benzene. It formed white plates, and melted at 158–159° with decomposition.

Anal. Calc'd for $C_{10}H_{15}NO$: C, 72.7; H, 9.1.
Found: C, 73.0; H, 9.0.

2,6-Dimethyl-3-ethylquinone (IX). The moist amino phenol from the above experiment was dissolved in hydrochloric acid (60 cc., 30%). Ferric chloride (400 g.) was added and the mixture was immediately steam distilled. The quinone, a golden yellow oil, was removed from the distillate by ether extraction. After washing the ethereal solution thoroughly with water, removal of the solvent left 56 g. (66%, based upon the phenol V) of the quinone, a golden yellow oil which boiled at 111° under 10.5 mm.

Anal. Calc'd for $C_{10}H_{12}O_2$: C, 73.17; H, 7.32.
Found: C, 73.05; H, 7.59.

Karrer and Hoffman (2b) obtained this quinone in 65% yield from the phenol, using the *p*-nitrosophenol as an intermediate. They report it also as a yellow oil.

2,6-Dimethyl-3-ethylhydroquinone. The quinone IX (10 g.) was dissolved in acetic acid (37 cc.) and water (27 cc.). Zinc (20 mesh, 9.2 g.) was added and the mixture was refluxed until it became colorless. Boiling water (37 cc.) was added, and the hot solution was decanted from the zinc. The zinc was washed with another portion (37 cc.) of hot water, which was combined with the main solution. The solution was cooled (0°) and the hydroquinone (8 g., 80%) was removed. It melted at 153–153.5°; an analytical sample melting at 158–158.5° was prepared by crystallizing a small portion (0.5 g.) from benzene.

Anal. Calc'd for $C_{10}H_{14}O_2$: C, 72.40; H, 8.44.
Found: C, 72.13; H, 8.61.

Karrer and Hoffman (2b) report this hydroquinone to melt at 157°.

2,3-Dimethyl-5-ethylbenzoquinone (X)

3-Amino-o-xylene. Catalytic reduction of the nitro compound (5)[5] to the amine results in much better yields than those obtained by the iron-acetic acid method previously described (5). 3-Nitro-*o*-xylene (300 g., b.p. 109–112° under 7 mm.) was shaken with Raney nickel in a 1-liter bomb under hydrogen at an initial pressure of 1475 lbs. (25°). With the temperature controller set at 110°, the temperature (88°), forty minutes after the heater was turned on, rose rapidly during the next thirty minutes to 172° while the pressure dropped to 1300 lbs. At this point the bomb

[5] We wish to thank Dr. R. T. Major and Merck and Co., Inc., for a very generous gift of 3-nitro-*o*-xylene.

began to cool; twenty minutes later the temperature was 140° and the pressure was 925 lbs. The bomb was then refilled with hydrogen (1500 lbs.) and shaken at 140–145° for half an hour longer, during which the pressure drop was only 100 lbs. The cooled bomb was washed out with ether, the water formed during the reaction was separated, and the catalyst was filtered off. After drying (Drierite), the ether was removed and the residue was distilled. The amine (251 g., 100%) boiled at 114° under 19 mm.

3-Iodo-o-xylene. The amine (251 g.) was added to a hot solution of sulfuric acid (190 cc.) in water (1500 cc.) and the mixture was boiled until the amine sulfate dissolved completely. The solution was then cooled and ice (800 g.) was added, causing the sulfate to reprecipitate as a granular solid. Sodium nitrite (150 g.) dissolved in water (500 cc.) was slowly added and the cooled mixture was allowed to stand until the solids had all dissolved. Then, at 0°, potassium iodide (350 g.) in water (450 cc.) was slowly added and the mixture was allowed to stand for twelve hours, gradually warming to room temperature, after which it was heated on the steam-cone until no more gas was evolved. Sodium hydroxide (280 g.) in water (400 cc.) was added and the mixture was steam distilled. The heavy oil was extracted with ether from the distillate and the ether was removed. The residue of iodo compound weighed 294 g. (61%).[6] The alkaline solution remaining from the steam distillation was acidified with sulfuric acid and again steam distilled, yielding 6 g. of impure 2,3-dimethylphenol.

2,3-Dimethylphenol. The above iodo compound (294 g.), copper wool (40 g.), and aqueous sodium hydroxide (160 g. in 850 cc. of water) were heated in a bomb. After three hours the temperature had reached 275°, where it was held for fifteen minutes to complete the reaction. The alkaline reaction-mixture was extracted with ether, and the aqueous layer was then acidified and steam distilled. Ether extraction removed 127 g. (79%) of 2,3-dimethylphenol from the distillate. The phenol melted at 65–69°.[7] The over-all yield of pure phenol from the amine was 55%.

An alternative procedure, which avoids the preparation of the iodo compound, is given below. While the yield of phenol produced by this method is 52%, the product is much more difficult to purify than that obtained *via* the iodo compound, because large amounts of 4-methylindazole (?) are simultaneously formed.

The amine (32 g.) was dissolved in boiling water (200 cc.) containing sulfuric acid (21.7 cc.). The solution was cooled, ice (250 g.) was added, and then sodium nitrite (20.7 g.) in water (100 cc.) was slowly dropped in with stirring. The mixture was stirred until all the solids had dissolved, after which it was allowed to warm to room temperature and to stand for twenty-four hours. It was then steam distilled. The distillate was extracted with ether and the phenol was removed from the ether by extraction with sodium hydroxide (10%). The alkaline solution was saturated with carbon dioxide and extracted with ether. After removal of the ether, the phenol was distilled under 10 mm. The product boiled at 91–94° and weighed 16.5 g. (52%). The residue from the steam distillation deposited a considerable quantity of long needles, probably 4-methylindazole.

2,3-Dimethylphenyl acetate (III). 2,3-Dimethylphenol (127 g.) was converted into the acetate (154.5 g., 95%), which boiled at 112–113° under 12.5 mm., 104° under 8 mm.[8]

2-Hydroxy-3,4-dimethylacetophenone (IV). The acetate III (34 g.) was rearranged

[6] Klages and Liecke (8) give the b.p. as 125–126° (15 mm.).

[7] Töhl (9) reported 2,3-dimethylphenol to melt at 75°.

[8] Von Auwers and Mauss (3b) give the b.p. as 226–228°.

by aluminum chloride (51 g.) giving the ketone IV (23.4 g., 69%), a yellow liquid which boiled at 120–124° under 8 mm., 127–129° under 10.5 mm.[9] A semicarbazone was prepared, which, after crystallization from ethyl acetate, melted at 247° with decomposition.

Anal. Calc'd for $C_{11}H_{15}N_3O_2$: C, 59.73; H, 6.78.
Found: C, 60.00; H, 6.84.

2,3-Dimethyl-6-ethylphenol (VI). The ketone IV (15 g.) was reduced by the Clemmensen method. The reaction-mixture was steam distilled and the distillate was extracted with ether. The ether was replaced by petroleum ether, and the solution was extracted with Claisen's alkali. The alkaline extract was diluted with water, acidified, and extracted with ether. Removal of the solvent left the phenol (10 g., 74%) which melted at 52–53°. V. Auwers and Mauss (3b) give the melting point as 53–54°. Catalytic reduction of the ketone (98.4 g.) using a copper chromite catalyst, a temperature of 200°, and an initial hydrogen pressure 1300 lbs., gave the phenol VI (78 g., 87%) which melted at 50–52°.

4-Amino-2,3-dimethyl-6-ethylphenol (VIII). The phenol VI (11.5 g.) was coupled with diazotized sulfanilic acid (15.6 g.) as described for VII above. After standing for twenty-four hours, sodium hydrosulfite (75 g.) was added and the mixture was stirred and heated until the orange color faded. The amino phenol was filtered from the cooled solution, and a small portion of it was crystallized five times from benzene. The product formed light brown needles which melted at 138–139° with decomposition.

Anal. Calc'd for $C_{10}H_{15}NO$: C, 72.7; H, 9.15.
Found: C, 73.0; H, 9.0.

2,3-Dimethyl-6-ethylquinone (X). The moist amino phenol VIII was oxidized to the quinone by treatment with ferric chloride as described for IX. The quinone formed a yellow solid which weighed 10.7 g. (86% based upon the phenol VI) and which melted at 37–38° and boiled at 111° under 9 mm.

Anal. Calc'd for $C_{10}H_{12}O_2$: C, 73.17; H, 7.31.
Found: C, 73.07; H, 7.48.

2,3-Dimethyl-6-ethylhydroquinone. The quinone X (14 g.) was reduced with zinc (15 g.), acetic acid (60 cc.), and water (45 cc.) as described above for the reduction of IX. The crude product (12 g., 85%) melted at 160–161°. An analytical sample, prepared by crystallizing a small portion of the product from benzene, melted at 160–160.5°.

Anal. Calc'd for $C_{10}H_{14}O_2$: C, 72.28; H, 8.43.
Found: C, 72.34; H, 8.46.

2,5-Dimethyl-6-ethylbenzoquinone (XIV)

p-Xyloquinone (56 g., 82%) was prepared from 2,5-dimethylphenol (61 g.) by coupling the phenol with diazotized sulfanilic acid as described previously (2), but the yield of quinone was greatly improved by reducing the azo compound with sodium hydrosulfite (150 g.) as described above. A small portion of the intermediate 4-amino-2,5-dimethylphenol, crystallized from dioxane darkened at 220°, softened at 238°, and melted at 241° (decomp.).

Anal. Calc'd for $C_8H_{11}NO$: C, 70.03; H, 7.90.
Found: C, 69.83; H, 8.06.

The moist amino phenol was dissolved in a slight excess of hydrochloric acid, ferric chloride (400 g.) in water (300 cc.) was added, and the mixture was steam dis-

[9] Von Auwers and Mauss (3b) give the b.p. as 122–124° (12 mm.).

tilled. The distillate was chilled and the yellow quinone was filtered off. It melted at 123–125°. A portion of the quinone (4 g.) was reductively acetylated by boiling it for thirty minutes in acetic acid (10 cc.), acetic anhydride (20 cc.) to which had been added zinc (10 g., 20 mesh) and sodium acetate (1 g.). The mixture was poured into water, then made basic with ammonium hydroxide and extracted with ether. The product (1 g.), after crystallization from ligroin and chloroform, melted at 133–134°. Curiously, this *diacetate of* p-*xylohydroquinone* does not appear to have been described before.

Anal. Calc'd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.45.
Found: C, 65.29; H, 6.58.

This reductive acetylation gives very poor results when it is applied to any but very small amounts of the quinone.

1,4-Dimethoxy-2,5-dimethylbenzene (XV). *p*-Xyloquinone, prepared as above from *p*-xylenol (31 g.), was reduced to the hydroquinone with zinc and acetic acid, as described for the reduction of quinones IX and X. The crude hydroquinone was dissolved in methanol (100 cc.), methyl sulfate (50 cc.) was added, and the solution was vigorously stirred under reflux while a saturated solution of potassium hydroxide in methanol was carefully added. When the solution became strongly basic, more methyl sulfate (50 cc.) was added slowly, followed by the base, then more methyl sulfate (50 cc.) and again the base until the mixture was strongly basic. The dimethoxy compound can be isolated by steam distillation, but this operation is very tedious when large amounts of material are involved and it was found better to add water, filter off the product, and purify it either by distillation or crystallization from methanol. The product (32 g., 78% based upon the original phenol) obtained in this experiment boiled at 118–120° under 9 mm., and melted at 108° in agreement with the value in the literature (10).

1,4-Dimethoxy-2,5-dimethyl-6-bromobenzene (XVI). The dimethyl ether XV (20 g.) was dissolved in carbon tetrachloride (30 cc.) and to the warm solution was rapidly (15 minutes) added a solution of bromine (20 g.) in carbon tetrachloride (40 cc.). There was a short induction period, after which the reaction proceeded quite regularly. The solution was washed, first with water, then with bisulfite (20%) followed by sodium hydroxide (10%). The solvent was removed and replaced by petroleum ether and this solution was extracted with Claisen's alkali and then washed with water. The yield of bromo compound (m.p., 51–54°) was 26 g. (88%). An analytical sample, melting at 59–60°, was prepared by crystallizing 0.5 g. of the material from methanol.

Anal. Calc'd for $C_{10}H_{13}BrO_2$: C, 48.98; H, 5.31.
Found: C, 49.65, 49.23; H, 5.49, 5.65.

2,5-Dimethyl-3,6-dimethoxybenzaldehyde (XX). The dimethyl ether XV (3.32 g., 0.02 moles) was dissolved in benzene (20 cc.), zinc cyanide (3.5 g.) was added and the mixture was vigorously stirred while a rather rapid stream of hydrogen chloride was passed through it for an hour. The yellow solution was cooled and aluminum chloride (4.0 g.) and more benzene (15 cc.) were added. The stream of hydrogen chloride was continued for two hours longer. After standing for one hour, more zinc cyanide (0.7 g.) was added and the gas was passed through the vigorously stirred mixture for another hour. The mixture was then warmed to 40–50° for two hours while stirring and introduction of hydrogen chloride was continued. After standing overnight, hydrochloric acid (50 cc., 15%) was added and the mixture was refluxed for thirty minutes and then steam distilled. The distillate, containing the benzene and a white solid (which rapidly turned orange in the light) was extracted with ether.

The solvents were removed from the combined extracts, and the residue (3 g.), an orange solid, was crystallized from methanol. It then melted at 51–53°. For analysis, a small sample was crystallized twice more from methanol, when it melted at 55–56°.

Anal. Calc'd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22.
Found: C, 68.37; H, 7.34.

Semicarbazone. The aldehyde (1 g.) was dissolved in a little methanol, water was added until the solution became cloudy and then the cloudiness was removed by addition of methanol. Semicarbazide hydrochloride (1 g.) and sodium acetate (1.5 g.) were added. The semicarbazone started to crystallize at once. More methanol and water were added and the mixture was boiled for ten minutes and then chilled. The product was removed and crystallized from methanol, when it melted at 216–217°.

Anal. Calc'd for $C_{12}H_{17}N_3O_3$: C, 57.37; H, 6.77.
Found: C, 57.16; H, 6.77.

2,5-Dimethyl-3,6-dimethoxyphenyl methyl carbinol (XIX). A. From the aldehyde XX. The aldehyde (5 g., 0.027 moles) in dry ether (25 cc.) was added to a solution of methylmagnesium bromide (prepared from methyl bromide (5 g.), magnesium (0.65 g.), and 25 cc. of ether). An orange precipitate formed immediately, but as the reaction proceeded, this gave way to a white granular precipitate. The mixture was refluxed for a few minutes and was then poured into iced ammonium chloride solution. The ether layer was removed and the aqueous layer was extracted three times with ether. The combined ether solutions were filtered, the solvent was distilled off and the residue, an oil (5 g.), was distilled. It boiled at 140–160° under 8 mm., and weighed 3.5 g.

Anal. Calc'd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57.
Found: C, 68.38; H, 8.90.

The above material was subjected for four hours to the action of hydrogen under 2650 lbs. at 175° in the presence of Raney nickel, but no reduction occurred. The product was an oil which boiled at 154–156° under 8 mm., and it was unchanged XIX as shown by the analysis.

Anal. Found: C, 68.74; H, 8.76.

B. From the bromo compound XVI. The bromo compound (41.5 g.), and ethyl bromide (18.5 g.) in ether (175 cc.) were added slowly and with stirring to magnesium turnings (8.25 g.). The reaction was slow in starting, but proceeded vigorously once it was under way. After the addition was complete (30 minutes) the mixture of solution and white precipitate was refluxed and stirred for three hours. Considerable metal remained undissolved. The mixture was cooled (0°) and a solution of freshly distilled acetaldehyde (30 g.) in ether (40 cc.) was slowly added. After the vigorous reaction was over, the mixture was stirred and refluxed for thirty minutes and then allowed to stand overnight. After decomposition of the reaction-mixture with dilute acetic acid, the ether layer was removed, washed with water and dried (Drierite). The residue was fractionated under 8 mm. through a short packed column and gave (A) a forerun (4 g.) mostly solid, boiling up to 137°, and (B) a liquid fraction (22 g.) boiling at 137–156°. Refractionation of (B) gave only 6 g. of material with the boiling point 154–156°; most of this fraction boiled at 137–153°. Considerable resinous material remained in the distillation flask.

2,5-Dimethyl-3,6-dimethoxystyrene (XXI). A drop of sulfuric acid was added to the above carbinol (6 g.) and the mixture was distilled under 8 mm. Water came over first, followed by a colorless liquid which boiled at 125–126°. A drop of sulfuric acid was added to the low-boiling material from fraction (B) above and from this

mixture more of the styrene boiling at 125–126° was obtained. A similar treatment of the resinous residue from (B) above gave still more of the styrene. Redistillation of the combined styrene fractions gave 16.3 g. of material which boiled at 125–129° under 8 mm., and which was regarded as XXI although the analytical values were poor.

1,4-Dimethoxy-2,5-dimethyl-6-ethylbenzene (XVII). A. From the bromo compound XVI. The bromo compound XVI (11.5 g.) was dissolved in dry ether (60 cc.) and the solution was placed in a three-necked flask equipped with reflux condenser, stirrer, and dropping-funnel. Magnesium (3.64 g.) and a crystal of iodine were added, the stirrer was started, and ethyl bromide (5.12 g.) in ether (30 cc.) was slowly (thirty minutes) dropped into the mixture. The reaction was brisk but easily controlled. After all the ethyl bromide had been added, the mixture was refluxed gently for four hours. At the end of this time the product was a pasty mass. Ethyl sulfate (39 g.) dissolved in ether (50 cc.) was added slowly (one hour) and with stirring. The mixture was refluxed for one hour longer and then was set aside for twelve hours. Iced ammonium chloride was added and the ether layer was removed and washed six times with sodium hydroxide (10%) followed by one washing with water. Removal of the ether left an oil (10 g.) which partially solidified in a bath of acetone and dry ice. The solid (m.p. 100–106°, XV) was filtered from the cold mixture and the filtrate was distilled under 8 mm. from a Hickman still. The first fraction (1.1 g.) boiled at 100–106° and was XV. The second fraction (3.7 g.) boiled at 125–128° and was the dimethoxy compound XVII. Repetition of this experiment, starting with 54 g. of the bromo compound XVI, gave 24.1 g. (56%) of the dimethoxy compound XVII boiling at 135–139.5° under 19 mm., but a considerable residue, which apparently was also XVI, could not be distilled out because of the design of the still (see below). The substance was not pure, however, for the analytical values were poor. Rather than risk the losses involved in handling this liquid any further, it was converted directly to the quinone XIV. B. From the vinyl compound XXI. The vinyl compound XXI (16 g.) was not reduced when its solution in an equal volume of ethanol was subjected to the action of hydrogen under 1800 lbs. pressure at 200° in the presence of a copper chromite catalyst. The catalyst was converted to a red powder which was removed, fresh catalyst was added, and the experiment was repeated, but the result was the same. The substance was then recovered (11.4 g.) and the recovered material, in an equal volume of ethanol, was subjected to the action of hydrogen in the presence of Raney nickel. Reduction was rapid at 50° under 1000 lbs. pressure. The product, on fractionation, gave 9.8 g. of the dimethoxydimethylethyl compound XVII which boiled at 119–120° under 8 mm. In view of the obvious impurity of this specimen, it was not analyzed but was converted directly to XVIII and the quinone XIV.

2,5-Dimethyl-6-ethylquinone (XIV). The dimethyl ether XVII (24.1 g.) was refluxed for one hour in acetic acid (320 cc.) containing hydrobromic acid (48%, 240 cc.). Ice was added and the mixture was extracted with ether. After washing the ether layer four times with water, the ether was evaporated and the residue was added to excess ferric chloride solution and steam distilled. The distillate was extracted with ether, the ether solution was washed with water and dried. Removal of the ether left the quinone as a golden yellow oil. The residue left in the still after removal of XIV (see above) was put through a similar treatment. The combined quinone weighed 24 g. (73% based upon 54 g. of bromo compound XVI).

Anal. Calc'd for $C_{10}H_{12}O_2$: C, 73.17; H, 7.31.

Found: C, 73.12; H, 7.74.

2,5-Dimethyl-6-ethylhydroquinone (XVIII). The quinone XIV (24 g.) was dis-

solved in acetic acid (100 cc.) and water (75 cc.) and reduced by boiling the solution with zinc (20 mesh, 24 g.) as described for the reductions of the other quinones. The product (22.5 g., 93%) melted at 158–159°. A small portion, crystallized from benzene, melted at 161–163°.

Anal. Calc'd for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43.
Found: C, 72.38, 72.02; H, 8.80, 8.70.

SUMMARY

1. The syntheses of the three dimethylethylquinones have been described.

2. The *p*-aminophenols corresponding to these quinones have been prepared.

3. Improvements in the preparation of 2,3-dimethylaniline, and the conversion of this amine into 2,3-dimethylphenol have been described.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE BODROUX-TSCHITSCHIBABIN, AND THE BOUVEAULT ALDEHYDE SYNTHESES

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Bodroux (2), who prepared triaryl methanes by action of Grignard reagents upon chloroform or bromoform, found that the yield was usually quite low and never better than 25%.

$$HCX_3 + 3RMgX \rightarrow R_3CH + 3MgX_2$$

Hoping to improve the yields, he substituted ethylorthoformate for the haloform, but in this case no triaryl methanes resulted; only aldehydes were formed.

$$HC(OC_2H_5)_3 + RMgX \rightarrow RCH(OC_2H_5)_2 + MgXOC_2H_5$$
$$RCH(OC_2H_5)_2 + H_2O \xrightarrow{H^+} RCHO + 2C_2H_5OH$$

Tschitschibabin (3), independently and at about the same time, discovered the same reaction. He discovered that if the orthoformic ester was first added to the ethereal solution of the Grignard reagent, and then most of the solvent removed by distillation, a point was reached at which a vigorous reaction ensued. Much heat was evolved and the reaction product was a viscous oil which gave the acetal on treatment with acidified water. The acetal could be obtained pure by fractionation and from it the aldehyde could be obtained. Tschitschibabin and Jelgasin (4) discovered somewhat later that the reaction was not confined to one of the ethoxyl groups of the ester, although Bodroux (5) found that replacement of the first ethoxyl group was a slow reaction and that yields (of benzaldehyde) were improved by refluxing the mixture after addition of the orthoformic ester.

Wood and Comley (6) also found that poor yields of aldehydes were obtained unless, after adding the orthoformic ester, most of the ether was removed and the residue was heated.

Bert (7) prepared an extensive series of aldehydes using chlorides of the type $Ar(CH_2)_nCl$, and a number of other investigators have prepared aldehydes by means of the orthoformate synthesis (8).

As the yields of aldehydes obtained by different investigators using this method have varied widely, it appeared that the reaction was greatly affected by relatively slight differences in procedure. In order to evaluate

these, a study was undertaken which had as its object the determination of the optimum conditions for preparation of a simple aromatic aldehyde, benzaldehyde, and the application of these conditions to the preparation of a few other aromatic aldehydes. In general, the Grignard reagents (0.2 moles) were prepared in ether in the usual way. After formation of the reagent, enough ether was added to bring the total amount up to 4.5 moles per mole of halogen compound. The orthoformic ester was then mixed with an equal volume of ether and slowly added to the Grignard solution, after which the mixture was processed. Four variants in the conditions were examined: 1. the length of time the reagents were allowed to stand after mixing; 2. the duration of the period of refluxing, after the ether was removed; 3. the relative amount of orthoformic ester used; 4. the effect of the nature of the solvent. In addition, the isolation and purification of the aldehyde itself was investigated.

Three experiments were made in which the time of standing was varied. After three hours, 10.7 g. (21.5%) of benzaldehyde bisulfite compound was obtained; after six and one-half hours, 37 g. (81%), and after fifteen hours, 40.2 g. (89.2%). Using a fifteen-hour period of standing, the ether was then boiled off and the residue was heated on the steam-bath. After fifteen minutes of heating, the yield of bisulfite compound was 40.2 g. (89.2%) and after sixty minutes the yield was 34.5 g. (75.6%). These results showed that heating after removal of the ether offered no advantages and might even be disadvantageous if the time of heating were prolonged.

Using a fifteen hour period of standing, then removing the ether and heating the residue for fifteen minutes, the effect of varying the amount of orthoformic ester was determined. The results showed that there was a slight increase in the yield (89.2% to 95.0%) of benzaldehyde when a 100% excess of the halogen compound was used. However, this advantage is more than offset when the halogen compound is a costly one.

In determining the effect of the solvent, the Grignard reagent (0.2 moles) was prepared in the usual way, then dry toluene (50 cc.) was added. The ether was distilled off and when the temperature reached 90°, orthoformic ester (0.2 moles) was added. The reaction-mixture was decomposed by boiling for fifteen minutes with 5 *N* sulfuric acid and the aldehyde was then isolated. The results showed that this procedure is not advantageous, but rather the reverse. Thus, when the reaction product was decomposed immediately after mixing the reagents, the yield of aldehyde bisulfite compound was 29.6%; when the mixture was heated for fifteen hours, the yield was 65.8%.

Blank experiments showed that the yield of bisulfite compound from benzaldehyde was from 85–90%. Decomposition of the bisulfite com-

pound with dilute sulfuric acid, followed by steam distillation, ether extraction of the distillate and fractionation of the aldehyde gave yields of aldehyde of about 80%. When the bisulfite compound was decomposed by dilute sodium hydroxide, the yield of aldehyde was only 55–60%.

It thus appeared that the maximum yield of benzaldehyde, weighed as the bisulfite compound, was around 90% and that this high yield could be obtained by observing the following conditions: 1. The reaction-mixture should be allowed to stand for fifteen hours after mixing the reagents; 2. The ether should be removed and the residue heated for not longer than fifteen minutes on the steam-bath; 3. Equimolecular quantities of the Grignard reagent and orthoformic ester should be used. Using these conditions, *o*-, *m*- and *p*-bromotoluenes were converted to the toluic aldehydes *via* the Grignard reagents in yields of 51.7, 56.2, and 50.4% respectively.

Bouveault, in 1903, prepared a series of aldehydes by means of the reaction between Grignard reagents and disubstituted formamides (9):

$$RMgX + R'R''NCHO \rightarrow RCH(OMgX)NR'R'' \rightarrow RCHO + R'R''NH + MgX_2$$

The unsubstituted formamide cannot be used, and Bouveault used dimethyl-, diethyl-, and piperidyl- formamides as well as methyl- and ethylformanilides. Bouveault did not give exact yields of his products, but stated that the yields were "generally good, although poor in some instances." Houben and Doescher (10) have also used this synthesis.

The Bouveault synthesis is complicated by the fact that bases, as well as hydrocarbons are also formed, a fact noted by Bouveault himself (11), by Viguier (12), and by Maxim and Mavrodineanu (13). Maxim (14) found that diethylformamide could react with Grignard reagents in two ways:

I. $$HCONEt_2 + RMgX \rightarrow RCHO + Et_2NH$$

II. $$HCONEt_2 + 2RMgX \rightarrow R_2CHNEt_2 + MgO + MgX_2$$

Ethylmagnesium bromide and ethylmagnesium iodide reacted entirely according to reaction II, while isobutylmagnesium bromide reacted about equally according to both equations. Using three moles of RMgX per mole of amide, Maxim obtained good yields of tertiary amines in all the cases he investigated. Using equimolecular amounts of amide and Grignard reagent, the aldehyde was the chief product when methyl- or ethyl- formanilide or diphenylformamide were employed, the latter giving only the aldehyde. But when diethylformamide or piperidylformamide were used, more amine than aldehyde was formed. The amount of

aldehyde increased as the molecular weight of R in RMgX increased, but in all cases large amounts of the amide were recovered. Phenylmagnesium bromide behaved in a rather specific manner, giving considerable amounts of tetraphenylethylene when its reaction product with piperidylformamide, dimethylformamide, or diethylformamide was decomposed by dilute sulfuric acid, while decomposition by ammonium chloride gave the tertiary amine $(C_6H_5)_2CHNR_2$. Methylformanilide and diphenylformamide re-

TABLE I

REACTION BETWEEN PHENYLMAGNESIUM BROMIDE AND METHYLFORMANILIDE

HALIDE, MOLES	METHYLFORMANILIDE, MOLES	BISULFITE COMPOUND, G.	YIELD, %
0.2	0.2	27.0	59
0.2	0.2	5	11[a]
0.2	0.37	30.5	67[b]
0.2	0.37	30.5	67[c]

[a] Ether boiled off, 50 cc. toluene added and reaction conducted at 90°.
[b] Excess formanilide added to the Grignard solution in ether.
[c] Grignard solution slowly added to the formanilide in ether.

TABLE II

YIELDS OF ALDEHYDES FROM GRIGNARD REAGENTS AND METHYLFORMANILIDE

HALOGEN COMPOUND, MOLES	PRODUCT, G.	YIELD, %	YIELD OF GRIGNARD REAGENT, %	YIELD OF PRODUCT BASED UPON RMgX, %.
o-Bromotoluene..... 0.2	11[a]	50	—	—
m-Bromotoluene..... 0.2	8[b]	33	—	—
p-Bromotoluene..... 0.2	9[c]	37	—	—
Bromohydroquinone dimethyl ether. 0.1	5[d]	22	52	43
Bromohydroquinone dimethyl ether. 0.1	3.9[d]	17	52	33
Bromomesitylene..... 0.144	6.0[e]	18.8	—	—

[a] Aldehyde; 100% excess methylformanilide used.
[b] Aldehyde; 25% excess methylformanilide used.
[c] Aldehyde.
[d] Aldehyde semicarbazone; 38% of hydroquinone dimethyl ether obtained.
[e] Aldehyde semicarbazone; 40% of mesitylene obtained.

acted with phenylmagnesium bromide to give benzaldehyde and benzhydrol exclusively.

Although the Bouveault reaction appeared to be a very complex reaction leading to a variety of products, the reaction between methylformanilide and several Grignard reagents was investigated to determine the best conditions for the formation of aldehydes. In the initial experiments, phenylmagnesium bromide was used. The reaction was conducted in

ether alone, in toluene after boiling off the ether, and by adding excess formanilide to the Grignard reagent in ether as well as by the inverse procedure. The results are given in Table I.

It thus appeared that the reaction produced chiefly benzaldehyde, although the yields were inferior to those obtained when ethylorthoformate was used. The reaction was then applied to several aromatic Grignard reagents, adding the methylformanilide to the Grignard solution in ether. Equimolecular quantities of reagents were used except as noted. The results are given in Table II.

Thus of the two syntheses, one using ethylorthoformate, and the other using methylformanilide, the former is superior for the preparation of aldehydes from aromatic halogen compounds.

EXPERIMENTAL PART

The apparatus consisted of a 1-liter 3-necked flask, fitted with a dropping-funnel, mechanical stirrer, and condenser. All openings to the air were protected by calcium chloride guard tubes. Magnesium turnings, which had been washed with ether and dried in a desiccator, were placed in the flask, the apparatus was assembled and heated on the steam-bath while a current of dry air was passed through. After the flask had cooled, ether (10 cc.) and a crystal of iodine were introduced. The halogen compound was mixed with an equal volume of ether and about 10 cc. of this solution was dropped onto the magnesium. After the reaction started, enough ether was added to the solution of the halogen compound to bring the total up to 4.5 moles per mole of halogen compound. This solution was then added, with vigorous stirring, at the rate of about two drops per second. After the addition was complete, the mixture was refluxed and stirred for fifteen minutes longer. Then, with stirring, the orthoformic ester, dissolved in an equal volume of ether, was added at the rate of about two drops per second. No apparent reaction occurred. After the addition of the reagent was complete, the reaction-mixture was processed as described under the several headings above. The reaction-mixture was decomposed by addition of ice and 5*N* sulfuric acid and refluxed for a few minutes to decompose the acetal. If the ether had been distilled off, the cooled mixture was extracted with ether three times (50 cc. each time); otherwise, the ether layer was merely separated. The combined ethereal solutions (volume about 150 cc.) were shaken vigorously with saturated sodium bisulfite solution (50 cc.) and filtered. The filtrate was shaken with fresh bisulfite solution and again filtered. The combined solids were washed with cold alcohol (50 cc.), then with ether (50 cc.), and spread in the air to dry. After fifteen minutes, the material was weighed.

In the experiments using methylformanilide, the Grignard reagent was formed as above and then made up to a volume of 300 cc. with ether. The methylformanilide was slowly added with stirring. A heavy white precipitate formed at once; this gradually darkened. After standing overnight, the reaction-mixture was decomposed with 5 *N* sulfuric acid and the aldehyde was removed by ether extraction. The aldehyde in the ether was converted into the bisulfite compound as described above, or the ether was evaporated and the residue treated with semicarbazide in the usual way.

Methylaniline formed in the reaction was recovered by making the aqueous solutions alkaline and extracting with ether.

SUMMARY

1. This paper reports the effect of changing various conditions in the Bodroux-Tschitschibabin synthesis of aldehydes. The optimum conditions for conversion of bromobenzene to benzaldehyde *via* the Grignard reagent have been investigated.

2. A similar investigation of the Bouveault aldehyde synthesis has been made.

3. The synthesis of aldehydes from Grignard reagents using ethylorthoformate is superior to that using methylformanilide.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

MOLECULAR REARRANGEMENTS INVOLVING OPTICALLY ACTIVE RADICALS. IX. FURTHER STUDIES ON THE WOLFF REARRANGEMENT OF OPTICALLY ACTIVE DIAZOKETONES

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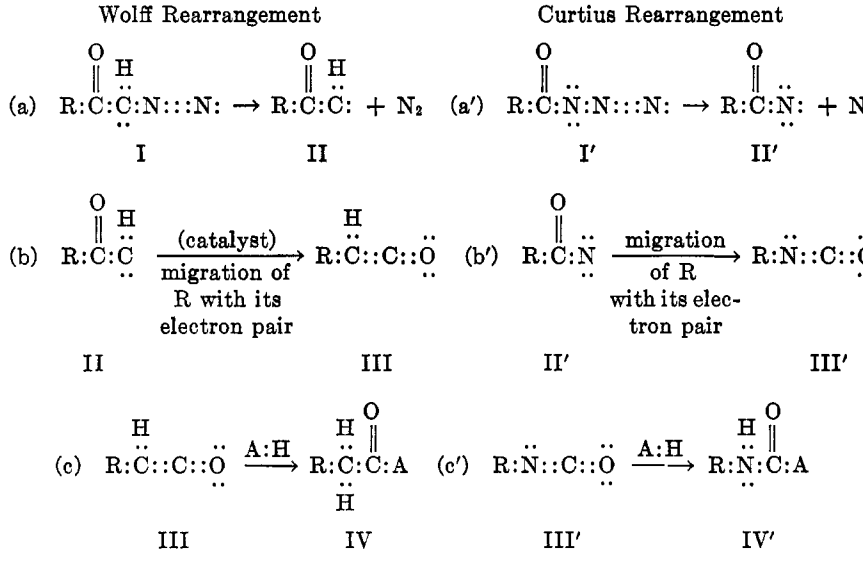
The mechanism for the Wolff rearrangement of diazoketones advanced recently by Eistert (1) and now generally accepted in discussions of this reaction (2) implies a strict similarity in the electronic behavior of the group, R, in both this and the well-known Curtius, Hofmann, and Lossen degradations.



In both rearrangement processes (b) and (b') the shift of the radical, R, is supposed to occur in such a fashion that the radical remains at all times in complete possession of its electron pair. Such a postulate was shown to explain most readily the complete retention of optical activity in the

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Curtius, Hofmann, and Lossen rearrangements where R is an asymmetric group of general structure

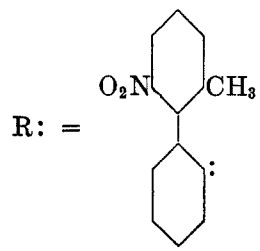
$$R: = R_2:\overset{\overset{R_1}{\cdot\cdot}}{\underset{\underset{R_3}{\cdot\cdot}}{C}}:$$

(R_1 and R_2 = alkyl or aryl groups; R_3 = H or an alkyl or aryl group)

in the earlier communications of this series (3). In the eighth communication (4), it was pointed out that if the Wolff rearrangement proceeded according to the mechanism outlined above, a similar retention of optical activity by the migrating group would be expected. The results presented in that paper, however, showed conclusively that for the Wolff rearrangement of dextrorotatory benzylmethyldiazoacetone, this was certainly not the case, since partial or complete racemization of the benzylmethylcarbinyl group occurred, depending on the conditions of the experiment.

It is the purpose of this paper to extend the study of the Wolff rearrangement of optically active diazoketones to different types of the radical, R, with a view to establish how far similarity or dissimilarity prevails between the two types of rearrangement, and to determine the cause or causes of the difference in the behavior of the benzylmethylcarbinyl group in the two processes.

In explaining this difference it would seem logical to assume that the group, R, at some time during the step (b) is released as a relatively free fragment and racemizes while in this state. Evidence was obtained by Wallis and Moyer (3d) that for rearrangements of the Curtius, Hofmann, and Lossen types this is not the case, a conclusion further supported by the subsequent investigations of Bell (5). To settle this point a study was made of the Wolff rearrangement of dextrorotatory α-diazo-*o*-(2-methyl-6-nitrophenyl)acetophenone. This compound was chosen since the migrating group would be that shown by Bell (5) to suffer no racemization during the Curtius degradation of the azide of dextrorotatory 6-nitro-2-methyldiphenyl-2′-carboxylic acid,

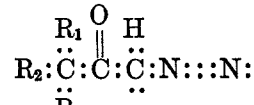


The diazoketone, $[\alpha]_D^{20}$ +115° (c = 6.00 in chloroform), was prepared by the action of diazomethane on the chloride of this acid, $[\alpha]_D^{20}$ +70.0° (c = 1.00 in methanol). Similarly, an optically impure levo-modification, $[\alpha]_D^{20}$ −46.1° (c = 5.99 in chloroform) was prepared from an incompletely resolved levorotatory 6-nitro-2-methyldiphenyl-2′-carboxylic acid, $[\alpha]_D^{20}$ −28.0° (c = 1.00 in methanol).

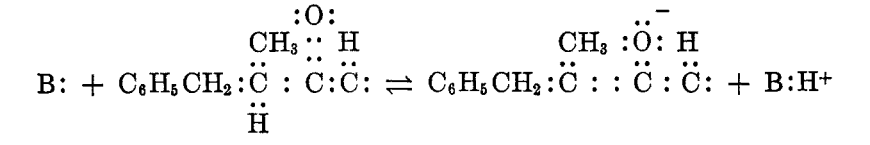
Portions of the diazoketone were then subjected to the Wolff rearrangement under two sets of conditions. First, the diazoketone was added in small portions to boiling aniline. Rapid rearrangement took place to give dextrorotatory *o*-(2-methyl-6-nitrophenyl)-α-toluanilide, m.p. 124°, $[\alpha]_D^{20}$ +481° (c = 0.96 in chloroform), without any accompanying racemization in detectable amount. Second, a portion of the diazoketone was dissolved in dioxane and treated at 65–70° with an aqueous solution of sodium thiosulfate containing some silver oxide as a catalyst. Rearrangement proceeded smoothly to give dextrorotatory *o*-(2-methyl-6-nitrophenyl)-α-toluic acid, $[\alpha]_D^{20}$ +53.0° (c = 1.00 in chloroform). This acid was then converted to the corresponding anilide, m.p. 123–124°, $[\alpha]_D^{20}$ +485° (c = 1.02 in chloroform), which was identical with the anilide obtained as outlined above.

These results indicate quite clearly that release of the migrating group as a free fragment is no more characteristic of the Wolff rearrangement than it is of the Curtius and Hofmann rearrangements. Otherwise racemization would have occurred, since in the free fragment unhindered rotation of the phenyl group about the C—C pivot bond would have taken place. The number of possible explanations for the divergence in behavior of the benzylmethylcarbinyl group during the two types of rearrangement is now reduced to two: (A) The observed racemization is due to a structural peculiarity of the compound studied and is not to be connected with the electronic behavior of the group, R, during the shift in step (b). (B) The racemization is the expression of a real difference in the electronic structure of the asymmetric center during step (b) as contrasted with (b′). Such would be the case, for example, if step (b) proceeded so that at some time the asymmetric center was left with a sextet or septet of electrons (3b, c, e).

As we have pointed out (4), a decision can be made between these possibilities by studying the rearrangement of a diazoketone of the form



where R_1, R_2, and R_3 are all alkyl or aryl groups. The structural peculiarity of benzylmethyldiazoacetone by which an enolization of the intermediate (II above)

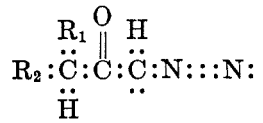


(B: = OH^-, NH_3, etc.)

might cause racemization is thereby eliminated. Racemization of such a trisubstituted diazoacetone then would be due only to electronic changes in step (b) which do not occur in step (b′), *i.e.*, changes by which the asymmetric group assumes a planar structure. Preliminary efforts in this direction were previously discussed (4), but the lack of available material of sufficient optical purity for obtaining conclusive results prevented a definite decision from being made at that time.

Accordingly, a study was made of the rearrangement of dextrorotatory 1-diazo-3-methyl-3-phenylheptan-2-one, $[\alpha]_D^{20}$ +65.0° (c = 14.1 in benzene), obtained by the action of diazomethane on the chloride of dextrorotatory 2-methyl-2-phenylhexanoic acid, α_D^{20} +24.5° (1 dm. tube without solvent). The diazoketone was first rearranged in boiling aniline to give the corresponding anilide. A levorotatory 3-methyl-3-phenylheptanoanilide, $[\alpha]_D^{20}$ −59.5° (c = 2.77 in benzene), m.p. 76°, was obtained. No evidence of accompanying racemization was detected. A subsequent rearrangement of a portion of the diazoketone in aqueous dioxane containing sodium thiosulfate and silver oxide gave an organic acid which was converted by the action of aniline on its chloride to an anilide of m.p. 76–77°, $[\alpha]_D^{20}$ −58.9°, (c = 2.82 in benzene), identical with the preceding product. Similar rearrangements of an incompletely resolved levorotatory diazoketone, $[\alpha]_D^{20}$ −29.4° (c = 15.4 in benzene), prepared from an incompletely resolved levorotatory 2-methyl-2-phenylhexanoic acid, α_D^{20} −10.5° (1 dm. tube without solvent), led to optically impure 3-methyl-3-phenylheptanoanilide from which, on repeated recrystallization, the racemic anilide, m.p. 87°, was obtained.

The results indicate that the racemization of optically active diazoketones during the Wolff rearrangement is by no means a general phenomenon. Rather it is a special property of diazoketones of the type



where the asymmetric center possesses an enolizable hydrogen. There still remains, however, the problem of reconciling this conclusion with the optical stability of the benzylmethylcarbinyl group during the Hofmann rearrangement (3b). Here, no enolization occurs, though the reaction proceeds in a strongly basic solution at 70–80°. We are inclined to attribute the difference to the effect of the silver ion-silver metal surface of the catalyst present in the Wolff rearrangement. This immediately raises the interesting question of the fate of optically active benzylmethyldiazoacetone in a Wolff rearrangement without a catalyst present. Such a state obtains, of course, in the rearrangements described above where diazoketones are treated with boiling aniline. The temperature of this reaction (184°) is so high, however, that in the basic medium the optical activity of any system of the form $R_1R_2HC-\underset{|}{C}=O$ would be expected to be short-lived. Such an experiment was in fact carried out on dextrorotatory benzylmethyldiazoacetone, but the β-benzyl-β-methylpropionanilide so obtained was completely optically inactive. So far, we have not found a method of rearranging this compound without the aid of a catalyst at temperatures below 100°. The use of liquid ammonia in a sealed tube at room temperature results in the formation of a black tar from which no recognizable product can be isolated.

We are aware, of course, that such enolization is not the only explanation consistent with the data now at hand. For example, a different mechanism may be involved when the migrating group is secondary than when it is tertiary, as in the solvolysis of secondary and tertiary halides. We contemplate, therefore, a thorough kinetic investigation of the reaction to settle this point.

EXPERIMENTAL

Preparation of α-diazo-o-(2-methyl-6-nitrophenyl)acetophenone. This compound was prepared from 6-nitro-2-methyldiphenyl-2′-carboxylic acid. The acid was prepared according to the method of Stoughton and Adams (6). Five grams of the acid was mixed with the calculated amount of phosphorus pentachloride and warmed for one-half hour on the steam-bath. The phosphorus oxychloride was then removed on the steam-bath at 15 mm. pressure, and the residue was recrystallized from a mixture of benzene and light petroleum ether; m.p. 85°. The purified acid chloride was dissolved in 100 cc. of dry ether and added slowly with shaking to a solution of 4 g. diazomethane in 500 cc. of dry ether at −10°. Vigorous evolution of nitrogen set in immediately, but subsided after about twenty minutes. The solution was allowed to stand overnight, filtered, and the ether removed under reduced pressure at 30°. The product, a bright yellow viscous oil, was not obtained crystalline.

For identification, 1 g. of diazoketone was warmed for thirty minutes at 80° with 5 cc. of glacial acetic acid. The mixture was cooled and diluted with light petroleum ether. Orange crystals of crude α-acetoxy-o-(2-methyl-6-nitrophenyl) acetophenone

separated immediately. These were recrystallized from dilute alcohol. There recrystallizations gave a pure product of m.p. 125°.

Anal. Calc'd for $C_{17}H_{15}NO_5$: C, 65.24; H, 4.83; N, 4.47.
Found: C, 65.3; H, 4.8; N, 4.6.

Rearrangement of α-diazo-o-(2-methyl-6-nitrophenyl)acetophenone in aniline. Two grams of the diazoketone was added in small portions over a period of two minutes to 10 cc. of boiling, freshly distilled aniline. A vigorous reaction ensued, accompanied by rapid darkening of the reaction-mixture. After one minute the mixture was cooled and poured into 150 cc. of 4 *N* hydrochloric acid. The product was taken up in ether and the extract washed well with dilute hydrochloric acid, then with water, and finally with dilute sodium bicarbonate solution. The ether solution was dried over anhydrous sodium sulfate and decolorized with animal charcoal. The product obtained on removal of the ether was recrystallized three times from dilute alcohol; m.p. 137°.

Anal. Calc'd for $C_{21}H_{18}N_2O_3$: C, 72.90; H, 5.24; N, 8.08.
Found: C, 72.9; H, 5.2; N, 8.1.

Rearrangement of α-diazo-o-(2-methyl-6-nitrophenyl)acetophenone in aqueous dioxane. Two grams of the diazoketone was dissolved in 25 cc. of dioxane and added to a mixture of 1.3 g. of silver oxide in 65 cc. of a solution of 3 g. sodium thiosulfate in 100 cc. of water. The mixture was stirred at 65–70° for two hours, then filtered and washed thoroughly with ether to remove impurities insoluble in water. The aqueous solution was then acidified with dilute nitric acid and the product taken up in ether. It was extracted from the ether by washing with several portions of 10% sodium carbonate solution. The extracts were united and acidified with hydrochloric acid. The organic acid was then extracted with ether, washed, dried over sodium sulfate, decolorized with animal charcoal, filtered, and the ether removed. The product, 1 g. of a viscous yellow oil, was not obtained crystalline.

For identification, it was converted to the acid chloride by refluxing for two hours with thionyl chloride. The chloride so obtained was then treated with excess of aniline in benzene solution. After the reaction was complete, the solution was diluted with ether and the excess aniline removed by thorough washing with dilute hydrochloric acid. The solution was then washed several times with 10% sodium hydroxide solution and dried over potassium carbonate. Removal of the solvent gave a product which, after three recrystallizations from dilute alcohol, melted at 136–137°. Mixed melting point with a specimen of *o*-(2-methyl-6-nitrophenyl)-α-toluanilide, 136–137°.

Preparation of dextrorotatory α-diazo-o-(2-methyl-6-nitrophenyl)acetophenone. Sixty grams of the 6-nitro-2-methyldiphenyl-2′-carboxylic acid described above was resolved into its enantiomorphs according to the method of Bell (5). Fifteen grams of the dextrorotatory acid, $[\alpha]_D^{20}$ +70.0° (*c* = 1.00 in methanol), was obtained. Five grams of this acid was converted to the corresponding diazoketone as described above under the preparation of the racemic form. The dextrorotatory diazoketone was not obtained crystalline. Optical rotation: $[\alpha]_D^{20}$ +115° (*c* = 6.00 in chloroform).

From the mother liquors of the resoltuion was obtained the pure levorotatory acid and an optically impure levo-modification, $[\alpha]_D^{20}$ −28.0° (*c* = 1.00 in methanol). From the latter was prepared an optically impure levo-modification of the diazoketone: $[\alpha]_D^{20}$ −46.1° (*c* = 5.99 in chloroform).

Rearrangement of the dextrorotatory diazoketone in aniline. Two grams of dextrorotatory α-diazo-*o*-(2-methyl-6-nitrophenyl)acetophenone was converted into the

corresponding anilide by the method described for the preparation of the racemic form. The dextrorotatory *o*-(2-methyl-6-nitrophenyl)-α-toulanilide so obtained had the following physical constants: m.p. 124°; $[\alpha]^{20}_{6563}$ +369°; $[\alpha]^{20}_{5893(D)}$ +481°; $[\alpha]^{20}_{5463}$ +624°; $[\alpha]^{20}_{4861}$ +875° (c = 0.96 in chloroform).

Anal. Calc'd for $C_{21}H_{18}N_2O_3$: C, 72.90; H, 5.24; N, 8.08.
Found: C, 73.0; H, 5.2; N, 8.2.

No racemate could be detected in the mother liquors from the recrystallizations.

Rearrangement of the optically impure levorotatory diazoketone gave a product of m.p. 125–134°; $[\alpha]^{20}_{D}$ −137.5° (c = 1.08 in chloroform).

Rearrangement of the dextrorotatory diazoketone in aqueous dioxane. Two grams of dextrorotatory α-diazo-*o*-(2-methyl-6-nitrophenyl)acetophenone was dissolved in 25 cc. of dioxane and treated as described above under the corresponding rearrangement of the racemic form. The resulting *o*-(2-methyl-6-nitrophenyl)-α-toluic acid, $[\alpha]^{20}_{D}$ +53.0 (c = 1.00 in chloroform), was not obtained crystalline. For identification it was converted to the corresponding anilide as described under the identification of the racemic acid. The product so obtained had the following physical constants: m.p. 123–124°; mixed m.p. with a specimen of dextrorotatory *o*-(2-methyl-6-nitrophenyl)-α-toluanilide: 123–124°; $[\alpha]^{20}_{6563}$ +363°; $[\alpha]^{20}_{5820(D)}$ +485°; $[\alpha]^{20}_{5463}$ +625° (c = 1.02 in chloroform). Again no racemate could be detected in the mother liquors of the recrystallizations.

Preparation of dextrorotatory 1-diazo-3-methyl-3-phenylheptan-2-one. This compound was prepared from dextrorotatory 2-methyl-2-phenylhexanoic acid. The acid, b.p. 145°/2 mm., was prepared by the method of Conant and Carlson (7), and was resolved by their method into its enantiomorphs. Four grams of the dextrorotatory acid, α^{20}_{D} +24.5° (1 dm. tube without solvent), $[\alpha]^{20}_{5463}$ +14.0° (c = 2.40 in alcohol), was refluxed four hours with an excess of thionyl chloride. The thionyl chloride was then removed at 15 mm. pressure on the steam-bath, and the acid chloride was dissolved in 50 cc. of dry ether. This solution was then added slowly and with shaking to a solution of 4 g. diazomethane in 500 cc. of dry ether at −10°. The mixture was allowed to stand overnight, filtered, and the ether removed at 30° under diminished pressure. The bright yellow diazoketone was not obtained crystalline. $[\alpha]^{20}_{D}$ +65.0 (c = 14.1 in benzene).

Similarly, an optically impure levo-modification, $[\alpha]^{20}_{D}$ −29.4° (c = 15.4 in benzene), was prepared from an incompletely resolved levorotatory acid, α^{20}_{D} −10.5° (1 dm. tube without solvent).

Rearrangement of the dextrorotatory diazoketone in aniline. One and one-half grams of dextrorotatory 1-diazo-3-methyl-3-phenylheptan-2-one was added in small portions to 10 cc. of boiling, freshly distilled aniline over a period of two minutes. After five minutes the reaction-mixture was cooled and poured into 200 cc. of 4 *N* hydrochloric acid. The product was then treated by the same methods used for the isolation of dextrorotatory *o*-(2-methyl-6-nitrophenyl)-α-toluanilide. Three recrystallizations from dilute alcohol gave a product having the following physical constants: m.p. 76°; $[\alpha]^{20}_{6563}$ −47.2°; $[\alpha]^{20}_{5893(D)}$ −59.5°; $[\alpha]^{20}_{5463}$ −72.2°; $[\alpha]^{20}_{4861}$ −96.0° (c = 2.77 in benzene).

Anal. Calc'd for $C_{20}H_{25}NO$: C, 81.36; H, 8.54; N, 4.75.
Found: C, 81.3; H, 8.5; N, 4.7.

No racemate could be detected in the mother liquors of the recrystallizations.

Similarly, 2 g. of the optically impure levorotatory diazoketone was converted

into an optically impure dextro-modification. This product, after two recrystallizations from dilute alcohol showed a rotation $[\alpha]_D^{20}$ +9.30° (c = 9.80 in methanol). Three more recrystallizations gave the racemic anilide, m.p. 87°.

Rearrangement of the dextrorotatory diazoketone in aqueous dioxane. One and one-half grams of dextrorotatory 1-diazo-3-methyl-3-phenylheptan-2-one was dissolved in 15 cc. of dioxane and treated with 40 cc. of a mixture of 2 g. of silver oxide and 100 cc. of an aqueous solution of 3 g. sodium sulfate, according to the method described above under the corresponding rearrangement of α-diazo-*o*-(2-methyl-6-nitrophenyl)acetophenone. The organic acid so obtained was converted to the corresponding anilide by the usual method. This anilide had the following physical constants: m.p. 76–77°; mixed m.p. with a specimen of levorotatory 3-methyl-3-phenylheptanoanilide: 76–77°; $[\alpha]_{6568}^{20}$ −46.5°; $[\alpha]_{5893(D)}^{20}$ −58.9°; $[\alpha]_{5461}^{20}$ −71.3°; $[\alpha]_{4861}^{20}$ −95.0° (c = 2.82 in benzene). No racemate could be detected in the mother liquors of recrystallization.

In the same way, an optically impure dextro-modification of the anilide resulted from treatment of the optically impure levorotatory diazoketone by these methods. This showed essentially the same properties as the optically impure anilide described in the preceding paragraph. Repeated recrystallization from dilute alcohol yielded ultimately the racemic anilide, m.p. 87°.

Rearrangement of dextrorotatory benzylmethyldiazoacetone in aniline. This compound was prepared from dextrorotatory benzylmethylacetic acid, α_D^{20} +22.7° (1 dm. tube without solvent), by a method previously described (4). The diazoketone had a rotation α_D^{20} +134° (1 dm. tube without solvent). Two grams of the diazoketone was added slowly in small portions to 10 cc. of boiling, freshly distilled aniline. The reaction was complete after about two minutes. The mixture was then cooled and the product worked up by the method described above for the isolation of the other anilides. The product so obtained was completely optically inactive. Three recrystallizations from benzene and light petroleum ether gave the racemic anilide, m.p. 102°.

Anal. Calc'd for $C_{17}H_{19}NO$: C, 80.65; H, 7.57; N, 5.53.
Found: C, 81.0; H, 7.6; N, 5.6.

In conclusion we wish to thank Merck and Co., Rahway, New Jersey, for the analyses published here; E. I. duPont de Nemours and Co., Wilmington, Delaware, for the grant of a fellowship to the junior author for the year 1939–1940, during which part of this work was accomplished; and Dr. E. M. May, Newark, New Jersey, for the preparation and resolution of the 2-methyl-2-phenylhexanoic acid used in certain of these experiments.

SUMMARY

α-Diazo-*o*-(2-methyl-6-nitrophenyl)acetophenone has been prepared in the racemic, pure dextro, and mixed levo-modifications.

From the racemic modification, α-acetoxy-*o*-(2-methyl-6-nitrophenyl)-acetophenone results on treatment with glacial acetic acid.

Evidence is submitted to show that on treatment of the optically active modifications of this compound with boiling aniline, a Wolff rearrangement takes place to give optically active *o*-(2-methyl-6-nitrophenyl)-α-tolu-

anilide without any accompanying racemization in appreciable amount. Similarly, on treatment with water in the presence of a catalyst, a Wolff rearrangement occurs to give optically active *o*-(2-methyl-6-nitrophenyl)-α-toluic acid without appreciable racemization.

1-Diazo-3-methyl-3-phenylheptan-2-one has been prepared in the pure dextro and mixed levo-modifications. Treatment of this compound with boiling aniline gives optically active 3-methyl-3-phenylheptanoanilide without appreciable racemization. Treatment with water and a catalyst gives optically active 3-methyl-3-phenylheptanoic acid without appreciable racemization.

Dextrorotatory benzylmethyldiazoacetone has been prepared and subjected to the Wolff rearrangement in boiling aniline. The resulting β-methyl-β-benzylpropionanilide is completely optically inactive.

A discussion of these results is given with special reference to the relation of the detailed mechanism of the Wolff rearrangement to that of the Curtius, Hofmann, and Lossen rearrangements. It is concluded that the partial or complete racemization of the products resulting from the Wolff rearrangement of optically active benzylmethyldiazoacetone under different conditions is due to the presence of an enolizable hydrogen on the asymmetric center. That enolization and racemization occur in the Wolff rearrangement and not in the Hofmann rearrangement where the benzylmethylcarbinyl group is involved, is attributed to the presence of the metallic catalyst in the former reaction.

PRINCETON, N. J.

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[CONTRIBUTIONS FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. VIII. THE STEROL OF SPONGES: CLIONASTEROL AND PORIFERASTEROL

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Cholesterol is the typical principal sterol of vertebrate animals; no exception to this rule has as yet been discovered. In contrast to this uniformity, marine invertebrates are characterized by a surprising diversity of principal sterols. In many species cholesterol is either partially or entirely replaced by other, as yet ill identified, sterols. Such sterols may be of the order C_{27}, as in the case of actiniasterol (1) or of the order C_{29}, as in the case of ostreasterol (2). There exists of course the possibility that sterols of other orders may yet be discovered. It has been suggested that this striking difference between vertebrates and marine invertebrates is due to a dependency on exogenous sterols by at least some of the members of the latter group of animals. Such an assumption would explain the presence of phytosterol-like sterols of the order C_{29} in herbivorous animals like the oyster and other bivalves (2) and the presence of cholesterol or other sterols of the order C_{27} in carnivorous animals like the sea anemones (1). Because of the paucity of available data, however, an accurate evaluation of this hypothesis is as yet impossible. At any rate, its application will have to be restricted to marine invertebrates, since other invertebrates with the possible exception of the fresh-water sponges (3) contain cholesterol as their principal sterol regardless of their feeding habits.

Studies on the sterols of sponges were the first to reveal the presence of sterols other than cholesterol in the animal kingdom. In 1904 Henze (4) described the isolation of spongosterol ($C_{27}H_{48}O$) from *Suberites domuncula*, and in 1908 Dorée (3) reported the presence of clionasterol ($C_{27}H_{46}O$) in *Cliona celata*. Many years later (1933) a third sterol was discovered in *Microciona prolifera* by Bergmann and Johnson (5). The presence of a different sterol in each of the species of sponges so far investigated is very surprising. It is conceivable that such a diversity of sterols is indeed typical for the phylum of *Porifera*, but it is also possible that these sterols are not uniform compounds but rather mixtures of some as yet unidentified sterols. Little credence only can be given the formulas which have been attributed to the sterols of sponges. They were proposed at a time when

the opinion prevailed that almost all naturally occurring sterols were of the order C_{27}. Since the recent methods for the accurate determination of the formulas of sterols have not yet been applied to the sterols of sponges, and since there was reason to suspect that these sterols, because of the feeding habits of sponges, were of the order C_{29} rather than C_{27}, the authors of the present communication have begun a reinvestigation of the sterols of sponges.

In a series of preliminary studies it was found that the loggerhead sponge, *Spheciospongia vesparia*, is a very suitable material for the preparation of larger quantitites of sponge sterols.[1] The air-dried sponge contains between one and one-half per cent of sterol. The bulk of sterols can be obtained directly by concentrating an acetone extract of the dried sponges. Additional quantities are obtained by the saponification of the residues from the mother liquors.

The sterol thus prepared showed a great similarity to clionasterol. Authentic clionasterol was therefore prepared from *Cliona celata*[2] according to the directions of Dorée (3). A direct comparison of the two sterols proved their identity. Further studies on clionasterol from either of the two sponges, however, revealed it to be a mixture. The absorption spectrum of the crude sterol indicated the presence of less than one per cent of a sterol with conjugated double bonds. Since the sponges had been dried in the open air it is quite probable that the bulk of the material of the nature of a provitamin D has been destroyed by oxidation. No attempt was made to isolate the remainder.

The principal constituents of the sterol mixture were identified as a mono- and di-unsaturated sterol. Their separation was effected by way of the acetate bromides according to the method of Windaus (6). The diunsaturated sterol, which represented about forty per cent of the sterol mixture is different from all other sterols which have so far been described. It is proposed to name this sterol poriferasterol because it appears to be a typical constituent of the marine representatives of the phylum *Porifera*. The formula for poriferasterol is $C_{29}H_{48}O$, as based on analyses of a series of derivatives. The properties and reactions of the monounsaturated sterol are reminiscent of those of the original clionasterol, and it is therefore proposed to retain this name for the monounsaturated sterol in the sponges under investigation. On the basis of analyses of a number of derivatives, the formula of clionasterol is to be changed from $C_{27}H_{46}O$ (3) to $C_{29}H_{50}O$. Hence in conformity with the working hypothesis concerning the sterols

[1] The authors are greatly indebted to Dr. C. L. Smith, Sponge Fishery Investigation, Nassau, Bahamas, for the generous gift of a large quantity of sponges.

[2] The authors want to express their gratitude to Dr. M. W. de Laubenfels, Pasadena, California for the identification of this sponge.

of marine invertebrates the two principal sterols of at least some of the representatives of the phylum *Porifera* are of the order of plant sterols. Table I gives a comparison of the sterols which have so far been isolated from sponges.

After the present report on clionasterol had been submitted for publication, a brief communication by Mazur (7) appeared in which it is stated that the typical sterol of the fresh-water sponge, *Spongilla lacustris*, is also of the order $C_{29}H_{50}O$. The sterols of this and another fresh-water sponge, *Ephydatia fluviatilis*, have already been the subject of a preliminary investigation by Dorée (3). This author has produced significant, if not convincing evidence for the presence of cholesterol in the sterol mixture. Since all other non-marine invertebrates which have so

TABLE I

COMPARISON OF THE DIFFERENT STEROLS OF SPONGES

NAME	STEROL		ACETATE		BENZOATE		*m*-DINITRO-BENZOATE	
	m.p. °C	$[\alpha]_D$	m.p. °C	$[\alpha]_D$	m.p. °C	$[\alpha]_D$	m.p. °C	$[\alpha]_D$
Clionasterol (old) (3)	138	−37	134	—	141	—	—	—
Clionasterol (new)	138	−37	138	−42	135	−17	203	−14
Poriferasterol	156	−49	147	−53	141	−22	227	−22
Spongosterol (4)	124	−20	124	—	128	—	—	—
Microcionasterol (5)	127	−20	126	−25	143	−11	—	—
Spongillasterol (7)	137	−42	137	−48	137	−17	200	−18

far been investigated have been found to contain cholesterol, the question of the presence of this sterol in fresh-water sponges assumes special significance.

Poriferasterol

The formula $C_{29}H_{48}O$ for poriferasterol is based on analyses of its acetate tetrabromide, acetate dibromide, *m*-dinitrobenzoate, *o*-iodobenzoate, and the *m*-dinitrobenzoate of poriferastanol. The presence of two double bonds has also been demonstrated by titration with perbenzoic acid and catalytic hydrogenation. The acetate, propionate, benzoate, and phenylurethane of poriferasterol have also been prepared to facilitate its identification.

Partial debromination of poriferasteryl acetate tetrabromide according to Fernholz and Stavely (8) gave an acetate dibromide. In analogy with the partial debromination of stigmasteryl acetate tetrabromide this evidence seemed indicative of the presence of a double bond in the side chain

of the sterol molecule, probably between C_{21} and C_{22}. This appears unlikely, however, because all attempts have so far failed to obtain an aldehyde, identifiable as a semicarbazone, by the ozonization of poriferasterol or its acetate.

Catalytic hydrogenation of poriferasterol proceeds smoothly to give the saturated poriferastanol. In Table II the properties of this sterol are compared with those of stigmastanol, ostreastanol (2), and ergostanol. The data at once show that poriferastanol is different from stigmastanol. The figures for poriferastanol and ostreastanol are sufficiently similar to arouse suspicion of the identity of the two compounds. Because of the properties of its acetate tetrabromide, poriferasterol and hence poriferastanol are more readily obtainable in a pure state than ostreasterol and ostreastanol. The slight discrepancies between the data of the two sterols

TABLE II

COMPARISON OF PORIFERASTANOL WITH OTHER SATURATED STEROLS

SUBSTANCE	PORIFERASTANOL		STIGMASTANOL		OSTREASTANOL		ERGOSTANOL	
	m.p. °C	$[\alpha]_D$	m.p. °C	$[\alpha]_D$	m.p. °C	$[\alpha]_D$	m.p. °C	$[\alpha]_D$
Stanol	143	+25	137	+25	141	+24	144	+15
Acetate	141	+16	131	+15	137	+15	145	+6
m-Dinitrobenzoate	213	+17	215	+13	—	—	203	+13
Stanone	161	+47	157	+42	157	+42	164	+35

may conceivably be due to the presence of impurites in ostreastanol. In their studies on the constitution of brassicasterol, Fernholz and Stavely (9) have pointed out that notwithstanding improved analytical methods the establishment of correct formulas for sterols remains a difficult problem. These authors found that while analytical data favored the formula $C_{29}H_{48}O$ for brassicasterol, the identity of brassicastanol with ergostanol proved that $C_{28}H_{46}O$ is the correct formula. Because of the experiences of these authors, the possible identity of poriferastanol and ergostanol has been taken into consideration. While it is true that some of the data for poriferastanol are not unlike those of a slightly impure brassicastanol (ergostanol) (9), the significant difference in the melting points of the *m*-dinitrobenzoates proves that the two compounds are not identical.

Investigations which are in progress in this laboratory have furnished evidence demonstrating the presence of poriferasterol in invertebrates other than sponges. They have also made it probable that the stigmasterol-like products occasionally met with among the sterols of mollusks (10, 11) are impure poriferasterol.

Clionasterol

The separation of clionasterol from the sterol mixture is a difficult process and it is questionable whether a product of a high degree of purity has as yet been isolated. Clionasteryl acetate obtained by the debromination of the soluble acetate bromides contains some poriferasteryl acetate, which can only be removed by frequent rebrominations. During these separations considerable quantities of clionasteryl acetate undergo decomposition.

The formula $C_{29}H_{50}O$ for the new clionasterol is based on analyses of its *m*-dinitrobenzoate and *o*-iodobenzoate. In Table I the data for the new clionasterol are compared with those of the old clionasterol and other sponge sterols. There exists such a striking similarity between clionasterol and the sterol of the fresh-water sponge, *Spongilla lacustris*, as to make their identity highly probable. Sterols of the formula $C_{29}H_{50}O$, and of properties resembling those of clionasterol, are frequently met with in marine invertebrates. In many instances they occur associated with other sterols from which they are difficult to separate. Thus the sterols of the coral *Meandra areolata* (12) and the gorgonia, *Xiphogorgia*, are mixtures of cholesterol and a sterol, $C_{29}H_{50}O$, closely resembling clionasterol.

EXPERIMENTAL

All melting points are corrected.

Preparation of the sterol mixture. The air-dried sponges of *Spheciospongia vesparia* or *Cliona celata* were cut into small pieces and extracted with acetone in a large Soxhlet apparatus for 24 hours. The extract was then filtered and concentrated to about one-fourth of its original volume. Upon cooling, a copious, almost colorless crystalline precipitate appeared, which was filtered and washed with acetone and methanol. In another experiment the total oily extract of a large quantity of sponges was diluted with an equal volume of ethanol, and the crystalline precipitate was filtered and washed with alcohol.

The precipitate was refluxed for one hour with a 5% solution of potassium hydroxide in methanol. The mixture was then diluted with water and the non-saponifiable material extracted with ether in the usual manner. Between the ether and aqueous layer a small amount of material was found suspended which was identified as the potassium salt of a hydroxy acid, which possessed a strong negative rotation and which gave the usual color reactions for sterols. Acidification of the aqueous layer with mineral acid yielded only an insignificant amount of fatty acids. This indicated that the bulk of the sterols is present in the sponge in an unesterified form.

The oil remaining after the evaporation of the mother liquor of the first precipitate was saponified with an alcoholic solution of potassium hydroxide, and the non-saponifiable matter was isolated in the usual manner. The latter, which consisted principally of sterols, contained a small amount of a steam distillable oil of pleasant odor, resembling that of terpenes.

The non-saponifiable fraction prepared by either of the two methods was refluxed for one hour with acetic anhydride. After cooling, the acetates were filtered and washed with glacial acetic acid and methanol.

Poriferasterol acetate tetrabromide. Ten-gram lots of the crude sterol acetate were dissolved in 100 cc. of anhydrous ether, and 125 cc. of a 5% solution of bromine in glacial acetic acid was added. After 24 hours standing in the refrigerator, a copious precipitate of rhombohedral prisms had formed. It was filtered, washed with acetic acid and methanol, and dried in a desiccator. On the average, 6.2 g. of acetate tetrabromide was obtained, corresponding to 3.5 g. of poriferasteryl acetate or to the presence of 35% of poriferasterol in the sterol mixture. After several recrystallizations from chloroform and alcohol the bromide melted at 185° with decomposition; $[\alpha]_D^{24}$ −43.5° (21.4 mg. in 3.03 cc. of chloroform). The tetrabromide is a remarkably stable compound; an analytical sample which had been kept in a stoppered tube for eleven months showed no signs of decomposition and gave the same analytical results as before.

Anal. Calc'd for $C_{30}H_{48}Br_4O_2$: C, 47.4; H, 6.4; Br, 42.0.
$C_{31}H_{50}Br_4O_2$: C, 48.1; H, 6.5; Br, 41.3.
Found: C, 48.0; H, 6.6; Br, 41.2.

Poriferasteryl acetate dibromide. To 3.2 g. of the acetate tetrabromide in 50 cc. of dry benzene was added 2 g. of sodium iodide in 20 cc. of ethanol, and the mixture allowed to stand at room temperature for eighteen hours. The mixture was then shaken with sodium sulfite to remove free iodine, washed with water, and dried over sodium sulfate. Addition of methanol to the solution gave 1.2 g. of a crystalline precipitate. It was dissolved in chloroform, and the solution treated with Norit and filtered. Methanol was then added, and the precipitate was recrystallized several times from chloroform-methanol. Poriferasteryl acetate dibromide crystallizes in long flat prisms; on heating it begins to darken at 202° and melts with decomposition at 211–212°, $[\alpha]_D^{25}$ −31° (34.2 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{30}H_{48}Br_2O_2$: C, 60.0; H, 8.1; Br, 26.6.
$C_{31}H_{50}Br_2O_2$: C, 60.6; H, 8.2; Br, 26.0.
Found: C, 60.4; H, 8.5; Br, 26.1.

Poriferasteryl acetate. Preliminary experiments proved that a complete debromination of the tetrabromide could not be effected by the method of Schoenheimer (13). The debromination was therefore carried out with zinc in glacial acetic acid. Since the bromide is only sparingly soluble in glacial acetic acid, it was dissolved in benzene (6.2 g. in 150 cc.), and glacial acetic acid (200 cc.) and zinc dust were then added. The solution was heated in such a manner as to permit the benzene to distil off gradually. After removal of the benzene the solution was refluxed for six hours with frequent addition of small amounts of zinc dust. The hot solution was then filtered and water was added to the filtrate to precipitate the acetate. The acetate was dissolved in ether, and the solution washed with sodium carbonate, water, dried over sodium sulfate, and evaporated to dryness. The remaining acetate was recrystallized several times from ether-methanol. It crystallizes in glistening plates, m.p. 146.5–147°, $[\alpha]_D^{24}$ −53.0° (31.6 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{31}H_{50}O_2$: C, 82.0; H, 11.1.
Found: C, 82.0; H, 11.2.

Titration with perbenzoic acid. By titration with perbenzoic acid in the usual manner the acetate took up oxygen after 48, 72, and 96 hours corresponding to 1.92, 1.95, and 2.08 double bonds.

Poriferasterol. The acetate was saponified by refluxing with a 5% solution of potassium hydroxide in 95% alcohol. The sterol was recrystallized several times from alcohol and finally from ether. It crystallizes in plates from both solvents,

m.p. 155–156°, $[\alpha]_D^{24}$ −49.7° (54.6 mg. in 3.03 cc. of chloroform). The sterol gives the Salkowski and Liebermann-Burchard reaction.

Anal. Calc'd for $C_{29}H_{48}O$: C, 84.5; H, 11.7.
Found: C, 84.7; H, 11.3.

Poriferasteryl propionate. Poriferasterol was refluxed with an excess of propionic anhydride for 45 minutes. The propionate which separated after cooling was recrystallized several times from dilute alcohol, m.p. 125–125.5°, $[\alpha]_D^{24}$ −48.1° (41.9 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{32}H_{52}O_2$: C, 82.0; H, 11.2.
Found: C, 82.0; H, 11.3.

Poriferasteryl benzoate. To a solution of poriferasterol in dry pyridine an excess of benzoyl chloride was added and the mixture kept at room temperature for eight hours. The benzoate was then precipitated with water, filtered, washed with water and alcohol, and recrystallized from alcohol. It crystallizes in plates; on heating it turns into a turbid liquid at 139.5–140.5° which becomes clear at 141.5°, $[\alpha]_D^{24}$ −21.95° (52.5 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{36}H_{52}O_2$: C, 83.7; H, 10.2.
Found: C, 83.7; H, 10.0.

Poriferasteryl phenylurethane. To a solution of 0.25 g. of poriferasterol in 15 cc. of dry benzene, 3 cc. of phenyl isocyanate was added, and the mixture refluxed for three hours. The benzene and the excess isocyanate were removed *in vacuo* at 100°. The residue was extracted three times with high-boiling ligroin and then recrystallized several times from ethyl acetate-ethanol; needles, m.p. 191–192.5°, $[\alpha]_D^{24}$ −33.2° (32.8 mg. in 3.03 cc. of chloroform).

Poriferasteryl m-*dinitrobenzoate.* A solution of 0.5 g. of poriferasterol and 0.5 g. of *m*-dinitrobenzoyl chloride in 30 cc. of dry pyridine was heated on the steam-bath for three hours. The mixture was then poured into dilute sulfuric acid, and the precipitate was filtered, washed with dilute acid, water, and hot acetone. After four recrystallizations from ethyl acetate-ethanol the *m*-dinitrobenzoate showed the m.p. 227–228°, $[\alpha]_D^{24}$ −22.1° (38.7 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{35}H_{48}N_2O_6$: C, 70.9; H, 8.2.
$C_{36}H_{50}N_2O_6$: C, 71.3; H, 8.3.
Found: C, 71.4; H, 8.4.

Poriferasteryl o-*iodobenzoate.* A solution of 0.25 g. of poriferasterol and 0.25 g. of *o*-iodobenzoyl chloride in 10 cc. of dry pyridine was heated for three hours on the steam-bath. It was then poured into dilute sulfuric acid and the solution extracted with ether. The ether extract was washed with a solution of sodium carbonate and water, dried over sodium sulfate, and evaporated to dryness. The residue was recrystallized several times from 95% alcohol; flat needles, m.p. 153–154.5°, $[\alpha]_D^{24}$ −25.3° (31.8 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{35}H_{49}IO_2$: C, 66.9; H, 7.9.
$C_{36}H_{51}IO_2$: C, 67.3; H, 8.0.
Found: C, 67.3; H, 7.9.

Poriferastyl acetate. Two grams of poriferasteryl acetate of m.p. 144–145.5° in 100 cc. of glacial acetic acid was hydrogenated at 60–70° in the presence of 0.5 g. of platinum oxide. Two moles of hydrogen was taken up rapidly. After five hours the solution was filtered and concentrated to a small volume *in vacuo*. The Liebermann test of the crystalline residue was negative. The acetate was recrystallized from ethanol, m.p. 140–141°, $[\alpha]_D^{24}$ +16.3° (35.7 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{31}H_{54}O_2$: C, 81.2; H, 11.9.
Found: C, 81.4; H, 11.8.

Poriferastanol. The acetate was hydrolyzed by refluxing with a 5% solution of potassium hydroxide in the usual manner. The sterol was recrystallized several times from alcohol and then from ether; plates from alcohol and needles from ether, m.p. 143–144°, $[\alpha]_D^{24}$ +24.7° (50.5 mg. in 3.03 cc. of chloroform). The carbon values were about 2% low due to solvent of crystallization.

Poriferastyl m-*dinitrobenzoate.* A solution of 0.25 g. of poriferastanol and 0.4 g. of *m*-dinitrobenzoyl chloride in 10 cc. of pyridine was heated on the steam-bath for three hours. The solution was poured into dilute sulfuric acid, and the precipitate was filtered, washed with water and hot acetone, and recrystallized several times from benzene-ethanol; colorless leaflets, m.p. 213–213.5°, $[\alpha]_D^{24}$ +17.1° (32.0 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{36}H_{54}N_2O_6$: C, 70.8; H, 8.9.
$C_{35}H_{52}N_2O_6$: C, 70.4; H, 8.8.
Found: C, 70.8; H, 8.9.

Poriferastanone. To a solution of 0.24 g. of poriferastanol in 10 cc. of 95% acetic acid was added 0.15 g. of chromic anhydride in a small amount of water. The mixture was heated on the steam-bath with frequent shaking for 30 minutes, cooled, and treated with dilute sulfurous acid. The precipitate was filtered, washed with water, and recrystallized several times from ethanol; m.p. 161–161.5°, $[\alpha]_D^{24}$ +46.7° (25.2 g. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{29}H_{50}O$: C, 84.0; H, 12.2.
Found: C, 83.9; H, 12.3.

Clionasteryl acetate. A stream of nitrogen was blown through the mother liquor remaining after the removal of poriferasteryl acetate tetrabromide until some solid had separated. This solid, which contained large quantities of tetrabromide, was filtered off. Zinc dust was then added to the filtrate, which was first heated on the steam-bath to remove the ether and then refluxed for six hours. Additional amounts of zinc dust were added at frequent intervals. The acetate was dissolved in ether, and the solution washed with sodium carbonate and water, dried over sodium sulfate, and evaporated to dryness. During frequent recrystallizations from ether-methanol and absolute ethanol the melting point of the acetate rose gradually from 132–133° to 141°. Titration with perbenzoic acid and bromination showed the presence of poriferasteryl acetate. The acetate was therefore subjected to a second bromination according to the method described above. Tetrabromide, corresponding to the presence of about 10% of poriferasteryl acetate, was filtered off, and the mother liquor was debrominated as described above. Clionasteryl acetate purified in this manner showed the m.p. 137° and $[\alpha]_D^{24}$ −41.9° (19.0 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{31}H_{52}O_2$: C, 81.5; H, 11.5.
Found: C, 81.3; H, 11.3.

Clionasterol. The acetate was saponified by a 5% solution of potassium hydroxide in 95% ethanol. The sterol was recrystallized several times from alcohol and finally from ether. The purest material showed the melting point 137.5–138.5°, $[\alpha]_D^{24}$ −37° (42.3 mg. in 3.03 cc. of chloroform). It gives the Liebermann-Burchard and the Salkowski reaction as cholesterol does. The solubility in different solvents is about the same as that of cholesterol.

Anal. Calc'd for $C_{29}H_{50}O$: C, 84.1; H, 12.2.
Found: C, 83.8; H, 12.0.

Clionasteryl propionate. Clionasterol was refluxed with an excess of propionic anhydride for 45 minutes. The propionate which separated after cooling was re-

crystallized three times from dilute alcohol, m.p. 117–118°, $[\alpha]_D^{22}$ −41.84° (49.9 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{32}H_{54}O_2$: C, 81.7; H, 11.6.
Found: C, 81.7; H, 11.6.

Clionasteryl benzoate. To a solution of clionasterol in dry pyridine an excess of benzoyl chloride was added and the mixture kept at room temperature overnight. The benzoate was then precipitated with water, filtered, washed thoroughly with water and alcohol, and then recrystallized five times from hot alcohol, in which it is more soluble than cholesteryl benzoate. The benzoate crystallizes in needles. It melts sharply at 134.5–135° to a clear liquid. On cooling, the liquid benzoate turns bluish-green at 131° and purple at 116°. Solidification begins at 106°; $[\alpha]_D^{22}$ −16.8° (56.2 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{36}H_{54}O_2$: C, 83.4; H, 10.5.
Found: C, 83.6; H, 10.3.

Clionasteryl phenylurethane. To a solution of clionasterol in dry benzene, phenyl isocyanate was added in excess and the mixture was refluxed for 3 hours. The solvent and the excess of phenyl isocyanate were removed *in vacuo* and the residue dried *in vacuo* at 100°. It was washed three times with boiling ligroin, and the remaining urethane was recrystallized from a mixture of ethyl acetate and ethanol until the melting point remained constant at 180.5–182°; $[\alpha]_D^{22}$ −29.36° (28.9 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{36}H_{55}NO_2$: C, 80.9; H, 10.4; N, 2.6.
Found: C, 81.2; H, 10.5; N, 2.9.

Clionasteryl m-*dinitrobenzoate.* To a solution of clionasterol in dry pyridine an excess of *m*-dinitrobenzoyl chloride was added and the mixture heated on the steam-bath for 4 hours. It was then poured into dilute sulfuric acid, and the precipitate was filtered, washed with water and warm acetone. The *m*-dinitrobenzoate was recrystallized several times from ethyl acetate and a mixture of ethanol and benzene; m.p. 201–203°, $[\alpha]_D^{23}$ −13.95° (35.3 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{36}H_{52}N_2O_6$: C, 71.0; H, 8.6; N, 4.6.
$C_{35}H_{50}N_2O_6$: C, 70.7; H, 8.5; N, 4.7.
Found: C, 70.9, 71.0, 70.8; H, 8.5, 8.6, 8.6; N, 4.8.

Clionasteryl o-*iodobenzoate.* To a solution of clionasterol in dry pyridine was added an excess of *o*-iodobenzoyl chloride, and the mixture was heated on the steam-bath for 3 hours. It was then poured into dilute sulfuric acid and the acid extracted with ether. The ether extract was washed with a solution of sodium carbonate and water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was then treated with hot ethanol, when all but a few drops of oily material went into solution. On cooling of the filtered solution, the *o*-iodobenzoate separated in the form of a gelatinous mass. It was recrystallized from ethanol until the melting point remained constant at 103.5–104.5°; $[\alpha]_D^{22}$ −19.76° (48.0 mg. in 3.03 cc. of chloroform).

Anal. Calc'd for $C_{36}H_{53}IO_2$: C, 67.1; H, 8.3.
$C_{35}H_{51}IO_2$: C, 66.7; H, 8.2.
Found: C, 67.1; H, 8.3.

SUMMARY

Clionasterol as isolated from the marine sponges *Spheciospongia vesparia* and *Cliona celata* is a mixture of a mono- and di-unsaturated sterol. The name clionasterol has been retained for the monounsaturated sterol which

represents about sixty per cent of the mixture. A number of derivatives of the new clionasterol have been described and it has been demonstrated that the formula is $C_{29}H_{50}O$ rather than $C_{27}H_{46}O$.

The name poriferasterol has been proposed for the diunsaturated sterol $C_{29}H_{48}O$. A number of derivatives of this new sterol have been described, and it has been shown that it is hydrogenated to a saturated sterol closely resembling ostreastanol.

NEW HAVEN, CONN.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING AT THE UNIVERSITY OF PENNSYLVANIA]

THE SYNTHESIS OF KETO ACIDS AND KETONES BY THE REACTION OF ACID ANHYDRIDES WITH CADMIUM ALKYLS

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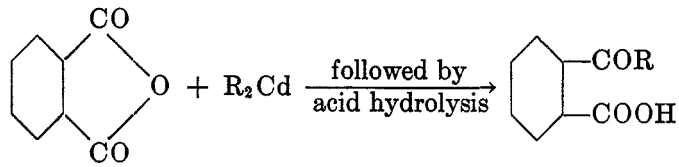
This investigation was undertaken because of the need of a variety of *o*-acylbenzoic acids as intermediates in another problem. The Friedel-Crafts synthesis, customarily used for the preparation of these compounds, was not applicable in cases where the acyl group was aliphatic, and reaction of phthalic anhydride with the Grignard reagent gave generally unsatisfactory yields. It was decided, therefore, to devise a more general synthesis for these compounds.

The preparation of ketones by the reaction of acyl halides with cadmium alkyls has recently been described (1). Use of the latter in reaction with phthalic anhydride appeared to offer a promising method for the preparation of *o*-acylbenzoic acids. The results were so satisfactory that the



reaction was extended to include the preparation of a γ-keto acid from succinic anhydride and to the synthesis of ketones.

$$(RCO)_2O + R'_2Cd \xrightarrow[\text{acid hydrolysis}]{\text{followed by}} RCOR' + RCOOH$$

The reaction of several cadmium alkyls and aryls with phthalic anhydride gave 60–70% yields of the corresponding *o*-acylbenzoic acids. Dimethyl-, diethyl-, diphenyl- and di-α-naphthyl-cadmium were used, all prepared from their corresponding alkyl- and aryl-magnesium bromides. When methylmagnesium iodide was used to prepare dimethylcadmium, a somewhat lower yield (47%) was obtained.[1] Reaction of succinic an-

[1] This was in accord with the results of Gilman and Nelson (1), who obtained lower yields when iodides were used in the preparation of cadmium alkyls.

hydride with diphenylcadmium gave a lower yield (30%) of keto acid, possibly because of the limited solubility of succinic anhydride in ether.

The preparation of ketones from non-cyclic anhydrides proved to be quite general, although yields varied considerably with the particular anhydride and cadmium alkyl used. In the preparation of alkylaryl ketones, it appears that when anhydrides of aliphatic acids are allowed to react with diphenylcadmium, higher yields (70%) are obtained than when benzoic anhydride and cadmium alkyls are used. Reaction of di-*i*-propylcadmium gave considerably reduced yields, particularly when the iodide was used in the preparation of the cadmium alkyl.[1] Di-*i*-propylcadmium and di-*t*-butylcadmium were used at the temperatures of ice and dry ice, respectively (1). In the latter case, a 3:1 ratio of magnesium to anhydride was used instead of the normal 2:1 ratio, because of the expected low yield of *t*-butylmagnesium chloride.

The formation of esters in the reaction of anhydrides with the Grignard reagent has been remarked (2). Esters were also obtained in small amounts in the preparation of ketones with cadmium alkyls. Since they could not be isolated because they distill at approximately the same temperature as the corresponding ketones, the amount of ester formed was determined by saponification of the ketone-ester fraction, and this method also served for their removal from the ketones.

When some hydrocarbons, such as naphthalene, are used in the Friedel-Crafts synthesis, it is necessary to determine the orientation of the entering group in the final product, since substitution may conceivably occur in one of several positions. It is of interest that the procedure outlined above yields products of known orientation, since the acyl group is necessarily introduced on the carbon attached originally to halogen.

EXPERIMENTAL PART

Materials. Methyl bromide was Eastman practical, dissolved in dry ether to make up a 15% solution. Other halides were Eastman pure grade or purified practical, or purified student preparations. All halides were dried over anhydrous sodium sulfate. Anhydrides were for the most part Eastman pure grade or purified technical. Phthalic anhydride, however, was unpurified technical. Some benzoic anhydride, as well as succinic and isobutyric anhydrides, was prepared by the method of Clarke and Rahrs (3).

General procedure for the reaction of anhydrides with cadmium alkyls. A 500-ml., three-necked, round-bottomed flask was fitted with mechanical sweep stirrer, condenser with soda-lime tube, and an addition tube to facilitate introduction of solid materials. To the vertical arm of the addition tube was fitted a dropping-funnel, the other opening being stoppered. The dropping-funnel was removed for the addition of solids. The Grignard reagent was prepared in this apparatus in the usual manner, from 7.3 g. (0.3 mole) magnesium and about 0.4 mole alkyl halide, with dry ether as solvent. The cadmium alkyl was then prepared by the addition of 31.2 g. (0.17 mole) anhydrous cadmium chloride, by the method of Gilman and Nelson (1).

TABLE I

PRODUCTS OF THE REACTION OF ACID ANHYDRIDES WITH CADMIUM ALKYLS

ANHYDRIDE	HALIDE	KETONE OR KETO ACID					ESTER % YIELD[a]
		B.p., °C uncorr.	mm.	M.p., °C uncorr.	Yield of Product	Derivative, m.p., °C uncorr.	
Phthalic.....	CH_3Br	—	—	114–115	62% *o*-Acetylbenzoic acid	Anhydro-oxime (7), 158–159	—
Phthalic.....	CH_3I	—	—	114–115	47% *o*-Acetylbenzoic acid	Anhydro-oxime (7), 158–159	—
Phthalic.....	C_2H_5Br	—	—	85–88	67% *o*-Propionylbenzoic acid	Anhydro-oxime (8), 116–117	—
Phthalic.....	C_6H_5Br	—	—	89–91	64% *o*-Benzoylbenzoic acid monohydrate	See footnote[b]	—
Phthalic.....	α-$C_{10}H_7Br$	—	—	168–169	57% *o*-α-Naphthoylbenzoic acid	Anhydro-oxime (9), 175–177	—
Succinic.....	C_6H_5Br	—	—	105–109	30% β-Benzoylpropionic acid	Lactone (10), 90–91	—
Acetic.....	*n*-C_4H_9Br	123–126	760	—	56% Methyl-*n*-butyl ketone	Semicarbazide (11), 120–121	2
Acetic.....	C_6H_5Br	103–104	31	—	75% Acetophenone	Semicarbazide (11), 198–199	0
Propionic....	C_6H_5Br	208–211	760	—	68% Propiophenone	Semicarbazide (11), 172–173	5
Isobutyric...	C_6H_5Br	210–217	760	—	72% Isobutyrophenone	Oxime (12), 56–57	5
Benzoic.....	C_2H_5Br	205–212	760	—	53% Propiophenone	Semicarbazide (11), 172–173	8
Benzoic.....	*i*-C_3H_7Br	98–100	26	—	44% Isobutyrophenone	Oxime (12), 56–57	8
Benzoic.....	*i*-C_3H_7I	88–91	14	—	33% Isobutyrophenone	Oxime (12), 56–57	4
Benzoic.....	*t*-C_4H_9Cl	97–98	16	—	40% Trimethylacetophenone	Oxime (13), 166–167	0

[a] Determined by quantitative saponification of a ketone-ester fraction in diethylene glycol (6).

[b] Melting point, anhydrous, 126–127°, mixed m.p. with authentic sample, 126–127°.

When a Michler's ketone test (4) showed the absence of Grignard reagent, the mixture containing the cadmium alkyl was surrounded by an ice-bath, and the anhydride (0.16 mole) slowly added with good stirring, either as liquid, as solution in dry ether, or, when the anhydride was insoluble in ether, as solid. This addition was over a period of fifteen to thirty minutes. When all of the material had been added, the ice-bath was removed and the contents of the flask heated on the water-bath for one to one and one-half hours, under gentle reflux with stirring. During this period, in many cases, a gummy precipitate formed, preventing further stirring. At the conclusion of this reflux period, the reaction-mixture was cooled, the flask surrounded with ice, and a quantity of 10% sulfuric acid slightly more than equivalent to the magnesium was very carefully added. When the hydrolysis was complete, the ether layer was separated and combined with an ether washing of the water layer. This ether extract was then treated according to the proper isolation technique described below. As recommended (1), reactions with di-*i*-propylcadmium were carried out with the flask surrounded by an ice-bath, and that with di-*t*-butylcadmium at the temperature of dry ice. The latter reaction is described below, since it involved some departure from the customary procedure. The products obtained in these reactions are outlined in Table I, with yields and other data.

Preparation of trimethylacetophenone. *t*-Butylmagnesium chloride was prepared in the customary manner (5), using 14.5 g. (0.6 mole) magnesium and an equivalent quantity of *t*-butyl chloride. The flask was then surrounded by a ligroin bath, and dry ice added to the ligroin until the latter was saturated. There was then slowly added 56.8 g. (0.31 mole) anhydrous cadmium chloride, with good stirring. Stirring was continued, with occasional addition of dry ice to the ligroin bath, and after the first half hour, the mixture was tested intermittently for Grignard reagent (4). At the end of one and one-half hours, only a very weak Michler's ketone test was obtained. To the reaction flask was then added, over a period of one-half hour, 47.5 g. (0.21 mole) of solid benzoic anhydride, with stirring. The contents of the flask were stirred, with occasional addition of dry ice to the surrounding bath, until the formation of a gummy precipitate (about one-half hour) prevented further stirring. Dry ice was then added to saturate the ligroin bath, and the mixture allowed to stand overnight. A total of five pounds of dry ice was required for this reaction. The following morning, hydrolysis and isolation were carried out in the prescribed manner. There was thus obtained 13.5 g. (40%) of trimethylacetophenone, b.p. 97–98° (16 mm.), free of ester and evolving no gas with sodium.

Isolation of ketones. The ether solution obtained following hydrolysis was carefully washed with 10% potassium carbonate solution to remove the acid which was the other main product of the reaction. This treatment also served to precipitate inorganic salts, which were to some extent soluble in ether, as their carbonates. Any emulsion was easily broken by filtration through a Büchner funnel. The ether solution was then dried over sodium sulfate, the ether removed, and the product distilled either at reduced pressure through a Widmer column containing a spiral 11 cm. long, or directly from a 50-ml. distilling flask at atmospheric pressure. When the product was desired free of ester, it was refluxed with 50 cc. of 25% sodium hydroxide solution for two hours and redistilled.

Isolation of keto acids. The ether solution obtained following hydrolysis was carefully washed with somewhat more than an equivalent of 10% potassium carbonate solution, in order to remove completely the product as its salt. The potassium carbonate solution was then filtered and added carefully to an excess of dilute sulfuric acid in order to precipitate the keto acid, which was then removed by filtration and recrystallized if necessary. This treatment avoided any difficulty from esters which

were probably formed in these reactions as in the preparation of ketones. In the case of *o*-acetylbenzoic acid, a small additional amount (8–10%) was obtained by extracting the acid filtrate with ether, drying the ether extract, removing the ether, and recrystallizing the semi-liquid residue from benzene and ligroin (boiling range 70–90°). The latter treatment served to separate the product from phthalic acid, which was insoluble in benzene and ligroin, and could be removed by hot filtration.

SUMMARY

It has been shown that a variety of ketones and keto acids may be prepared through the reaction of the appropriate acid anhydride and organocadmium compound. This reaction has been applied to both cyclic anhydrides, yielding keto acids, and non-cyclic anhydrides, yielding ketones, and to both dialkyl- and diaryl-cadmium compounds. The method offers more satisfactory yields than are obtained from the reaction of anhydrides with the Grignard reagent, and is more generally applicable than the Friedel-Crafts synthesis, with the added advantage over the latter of predictable orientation of groups in the product.

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[FROM THE CHICAGO CITY COLLEGES]

STUDIES IN AMMONOLYSIS. II. AMMONOLYSIS OF α-HALOGEN ACIDS IN LIQUID AMMONIA[1]

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In a previous paper (1) in this series, mention was made of some preliminary experiments on the ammonolysis of chloroacetic acid in liquid ammonia. These studies indicated that the yield of glycine is less than in the aqueous system where the same mole ratios of ammonia to chloroacetic are used. Most of the studies of the ammonolysis of halogen acids, however, have been concerned with reactions in the aqueous system.

Studies in the aqueous system (1) have shown that the yield of the primary amino compound is profoundly affected by change in the *p*H of the ammonolytic solution since decreasing the *p*H inhibits the secondary and tertiary reactions. This is shown by the following equation:

$$H_2NCHRCOO^- + H_3O^+ \rightleftharpoons H_3N^+CHRCOO^- + H_2O$$

In the presence of high concentrations of hydronium ion, the equilibrium is forced to the right, covering up the free pair of electrons on the nitrogen atom, and inhibiting the secondary and tertiary reactions. If we assume that the ammonolytic reaction proceeds according to the same mechanism in liquid ammonia as in aqueous ammonia, the yield of the primary amino compound should be increased by the addition of considerable quantities of ammonium salts, since such salts have been shown to act as acids in liquid ammonia (2).

Preliminary experiments had indicated that the ammonolysis of α-halogen acids proceeds at a faster rate in liquid ammonia than in the aqueous system; consequently, liquid ammonia might serve as a desirable ammonolyzing medium for the less reactive α-halogen acids. For example, one mole of α-chloropropionic acid in 60 moles of ammonia in the form of 27.7% aqueous solution requires 350 hours for complete reaction at 25°. The rate of this reaction can be increased by raising the temperature, but this brings about lowering of the yield due to the considerable hydrolysis which takes place.

A search of the literature revealed no quantitative data on the reaction

[1] Presented at the meeting of the American Chemical Society, Detroit, Michigan, September 12, 1940.

of these halogen acids with liquid ammonia. It was therefore deemed desirable to undertake a quantitative investigation of these reactions in order to determine if generalizations found to hold for reactions in the aqueous system would hold as well for anhydrous ammonia. The following studies were made:

The reaction of chloroacetic acid with liquid ammonia was carried out using various mole ratios of acid to ammonia in order to determine the effect of varying this ratio on the extent of conversion of the halogen acid to lgycine.

A series of ammonolyses using various chloro and bromo acids in the presence of considerable amounts of ammonium chloride, ammonium nitrate, or ammonium acetate was carried out to determine the effect of acidity on the extent of conversion to the primary amino compound.

To determine the effect of the length of the carbon chain on the per cent of the halogen acid converted to the primary amino compound, experiments with a series of α-bromo acids were carried out using in each case the same mole ratio of acid to ammonia. The bromo acids were used because they were found to undergo ammonolysis more rapidly than the chloro acids.

The rates of reaction of chloroacetic, α-chloropropionic, and α-bromoisovaleric acids in liquid ammonia were studied in order to determine whether or not the mechanism of ammonolysis under these conditions is similar to that of analogous reactions in the aqueous system.

Procedure. Reaction tubes were prepared by sealing Pyrex tubes 11 × 373 mm. at one end to form long test tubes. Weighed quantities of the halogen acid (see Table I) were placed in the tubes. Where a liquid acid was used, the acid was first weighed in a small open capsule which was then placed in the reaction tube. In experiments where the effect of ammonium salts was studied, the weighed quantity of ammonium salt was also added. Each reaction tube was cooled to approximately −80° in a dry ice-acetone mixture, and the calculated volume of liquid ammonia (see Table I) added. This operation was carried out by quickly siphoning the required volume of ammonia into a precooled graduated cylinder, and then pouring the measured volume of ammonia into the reaction tube. With the reaction tube immersed in the cooling bath to a level above the level of the contents of the tube, the upper end was sealed. After the seal had cooled, the tube was removed from the cooling bath and shaken until a clear solution was obtained. The tubes were allowed to stand at room temperature for various periods of time. At the end of the reaction period each tube was again cooled in the dry ice-acetone mixture and the seal broken. The contents of the tube were emptied into an Erlenmeyer flask and the excess ammonia allowed to evaporate. The contents of the reaction tube were thoroughly washed out into the flask, dissolving the reaction product. The solution thus obtained was diluted to standard volume. Aliquot portions of the solution were analyzed for ionic halogen and for amino nitrogen. From these two values the per cent conversion to the primary amino compound was calculated.

Ionic halogen was determined by the Volhard volumetric method using the Cald-

well-Moyer modification. Samples for amino nitrogen analysis were prepared as follows: A 5 or 10 ml. portion of the solution of the ammonolytic products was digested with 5 ml. of a twenty per cent solution of sodium hydroxide until ammonia ceased to be evolved. The solution was then diluted to standard volume and aliquot portions analyzed for amino nitrogen in the micro-Van Slyke apparatus. Dilution and size of sample were adjusted so that the volume of nitrogen obtained in each analysis would not be less than 0.5 ml. If the volume is less than this the accuracy of the method is greatly reduced. The apparatus had been calibrated with a standard glycine solution and the empirical factor so obtained was used in calculating the analytical data, thus eliminating the error obtained when glycine analysis is based on the theoretical volume of nitrogen. The empirical factors for the higher molecular weight amino acids were found to be close to the theoretical; hence, with these higher acids calculations were based on the theoretical volume of nitrogen. The maximum error using the above procedure and methods of analysis has been found to be two or three per cent.

TABLE I

AMMONOLYSIS OF $ClCH_2COOH$ IN LIQUID AMMONIA AT ROOM TEMPERATURE

MOLES ACID	MOLES NH_3	MOLE RATIO	TIME (HRS.)	Cl^-[a] (%)	CONVERSION[b] TO GLYCINE (%)	AVERAGE[c] CONVERSION (%)
0.0482	0.289	1:6	78	98.8	42.1	42.3
.0482	.386	1:8	72	97.5	41.4	41.1
.0320	.384	1:12	72	98.5	42.4	41.5
.0273	.546	1:20	78	99.0	41.5	40.5
.0137	.411	1:30	78	98.6	44.1	44.5
.0137	.822	1:60	78	99.0	48.0	47.0
.0137	1.150	1:84	67	100.1	52.0	48.6
.00795	.954	1:120	61	98.6	57.1	56.6
.00636	1.272	1:200	61	104.0	63.6	63.8

[a] Based on original weight of acid.

[b] Based on ionic Cl^- analysis.

[c] Average of all runs at the given mole ratio.

Using the above procedure, experiments were carried out with chloroacetic acid employing mole ratios of acid to ammonia varying from 1:6 (0.167) to 1:200 (0.005). The results of these determinations are summarized in Table I. It had previously been found that α-chloropropionic and higher α-chloro acids are ammonolyzed in aqueous systems at a much slower rate than chloroacetic acid. Experiments with α-chloropropionic acid showed that this decrease in reactivity also holds true in liquid ammonia solution. These experiments are described below. Due to this large decrease in reactivity of the higher α-chloro acids, the α-bromo acids were used in studies which were carried out to determine the effect of the length of the carbon chain on the yield of the primary amino compound. Bromoacetic, α-bromopropionic, α-bromobutyric, α-bromo-*n*-valeric, and α-bromoisovaleric acids at ratios of one mole of acid to twenty moles of ammonia were used in these experiments. A few determinations using ratios of one to twelve were also carried out. The results of these studies are summarized in Table II.

To determine the effect of ammonium salts on the ammonolysis of α-halogen acids, experiments were carried out using ammonium nitrate, ammonium chloride, and ammonium acetate, at ratios of one mole acid to twenty moles of ammonia with two, four, and six moles of the ammonium salt. Experiments were also carried out with α-chloropropionic, bromoacetic, and α-bromoisovaleric acids using one mole of acid, twenty moles of ammonia, and two moles of ammonium nitrate. Recent studies have shown that not only ammonium salts but also other electrolytes increase the rate of ammonolysis of esters in liquid ammonia (3). In order to determine whether it is the ammonium ion which affects the course of the ammonolysis of α-halogen acids or merely the presence of any electrolyte, the conversion of chloroacetic acid to glycine in saturated solutions of sodium nitrate and sodium chloride in liquid ammonia was checked. The results of these experiments are given in Table III.

TABLE II

AMMONOLYSIS OF α-BROMO ACIDS IN LIQUID AMMONIA

ACID	MOLES ACID	MOLES NH_3	MOLE RATIO	TIME (HRS.)	Br[a] (%)	CONVERSION[b] TO PRIMARY AMINO COMP. (%)	AVERAGE[c] CONVERSION (%)
$BrCH_2COOH$	0.0160	0.320	1:20	33	99.1	37.8	37.8
$CH_3CHBrCOOH$	.0215	.430	1:20	48	94.5	63.0	63.3
$CH_3CH_2CHBrCOOH$	.0170	.339	1:20	48	98.4	78.2	79.5
$CH_3(CH_2)_2CHBrCOOH$	.0139	.278	1:20	48	90.3	74.6	75.8
$(CH_3)_2CHCHBrCOOH$	.0160	.320	1:20	33	91.8	100.0	99.0
$BrCH_2COOH$	.0250	.300	1:12	67	98.5	38.5	38.5
$CH_3CHBrCOOH$	.0186	.223	1:12	67	98.0	42.6	42.6
$CH_3CH_2CHBrCOOH$	.0149	.180	1:12	67	100.0	48.3	48.3
$(CH_3)_2CHCHBrCOOH$	.0160	.128	1:8	48	71.5	84.5	85.0

[a] Based on weight of original sample.

[b] Based on ionic halogen.

[c] Average of all runs on the given acid at the given mole ratio.

Studies previously reported in this series (1) have shown that the presence of carbonates in the aqueous system causes a pronounced increase in the yield of glycine. This effect has been shown to be attributable to the blocking of the amino group by the formation of the carbamino compound of the amino acid. Although ammonium carbamate is only slightly soluble in liquid ammonia, experiments were carried out in which chloroacetic acid was treated with twenty moles of ammonia in which two or four moles of ammonium carbamate was suspended. The results of these experiments are also listed in Table III.

Rate studies. The rates of ammonolysis of chloroacetic acid in liquid ammonia at 25°, with mole ratios of one mole of acid to twenty moles of ammonia, and with one mole of acid, twenty moles of ammonia, and two moles of ammonium nitrate, were determined. The determinations were carried out according to the same procedure as in the experiments described above with the following modifications: After sealing, the reaction tubes were quickly shaken while still cold until a clear solution was obtained and were then placed in a thermostat at 25 ± .05°. These tubes were removed at definite intervals of time and opened. The reaction products were analyzed

for ionic halogen and amino nitrogen according to the procedures described above. In addition, total halogen analyses were carried out according to standard methods.[2]

TABLE III

AMMONOLYSIS OF α-HALOGEN ACIDS IN LIQUID AMMONIA IN THE PRESENCE OF AMMONIUM SALTS

MOLES ACID	MOLES NH_3	MOLES NH_4-SALT		MOLE RATIO	TIME (HRS.)	HALIDE[a] (%)	CONVERSION[b] TO PRIMARY AMINO ACID (%)	AVERAGE[c] CONVERSION (%)
			(A) $ClCH_2COOH$					
0.0273	0.540	—		1:20:0	78	99.0	41.5	40.5
.0320	.640	0.0640	NH_4NO_3	1:20:2	67	99.0	53.5	55.6
.0160	.320	.0640	NH_4NO_3	1:20:4	61	98.6	70.7	70.5
.0160	.320	.0960	NH_4NO_3	1:20:6	81	98.6	69.4	69.5
.0160	.320	.0320	NH_4Cl	1:20:2	61	96.0	59.6	59.1
.0160	.320	.0640	NH_4Cl	1:20:4	61	95.2	66.4	66.5
.0160	.320	.0960	NH_4Cl	1:20:6	81	95.5	71.5	71.5
.0160	.320	.0320	$NH_4C_2H_3O_2$	1:20:2	81	97.2	53.1	53.1
.0160	.320	.0640	$NH_4C_2H_3O_2$	1:20:4	81	95.8	59.1	59.1
.0160	.320	.0320	$H_2NCOONH_4$[d]	1:20:2	34	98.2	51.8	51.9
.0160	.320	.0640	$H_2NCOONH_4$[d]	1:20:4	48	98.2	56.6	55.3
.0160	.320	.0320	$NaNO_3$[d]	1:20:2	53	99.3	42.9	43.1
.0160	.320	.0320	NaCl[d]	1:20:2	53	99.0	42.6	42.1
			(B) $BrCH_2COOH$					
.0160	.320	—		1:20:0	33	99.1	37.8	37.8
.0160	.320	.0320	NH_4NO_3	1:20:2	33	99.4	43.9	43.7
			(C) $CH_3CHClCOOH$					
.0191	.382	—		1:20:0	116	88.2	71.2	70.8
.0196	.392	.0392	NH_4NO_3	1:20:2	116	91.4	81.5	80.0
			(D) $(CH_3)_2CHCHBrCOOH$					
.0160	.320	—		1:20:0	33	91.8	100.0	99.0
.0160	.320	.0320	NH_4NO_3	1:20:2	33	63.4	97.4	96.2

[a] Based on weight of original sample.

[b] Based on ionic halogen.

[c] Average of all runs on the given acids at the given mole ratio.

[d] Suspension. NaCl and $NaNO_3$ did not dissolve completely. Ammonium carbamate only slightly soluble.

Thus, it was known exactly how much halogen acid was present in each tube, the total amount that had reacted in a given time, and the amount converted to the pri-

[2] The unreacted halogen was removed from the acid by refluxing with alcoholic sodium hydroxide over a period of several hours.

mary amino compound during the same time. Since some reaction takes place during the preparation of the samples for analysis, some error may have been introduced which was appreciable only in the early stages of the reaction. The results of these rate studies are represented in Figure 2. The rate of ammonolysis of α-chloropropionic acid was determined in the same manner. These results are depicted in Figure 3.

Similar studies were carried out on α-bromoisovaleric acid, but in this case only total and ionic halogen were measured since it had already been shown that the conversion to the primary amino acid was approximately complete (see Table III). The results of these determinations are represented graphically in Figure 4.

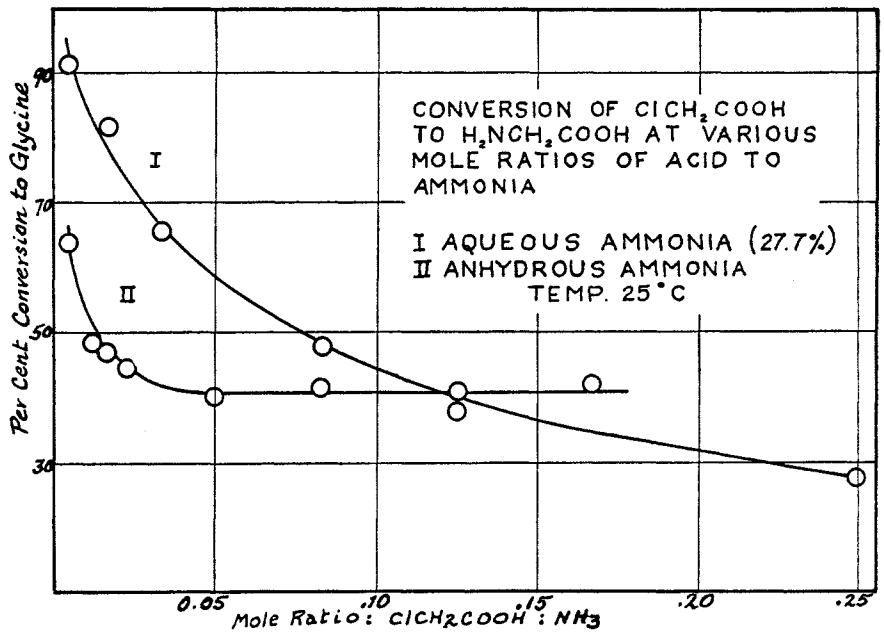


FIG. 1

DISCUSSION

To compare the effect of varying the mole ratio of chloracetic acid to ammonia on the per cent conversion to glycine in liquid ammonia with that obtained in aqueous ammonia, the data obtained in the first part of the present study are plotted on the same graph (Figure 1) with data which one of the authors obtained in a previous study using a 27.7% aqueous solution of ammonia (1). Two very striking facts may be noted from a comparison of these two curves: (a) For all except very high mole ratios of acid to ammonia the yield of glycine from the liquid ammonia reaction is less than that from the reaction in aqueous ammonia using the same mole ratio of acid to ammonia. (b) The extent of conversion to the

primary amino compound remains practically constant in the anhydrous system until the ratio of acid to ammonia is decreased to less than 0.05, whereas in aqueous ammonia a steady rise in per cent conversion with decreasing ratio of acid to ammonia is obtained throughout. The first fact is readily explained as will be seen below, but the theoretical implica-

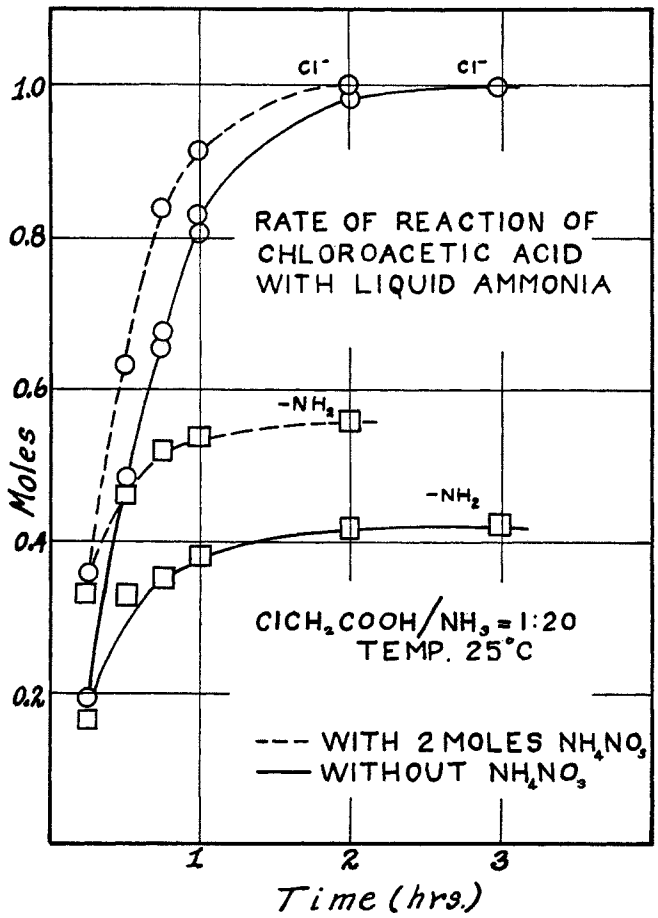


FIG. 2

tions of the second are rather obscure, and require a more complete knowledge of the kinetics of the reaction for satisfactory explanation.

Before going into the explanation of the lower yield of glycine in liquid ammonia than in aqueous solution the results of the experiments using ammonium salts should be considered. The results of these experiments are presented in Table III. These data show that the yield of glycine is

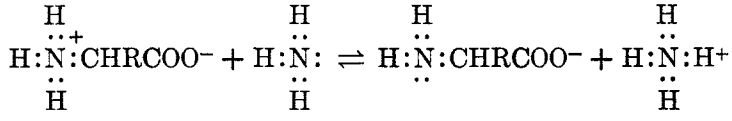
definitely increased when two moles of ammonium salt is used. There is still further increase when four moles of the ammonium salt is used. However, six moles of ammonium nitrate produces no further increase, while six moles of the chloride causes only a slightly larger effect than four moles. Experiments carried out using bromoacetic and α-chloropropionic acids in the presence of two moles of ammonium nitrate corroborate these findings. Moreover, the saturated solutions of sodium chloride and sodium nitrate produce no appreciable increase in the yield of glycine. This indicates that the effect of ammonium salts is due to the ammonium ion and not to the mere presence of electrolytes. Ammonium ions are always formed in these reactions as shown by the equations,

$$ClCH_2COOH + NH_3 \rightarrow ClCH_2COO^- + NH_4^+$$

$$ClCH_2COO^- + 2NH_3 \rightarrow H_2NCH_2COO^- + NH_4^+ + Cl^-,$$

but when the ammonium salts are added, the concentration of ammonium ions present at the start and throughout the reaction are greatly increased.

Liquid ammonia is a more basic solvent than water, and hence has a higher affinity for protons. Thus, liquid ammonia favors the existence of the ion, $H_2NCHRCOO^-$, rather than the zwitterion, $H_3N^+CHRCOO^-$. The situation is expressed by the following equilibrium equation:



(A) (B)

Since (B) has a free pair of electrons on the nitrogen, it is open to further reaction with the halogen compound, leading to the formation of secondary and tertiary ammonolytic products. Thus liquid ammonia favors the formation of these secondary and tertiary products more than does aqueous ammonia.

If, however, as in the experiments employing ammonium nitrate, chloride, and acetate, the ammonium ion concentration is very high, the above equilibrium is forced somewhat to the left. Thus, the concentration of (B) is reduced. Hence, the secondary and tertiary ammonolytic reactions are inhibited. The effect of high concentrations of ammonium salts may, therefore, be explained as the result of the inhibition of the secondary and tertiary reactions by covering up the free pair of electrons on the nitrogen by a proton from an ammonium ion. Ammonium salts are acids in liquid ammonia, and their effect on the ammonolysis of halogen acids in liquid ammonia is analogous to the pH effect observed in aqueous systems.

It should be noted that the concentrations of ammonium ion in the experiments using ammonium salts are very high, and the activity coefficients of the ammonium ion in such solutions undoubtedly vary widely from unity. Moreover, in such concentrated solutions, the activity coefficients of the different ammonium salts cannot be assumed to be the same. Shatenshteĭn (4) and Audrieth (5) and co-workers, in studies of the effect of ammonium salts on the ammonolysis of esters, have also noted a difference in behavior of the various ammonium salts. Hence, the somewhat different results obtained with ammonium chloride, ammonium nitrate,

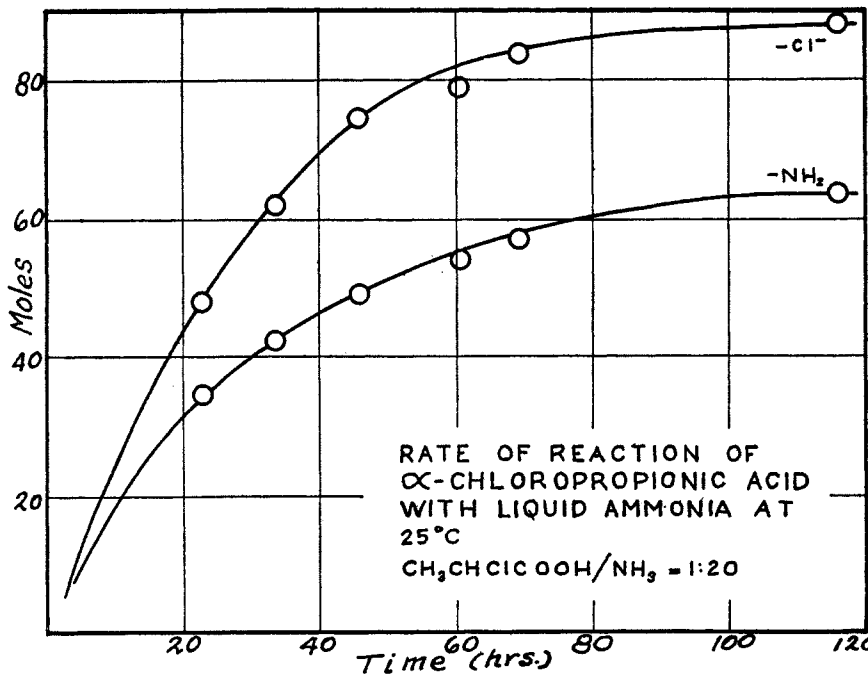


FIG. 3

and ammonium acetate at the same concentrations as shown in Table III are not unexpected.

It is interesting to note the pronounced increases in per cent conversion obtained in the experiments using ammonium carbamate. In view of the fact that only a small amount of ammonium carbamate dissolves in liquid ammonia, it is rather surprising that it should exhibit such a pronounced effect. It may be that this is an example of the carbamate effect in liquid ammonia solution. It is difficult to see how the small amount of ammonium ion dissolved could in itself produce such a large effect. This point, however, requires further investigation.

The effect of acidity on such ammonolyses in liquid ammonia has heretofore been overlooked, and it is the opinion of the authors that herein lies the key to many problems which obtain in the use of anhydrous ammonia as an ammonolyzing medium. Not only is this principle applicable to reactions with halogen acids, but it also should apply to the preparation of amines from organic halides to inhibit the formation of secondary and

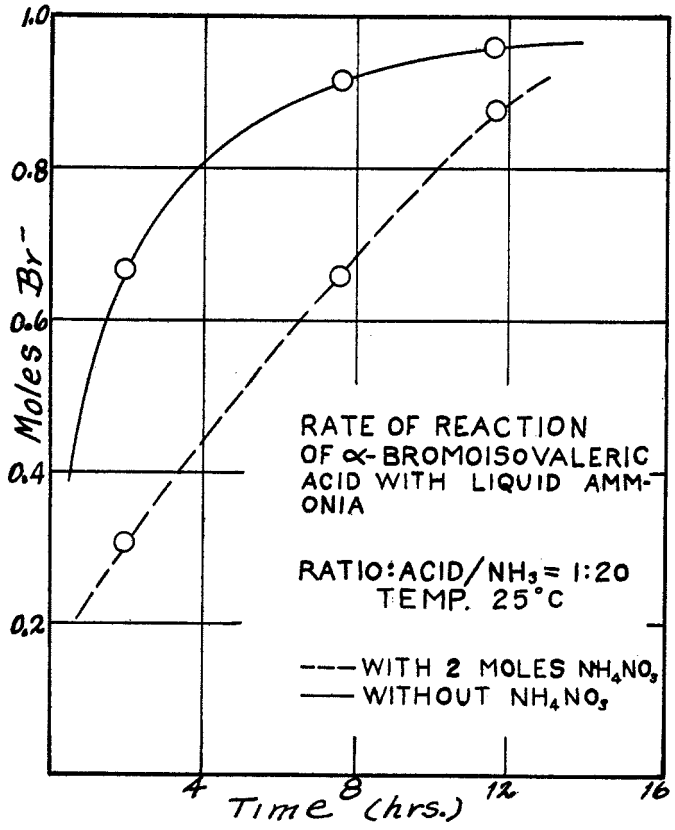


FIG. 4

tertiary amines. Experimental work is now in progress to test this principle.

From a practical point of view, ammonolysis in liquid ammonia shows greater promise with the less reactive halogen acids of higher molecular weight, than with chloroacetic acid. These acids exhibit much less tendency towards formation of secondary and tertiary ammonolytic products than do the haloacetic acids. This is shown by the data obtained from the study of ammonolysis of the α-bromo acids (Table II). With

less active halogen acids liquid ammonia is superior to aqueous ammonia, since the rates of reaction are faster and the temperatures may be raised without fear of hydrolytic side reactions.

With both bromoacetic acid and chloroacetic acid, a change in the ratio of acid to ammonia from one to twelve to one to twenty does not affect the per cent conversion to glycine. However, with α-bromopropionic acid a marked improvement in yield of primary amino compound is observed if the acid-ammonia ratio is one to twenty rather than one to twelve. With α-bromobutyric acid, a still greater increase was noted on changing this same ratio from one to twelve to one to twenty. These data indicate that the effect of decrease in the mole ratio of acid to ammonia on the per cent conversion to the primary amino compound is greater for the longer chain α-halogen acids than for the haloacetic acids. This is borne out by the fact that α-bromoisovaleric acid gives an 84.5% conversion at a ratio of one to eight, whereas, at one to twenty, the conversion to the primary amino compound is practically one hundred per cent.

Several pertinent conclusions can be drawn from the data obtained in studying the rates of ammonolysis of chloroacetic, α-chloropropionic, and α-bromoisovaleric acids in anhydrous ammonia: (a) The ionic halogen and amino nitrogen curves obtained with chloroacetic acid resemble those characterizing similar studies in aqueous solutions (1, 6). These curves indicate that at the beginning of the ammonolysis the reaction product is almost entirely the primary amino acid. However, the rapid leveling-out of the amino nitrogen curve indicates that as soon as an appreciable quantity of primary amino acid is formed the secondary reactions become appreciable. (b) Ammonium nitrate increases the rate of ammonolysis of chloroacetic acid and α-chloropropionic acid in liquid ammonia but decreases the rate of reaction of α-bromoisovaleric acid. No explanation can be offered at present for this apparent anomaly. (c) The rates of ammonolysis of the acids studied are greater in liquid ammonia than in aqueous ammonia. (d) The relative position of the amino nitrogen curves for chloroacetic acid in the presence and in the absence of ammonium nitrate support previous observations on the effect of ammonium salts.

SUMMARY

1. The ammonolysis of various α-halogen acids in liquid ammonia has been studied.

2. The effect of varying the mole ratio of chloroacetic acid to ammonia on the per cent converted to glycine has been studied and compared with the analogous effects which have been observed in aqueous systems.

3. It has been shown in studies with chloroacetic acid, α-chloropropionic acid, and bromoacetic acid, that the presence of considerable concentra-

tions of ammonium salts in the liquid ammonia solution inhibits the secondary and tertiary reactions, causing a higher per cent conversion to the primary amino acid. This principle is believed to be applicable to the ammonolysis of other halogen compounds.

4. The effect of the length of the carbon chain on the per cent of the α-halogen acid converted to the primary amino compound has been studied. The per cent conversion was found to be higher for the longer chain acids.

5. The rates of ammonolysis of chloroacetic, α-chloropropionic, and α-bromoisovaleric acids in liquid ammonia have been determined. The rates have also been measured in the presence of ammonium nitrate.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE LABORATORIES OF THE SHELL DEVELOPMENT COMPANY]

THE HIGH-TEMPERATURE CHLORINATION OF SATURATED ALIPHATIC MONOCHLORIDES. A "VICINAL" EFFECT[1]

FREDERICK F. RUST AND WILLIAM E. VAUGHAN

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Although a considerable amount of study has been given the subject of the production of dichlorides from monochlorides at low temperatures, usually in liquid phase and in the presence of catalysts, the high-temperature, vapor-phase reactions received little attention until Hass, McBee, and their co-workers entered the field. These investigators (4, 5, 6, 7, 10, 11, 12) have intensively studied many factors affecting the yields of isomeric monochlorides and dichlorides and have presented a set of rules to cover the data. For example, they report (7) that whereas the ordinary reactivity of hydrogen atoms towards substitution by chlorine is in the order primary<secondary<tertiary, with rise in temperature there is an increasingly close approach to relative rates of 1:1:1 in both liquid and vapor phase. No method for calculating yields of dichlorides from monochlorides is presented. However, four of the rules (No's. 7–10) qualitatively cover this subject. To illustrate, replacement of the hydrogen atoms on a carbon atom is hindered if the carbon atom is already bonded to chlorine. Further, it is concluded that Herzfelder's rule (1893) (postulated on the basis of liquid-phase experiments), which states that the second chlorine atom is always introduced on the carbon atom situated next to the carbon atom already united with halogen, is not applicable to chlorinations.

In the course of an investigation of high-temperature paraffin hydrocarbon chlorination in this laboratory (16), an attempt was made to clarify some of the secondary reactions. Thus, the chlorination of certain monochlorides indicated that the chlorine atom in the molecule profoundly affected the position of subsequent substitution. For example, even at relatively high temperatures, 1,1-dichloroethane (and even the 1,1,1-trichloride) predominates over the 1,2-isomer. Experiments on the propyl monochlorides showed similar results. The effects were deemed to merit further study, the results of which are summarized in the present paper. These suggest amendment of some of the previously proposed

[1] Presented at the Spring Meeting of the American Chemical Society, St. Louis, Mo., April 7–11, 1941.

generalizations. This effect of the chlorine atom on the reactivities of the various hydrogen atoms is, we believe, related to the relative ease of hydrolysis of various isomeric dichlorides, studied by Tishchenko (15), who found that the ease of hydrolysis decreases as the chlorine atoms approach one another. He applied the term "vicinal" effect to the phenomenon and we have adopted this name as descriptive of our findings.

MATERIALS AND TECHNIQUE

The present experiments have been limited to a study of the chlorinations of ethyl chloride, normal propyl and isopropyl chlorides, and normal and secondary butyl chlorides, because the analyses of mixtures from the chlorinations of higher chlorides become increasingly complicated. The results, however, indicate clear-cut generalizations which are probably applicable to higher homologs.

The ethyl chloride, a commercial material which analyzed better than 99.8%, was freed of oxygen and metered as vapor to the reactors. The propyl and butyl chlorides were Eastman products which were carefully refractionated through a small 17-theoretical plate, helices-packed column; the boiling ranges were as follows:

CHLORIDE	DIST'N. RANGE (°C. UNCORRECTED)	LITERATURE °C.
n-propyl	46.3–46.7	46.4 (9)
isopropyl	36.2–36.5	36.5 (9)
n-butyl	78.4–78.7	78.5 (6)
sec-butyl	68.4–68.6	68.25 (6)

The chlorine used was the distilled material already described (3, 16). Tank nitrogen (or carbon dioxide), freed of oxygen by chromous chloride solution, was used as a diluent to control the reactions and thus minimize pyrolysis, especially at the higher temperatures (16). It also served to pick up desired proportions of the normally liquid monochlorides from saturating devices held at predetermined temperatures.

The technique and apparatus were identical with those previously employed (14, 16). The chlorides effluent from the furnace were washed with dilute caustic to remove hydrogen chloride and the small amount of unreacted chlorine, and were condensed and dried. The material was then subjected to careful distillation through a column of 17 theoretical plates. Sufficiently high-boiling, inert hydrocarbons were added to the still pots to drive over all of the dichloride fractions. Examination of Figures 1, 2, 3, and 4, which do not show the unreacted foreruns, will give an idea of the separations obtained. Obviously, interpretation of these curves is somewhat arbitrary, but we believe that the conclusions reached are fully justified.

The possibility of preferential thermal decomposition of the dichlorides in the reaction zone must be considered. The chlorinations are, to some extent, especially at higher temperature, accompanied by processes other than that of dichloride formation. These side reactions, such as decomposition to olefins, unsaturated mono- and di- chlorides, and carbonaceous material, occur to varying extents and in some instances constitute a large part of the over-all reaction. This feature has been discussed at some length by Hass, McBee, and Weber (7), who show that failure to

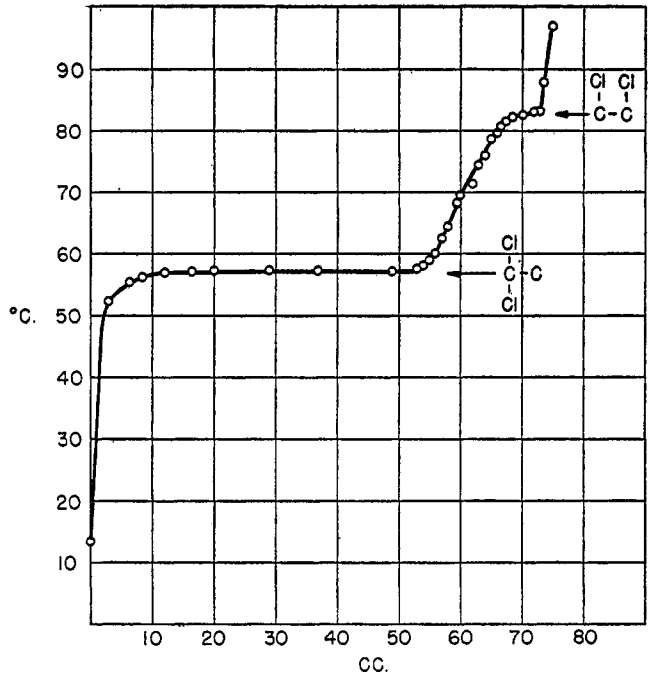

FIG. 1. DICHLORIDE FORMATION FROM CHLORINATION OF ETHYL CHLORIDE AT 208°
Flows (cc./min.): 50Cl_2; 100 C_2H_5Cl; 150 CO_2 (tetraethyllead as a catalyst)

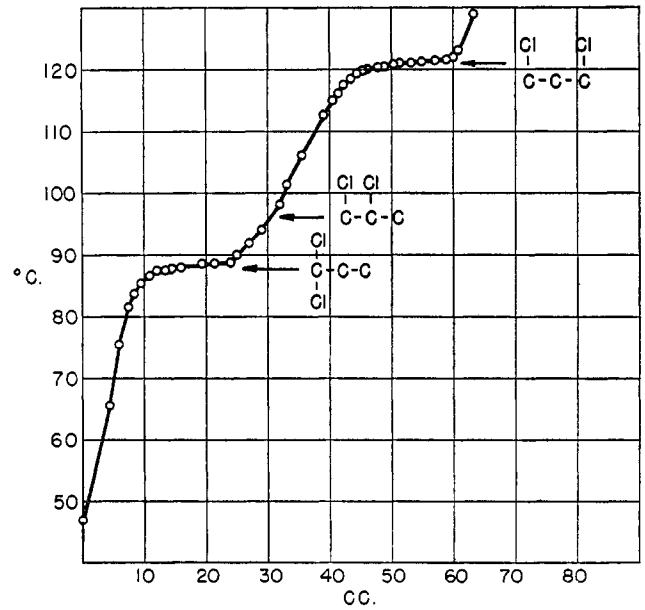

FIG. 2. DICHLORIDE FORMATION FROM CHLORINATION OF *n*-PROPYL CHLORIDE AT 380°
Flows (cc./min.): 200Cl_2; 400 n-C_3H_7Cl; 600 N_2

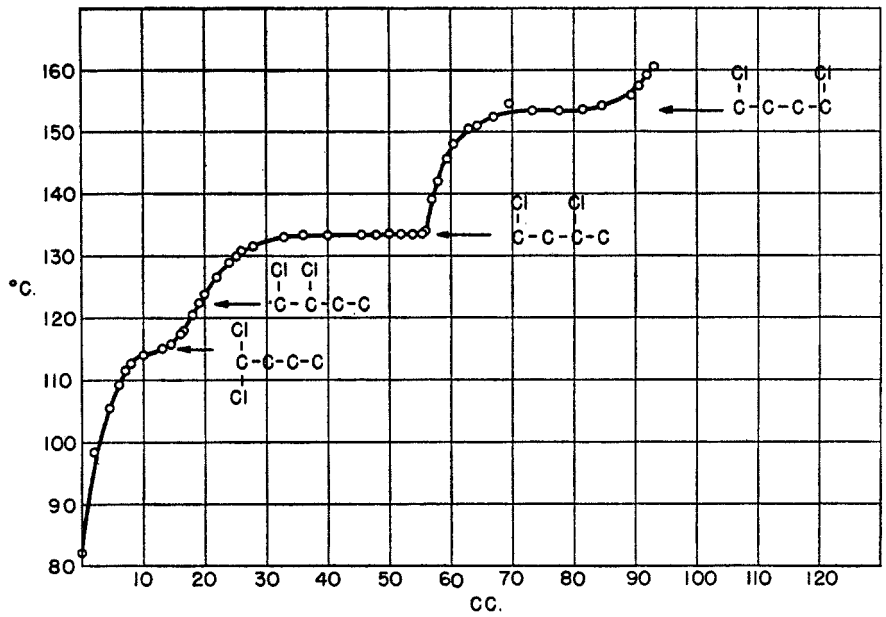

FIG. 3. DICHLORIDE FORMATION FROM CHLORINATION OF *n*-BUTYL CHLORIDE AT 312°
Flows (cc./min.): 200Cl_2; 400 n-C_4H_9Cl; 600 N_2

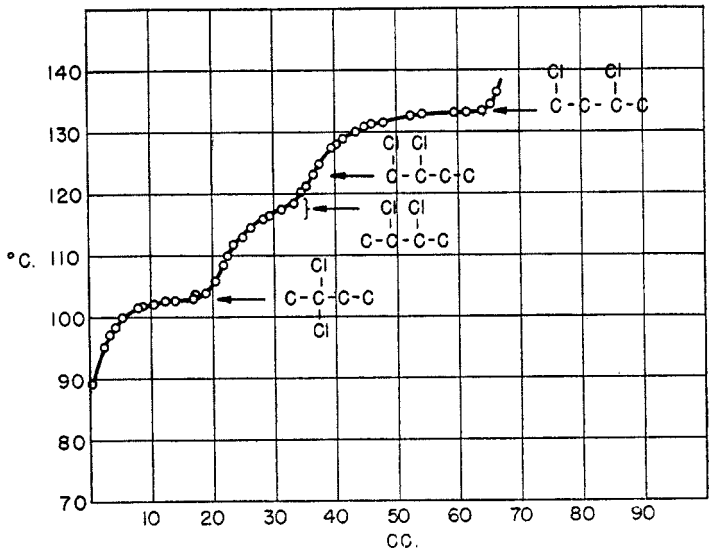

FIG. 4. DICHLORIDE FORMATION FROM CHLORINATION OF *sec*-BUTYL CHLORIDE AT 314°
Flows (cc./min.): 200Cl_2; 400 sec-C_4H_9Cl; 600 N_2

TABLE I

CHLORINATION OF ETHYL CHLORIDE.
DICHLORIDE FORMATION

Flow (cc./min.): 50 Cl_2; 100 C_2H_5Cl; 150 CO_2

PRODUCT	B.P., °C.	GROUP CHLORINATED	208°[a]			320°			415°		
			g.	moles	R.R.[b]	g.	moles	R.R.[b]	g.	moles	R.R.[b]
1,1-$C_2H_4Cl_2$	57.3 (9)	$ClCH_2$—	70.5	0.71	8.7	46.5	0.47	8.6	36.6	0.37	9.4
1,1,1-$C_2H_3Cl_3$	74.1 (9)	Cl_2CH—	—	—	—	—	—	—	14.7	0.11	9.4
1,2-$C_2H_4Cl_2$	83.7 (9)	—CH_3	16.3	0.16	1.3	11.9	0.12	1.4	5.0	0.05	0.6

[a] Using tetraethyllead as a catalyst [see (16)]

[b] "Relative Reactivity" of the various types of H-atoms on the basis of "total reactivity" being taken as ten. Example: at 320°,

0.47/0.59 = 0.80 = mole fraction of 1,1-$C_2H_4Cl_2$

0.12/0.59 = 0.20 = mole fraction of 1,2-$C_2H_4Cl_2$

0.80/2 + 0.20/3 = 0.467; (0.40/0.467)10 = 8.6 = R.R. of the hydrogen atoms of the ClH_2C— group.

TABLE II

CHLORINATION OF n-PROPYL CHLORIDE.
DICHLORIDE FORMATION

Flow (cc./min.): (a) 50 Cl_2; 100 n-C_3H_7Cl; 150 N_2

(b) 200 Cl_2; 400 n-C_3H_7Cl; 600 N_2

PRODUCT	B.P., °C.	GROUP CHLORINATED	158°[a] (a)			260° (b)			340° (b)			380° (b)		
			g.	moles	R.R.	g.	moles	R.R.	g.	moles	R.R.	g.	moles	R.R.
1,1-$C_3H_6Cl_2$	87.0 (5)	$ClCH_2$—	3.7_5	0.033	2.5	14.4	0.127	3.0	5.7	0.050	4.1	34.2	0.303	5.9
1,2-$C_3H_6Cl_2$	96.8 (5)	—CH_2—	7.8	0.069	5.1	24.3	0.215	5.0	3.6	0.032	2.6	0(?)	—	—
1,3-$C_3H_6Cl_2$	120.4 (5)	—CH_3	5.3_5	0.047	2.4	14.2	0.126	2.0	6.9	0.061	3.3	35.8	0.317	4.1

[a] Using tetraethyllead as a catalyst.

evaluate such conditions may lead to erroneous conclusions regarding product distributions. However, in the present instance, the α,β-dichlorides, which are in general obtained in the smallest amounts especially at the highest temperatures, are thermally the most stable (8). Consequently the conclusions drawn are more likely to be in error on the side of understatement.

RESULTS

Ethyl chloride. The reactivity of ethyl chloride towards vapor-phase chlorination has been briefly discussed (16). It was shown that at low temperatures, ethyl chloride is considerably less reactive than the parent hydrocarbon ethane, indicating that the Cl atom retards substitution on both the methyl and chloromethyl groups. When an ethane-ethyl chloride mixture is chlorinated, the behavior of the system is very closely that of

TABLE III

CHLORINATION OF ISOPROPYL CHLORIDE.
DICHLORIDE FORMATION

Flow (cc./min.): 200 Cl_2; 400 iso-C_3H_7Cl; 600 N_2

PRODUCT	B.P., °C.	GROUP CHLORINATED	208°[a]			319°			383°		
			g.	moles	R.R.	g.	moles	R.R.	g.	moles	R.R.
2,2-$C_3H_6Cl_2$	69.7 (5)	—CHCl—	50.0	0.442	8.8	32.2	0.285	9.0	63.5	0.561	9.5
1,2-$C_3H_6Cl_2$	96.8 (5)	H_3C—	40.0	0.354	1.2	21.5	0.190	1.0	20.8	0.184	0.5

[a] Using tetraethyllead as a catalyst.

ethane alone. Chlorination of ethyl chloride does, however, yield 1,1-dichloroethane, and at higher temperatures, even 1,1,1-trichloroethane, in excess of the 1,2-dichloride. This preponderance of the 1,1-compound over the 1,2- is also found in the chlorination of ethane itself. Table I is a summary of pertinent data. The relative reactivities of the various hydrogen atoms towards substitution by chlorine can be evaluated approximately by taking the mole fractions of the various dichlorides formed and weighting them according to the numbers of the various kinds of hydrogen atoms. An example of such a computation is given in the table, wherein the 1,1,1-trichloride is considered with the 1,1-dichloride. In this distribution other products such as unsaturates are neglected; this is also done in the other examples.

n-*Propyl chloride and isopropyl chlorides.* The temperature profiles for the high-temperature, vapor-phase chlorination of these two materials have been given previously (16), and it has been pointed out that the chlorine atom attached to a carbon atom in the molecule inhibits chlorina-

TABLE IV

CHLORINATION OF n-BUTYL CHLORIDE.
DICHLORIDE FORMATION

Flow (cc./min.): 200 Cl_2; 400 n-C_4H_9Cl; 600 N_2

[$ClCH_2$ CH_2 CH_2 CH_3]
1— 2— 3— 4—

PRODUCT	B.P., °C.	GROUP CHLORINATED	202°[a]			312°			380°		
			g.	moles	R.R.	g.	moles	R.R.	g.	moles	R.R.
1,1-$C_4H_8Cl_2$	113.0	$ClCH_2$— 1—	14.5	0.115	1.3	17	0.135	2.0	9.5	0.075	2.2
1,2-$C_4H_8Cl_2$	123 (8)	—CH_2— 2—	13.5 (?)	0.105	1.2	0(?)	—	—	0(?)	—	—
1,3-$C_4H_8Cl_2$	133.5	—CH_2— 3—	58.5	0.465	5.2	42.5	0.34	5.0	22.5	0.18	5.3
1,4-$C_4H_8Cl_2$	153.5[b]	—CH_3 4—	39.5	0.315	2.3	38	0.31	3.0	16.5	0.13	2.5

[a] Using tetraethyllead as a catalyst.
[b] See text.

TABLE V

CHLORINATION OF SEC.-BUTYL CHLORIDE
DICHLORIDE FORMATION

Flow (cc./min.): 200 Cl_2; 400 sec.-C_4H_9Cl; 600 N_2

[CH_3 $CHCl$ CH_2 CH_3]
1— 2— 3— 4—

PRODUCT	B.P., °C.	GROUP CHLORINATED	200°[a]			314°			380°		
			g.	moles	R.R.	g.	moles	R.R.	g.	moles	R.R.
2,2-$C_4H_8Cl_2$	103.0	—CHCl— 2—	18.5	0.145	4.2	22	0.175	5.4	21.5	0.17	6.7
2,3-$C_4H_8Cl_2$	117-119 (2)	—CH_2— 3—	30	0.235	3.4	16	0.125	1.9	0(?)	—	—
1,2-$C_4H_8Cl_2$	123 (8)	H_2C— 1—	0(?)	—	—	0(?)	—	—	0(?)	—	—
1,3-$C_4H_8Cl_2$	133.5	—CH_3 4—	30.5	0.240	2.4	33	0.26	2.7	31.5	0.25	3.3

[a] Using tetraethyllead as a catalyst.

tion on the adjoining carbon atoms. However, inspection of Tables II and III will show that this effect becomes even more marked as the temperature is increased, resulting in the virtual disappearance of the 1,2-isomer. In the case of *n*-propyl chloride an additional experiment at high temperature (400°) confirmed the absence of the 1,2-compound.

n-*Butyl chloride and sec-butyl chloride.* The chlorination of these compounds results in more complex mixtures of isomers. However, the data presented in Tables IV and V form a consistent picture on the whole, which agrees with the other information.

The relatively large amount of 1,4-dichlorobutane from the chlorination of *n*-butyl chloride is of interest. Muskat and Northrup (13) photochlorinated *n*-butyl chloride while it was being refluxed. Although their fractionation was not sharp, it can be estimated from their data that approximately 12% of the dichloride product consisted of the 1,4-isomer. Under our high-temperature conditions, the 1,4-compound accounts for 35–40% of the dichloride fraction. Hass, McBee, and Weber (6) mention the 1,2- and 2,3-dichlorides as being produced by chlorination of *n*-butane, but make no comment regarding the 1,4-isomer. It is also of interest to point out that an early reference (1) gives the boiling point as 161–163°. The present work indicates that 153.5° is more nearly accurate; this is in better agreement with the value 155.0° given by Hass (3a) and confirmed by Tishchenko (154.7–155°) (15).

DISCUSSION

Consideration of the evidence in Tables I–V leads to the following conclusions:

1. In vapor-phase chlorination, the carbon-chlorine group in a straight-chain aliphatic monochloride markedly retards subsequent substitution on the adjacent (once removed) carbon atoms. This effect becomes increasingly pronounced with progressively higher temperatures.

2. This "vicinal" effect extends in a lesser degree to the carbon atoms twice removed from the C—Cl group.

3. In vapor-phase chlorination of straight-chain aliphatic monochlorides, substitution of the hydrogen atoms on the carbon atom bonded to chlorine is mildly retarded. This retardation decreases with increasing temperature.

These statements are illustrated by Table IV dealing with *n*-butyl chloride. It is seen that the small amount of the 1,2-dichloride formed at 202° vanishes when the chlorination is performed at higher temperatures. At the same time, the relative reactivity of the hydrogen atoms of the chloromethyl group as compared with those of the uninfluenced methyl group

steadily increases. The reactive secondary H-atoms in the 3-position are seemingly not as greatly affected.

Likewise Table II, dealing with *n*-propyl chloride, reveals that as the temperature rises, there occurs a progressive decrease in the proportion of 1,2-dichloropropane, while the relative reactivities of the hydrogen atoms on both the 1- and 3-carbon atoms are enhanced.

That this "vicinal" effect of the chlorine atom in the monochloride is not confined to the C—H bonds on the once-removed C-atoms, but extends at least to those twice removed is shown by the following comparison of relative reactivities:

AT 310–320°C	RATIO OF H-ATOM REACTIVITIES, $ClH_2C—/H_3C—$
$ClH_2C—CH_3$	6.1
$ClH_2C—CH_2—CH_3$	1.3
$ClH_2C—CH_2—CH_2—CH_3$	0.7

Substitution into the methyl group of *n*-propyl chloride does not occur as readily as it does into the chloromethyl group. It is only when the methyl group is sufficiently removed from the chlorine atom, as in *n*-butyl chloride, that its hydrogen atoms approach the reactivity of those in ethane.

ACKNOWLEDGMENT

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SUMMARY

1. In vapor-phase chlorination, the carbon-chlorine group in a straight-chain aliphatic monochloride markedly retards subsequent substitution on the adjacent (once-removed) carbon atoms. This effect becomes increasingly pronounced with progressively higher temperatures.

2. This "vicinal" effect extends to a lesser degree to the carbon atoms twice removed from the C—Cl group.

3. In vapor-phase chlorination of straight-chain aliphatic monochlorides, substitution of the hydrogen atoms on the carbon atom bonded to chlorine is mildly retarded. This retardation decreases with increasing temperature.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE SYNTHESIS OF ALDEHYDES FROM GRIGNARD REAGENTS. II. POLYMETHYLBENZALDEHYDES

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The literature records the use of eight different substances which react with Grignard reagents leading to the formation of aldehydes according to the type reaction $RX \rightarrow RMgX \rightarrow RCHO$. One of the earliest of these studies was that of Gattermann and Maffezzoli (1) who found that at very low temperatures ($-50°$) an excess of ethyl formate (3 moles) reacted with Grignard reagents to give products consisting largely of aldehydes rather than of the secondary alcohols formed in a subsequent reaction. In a continuation of this study, Gattermann (2) prepared a series of aldehydes in yields of from 10 to 50%, and the use of some other formates, particularly the methyl and amyl esters was meanwhile investigated by others (3).

Bodroux and Tschitschibabin (4) independently discovered a synthesis of aldehydes which involved the reaction between a Grignard reagent and ethyl orthoformate. This synthesis of aldehydes has been used by many investigators and, in favorable cases, it gives excellent yields.

Zelinsky (5) prepared aldehydes by the reaction between formic acid and Grignard reagents and although he did not state the yields, presumably they were small, for Houben (6) in a continuation of this study was able to obtain phenylacetaldehyde in a maximum yield of but 30% from benzylmagnesium chloride and formic acid. Houben also obtained butyraldehyde from propylmagnesium chloride by this method, but the yield was extremely poor and Houben was led to try the salts of formic acid, rather than the acid itself. Benzylmagnesium chloride reacted with copper formate to produce phenylacetaldehyde, but the yield was very low.

Bouveault (7) introduced the use of disubstituted formamides as reagents which were capable of converting Grignard reagents into aldehydes. This reaction, while successful in certain cases, is very complicated and frequently produces tertiary amines as the chief products. Moreover, even when the aldehyde is the chief product, the reaction does not compare in efficiency with the one using ethyl orthoformate (4).

[1] Abstracted from a thesis by Joseph Nichols, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the M.S. degree, 1941.

Sachs and Loevy (8) have reported a synthesis of aldehydes which involves addition of a Grignard reagent to an isocyanide. While these authors used only phenylmagnesium bromide and methyl isocyanide, the fact that benzaldehyde was obtained led them to predict that the synthesis would be successful in other cases. Gilman and Heckert (9) attempted to extend the reaction; they added phenylmagnesium bromide to a number of isocyanides, including hydrocyanic acid (7a) but benzaldehyde was obtained only when methyl isocyanide was used.

Monier-Williams (10) discovered a synthesis for aldehydes which involved the reaction between a Grignard reagent and ethoxymethyleneaniline.

$$RMgX + C_6H_5N{=}CHOC_2H_5 \rightarrow RCH{=}NC_6H_5 + C_2H_5OMgX$$

$$RCH{=}NC_6H_5 + H_2O + HCl \rightarrow RCHO + C_6H_5NH_2 \cdot HCl$$

Monier-Williams was interested chiefly in preparing aromatic aldehydes containing a thio ether group attached to the ring, but he prepared a number of other aldehydes as well, and somewhat later Gattermann (2) also used the method for preparing a series of aldehydes. The yields obtained by the two investigators checked very well and were of the order of 30–60%. It is of interest that Monier-Williams attempted to improve the yields of aldehydes by operating in boiling toluene; the results were quite unsatisfactory.

Wuyts and his collaborators discovered and developed a synthesis for aldehydes in which a Grignard reagent reacted with carbon disulfide to produce a dithio acid which was in turn, converted into an aldehyde derivative by action of semicarbazide, phenylhydrazine, or hydroxylamine. The aldehyde derivative was then hydrolyzed to the aldehyde in the usual way.

$$RMgX + CS_2 \rightarrow RCSSH$$

$$RCSSH + H_2NCONHNH_2 \rightarrow RCH{=}NNHCONH_2 + H_2S + S$$

$$RCH{=}NNHCONH_2 + HCl + H_2O \rightarrow RCHO + H_2NCONHNH_2 \cdot HCl$$

When phenylhydrazine was used in the second step, Wuyts (11) found that in general at low temperatures a salt was first formed. As the temperature rose, this salt evolved hydrogen sulfide to give a thiohydrazide, which in turn became converted into the hydrazone with elimination of sulfur.

$$RCSSH \rightarrow RCSSNH_2NH_2C_6H_5 \rightarrow RCSNHNHC_6H_5 + H_2S$$

$$RCSNHNHC_6H_5 \rightarrow RCH{=}NNHC_6H_5 + S$$

The transformation into the hydrazone was not always complete, for in many cases mixtures of the thiohydrazide and hydrazone resulted, and

Wuyts (12) found that the nature of the group R in the dithio acid determined the course of the reaction. When R was aliphatic, alicyclic, or aliphatic-aromatic, thiohydrazides were formed and the presence of the hydrazone could not be established with certainty.

Hydroxylamine reacted with aromatic dithio acids to form oximes and in this way Wuyts and Koeck (13) prepared a number of aromatic aldoximes in yields of 70–90% based upon the dithio acids. However, when the dithio acid was aliphatic, alicyclic, or aliphatic-aromatic, the reaction proceeded beyond the oxime stage and nitriles were formed.

$$ArCSSH + H_2NOH \rightarrow ArCH{=}NOH + S + H_2S$$

$$RCSSH + H_2NOH \rightarrow RCN + S + H_2S + H_2O$$

Hydrolysis of oximes or hydrazones to the aldehyde offers many difficulties and the yields are frequently very poor. Hydrolysis of a semicarbazone, on the other hand, usually proceeds smoothly and results in good yields of aldehydes. Consequently, as a practical method of synthesizing aldehydes, the reaction of the dithio acid with semicarbazide was the most feasible and Wuyts, Berman, and Lacourt (14) prepared a number of aldehydes in this way. The theoretical quantity of carbon disulfide was slowly added to an ethereal solution of a Grignard reagent; the reaction-mixture was allowed to stand for a few hours and was then decomposed with iced hydrochloric acid. The dithio acid was extracted from the ether solution with alkali and was immediately liberated from the alkaline solution with iced acid and taken up in ether. After drying the solution, the solvent was removed and the thio acid was dissolved in pyridine and poured into a warm solution of semicarbazide hydrochloride in pyridine. The semicarbazone was isolated, washed free of sulfur with carbon disulfide and benzene, and hydrolyzed to the aldehyde with dilute hydrochloric acid. The free aldehyde was removed by steam distillation.

The yields obtained by Wuyts and his collaborators were not clearly stated. The yields of aldehydes obtained from the semicarbazones were given, but the yields of the latter obtained from the thio acids were not always given. Moreover, the yield of dithio acid obtained from the aromatic halide was given in only one case, 46% for *p*-bromodithiobenzoic acid. Table I gives the results reported by Wuyts. The same differences in behavior were noticed between the aromatic and aliphatic dithio acids in their reaction with semicarbazide as were noticed in their reaction with phenylhydrazine. When the dithio acid was aromatic, a semicarbazone was formed, but when the dithio acid was aliphatic or alicyclic, the semicarbazide of the thio acid resulted.

Savariau (15) prepared aromatic aldehydes by action of Grignard reagents upon chloral.

$$RMgX + CCl_3CHO \rightarrow RCHOHCCl_3 \rightarrow RCHOHCOOH \rightarrow RCHO$$

The secondary trichloro alcohols were transformed into hydroxy acids by action of alkali, and the latter, when heated with aqueous potassium carbonate, gave the aldehydes.

In addition to the reactions discussed above, in which Grignard reagents RMgX were converted into aldehydes RCHO, the literature contains a few examples in which two carbon atoms were introduced to give aldehydes RCH_2CHO. Späth (16), by a modification of the orthoformate synthesis, has used the reaction between ethoxyacetal and a Grignard reagent to prepare a number of substituted phenylacetaldehydes.

TABLE I

YIELDS OF ALDEHYDES FROM DITHIOACIDS

DITHIO ACID	ALDEHYDE	YIELD OF ALDEHYDE, %	
		Based on semicarbazone	Based on dithio acid
Benzoic	Benzaldehyde	80.2	66.5
p-Bromobenzoic	*p*-Bromobenzaldehyde	80.3	—
o-Toluic	*o*-Tolualdehyde	83.4	81.5
p-Toluic	*p*-Tolualdehyde	88.5	86 (?)
α-Naphthoic	α-Naphthaldehyde	89.7	79.7
β-Naphthoic	β-Naphthaldehyde	93.8	—

Hershberg (17) prepared phenylacetaldehyde and hexanal by the following novel series of reactions:

$$RMgBr\ (R = C_4H_9 \text{ or } C_6H_5) + CH_2{=}CHCH_2Br \rightarrow RCH_2CH{=}CH_2.$$

$$(82\%,\ R = C_6H_5)$$

$$RCH_2CH{=}CH_2 \rightarrow RCH_2CHBrCH_2Br \rightarrow RCH_2CHOHCH_2OH$$

$$RCH_2CHOHCH_2OH + Pb(OCOCH_3)_4 \rightarrow RCH_2CHO + CH_2O$$

$$(R = C_4H_9).$$

$$C_6H_5CH_2CH{=}CH_2 + (C_6H_5CO\cdot O)_2AgI \rightarrow C_6H_5CH_2CH(OCOC_6H_5)CH_2OCOC_6H_5\ (85\%)$$

$$\xrightarrow{KOH} C_6H_5CH_2CHOHCH_2OH\ (84\%) \xrightarrow{Pb(OAc)_4} CH_2O + C_6H_5CH_2CHO\ (72\%)$$

Behal and Sommelet (18) prepared aldehydes of the type R_2CHCHO from Grignard reagents RMgX by use of ethyl ethoxyacetate and Stoermer (19) also investigated this reaction, using ethyl ethoxyacetate end ethyl phenoxyacetate.

$$C_2H_5OCH_2COOC_2H_5 + 2\ RMgX \rightarrow C_2H_5OCH_2C(OH)R_2$$

$$C_2H_5OCH_2C(OH)R_2 \xrightarrow{H_2SO_4} R_2C{=}CHOC_2H_5 \rightarrow R_2C{=}CHOH \rightarrow R_2CHCHO.$$

The phenoxy compounds, which are more easily handled in the Grignard reaction, can be converted to the ethoxy compounds by heating under pressure with alcoholic potassium hydroxide; this is advantageous, because the ethoxy compounds are more readily converted into the aldehydes. Behal and Sommelet have also prepared aldehydes R^1R^2CHCHO by action of Grignard reagents upon ethoxy ketones:

$$R^1MgX + R^2COCH_2OC_2H_5 \rightarrow R^1R^2C(OH)CH_2OC_2H_5 \rightarrow R^1R^2CHCHO.$$

DISCUSSION

A consideration of the results in the literature, together with ease of manipulation and preparation of the reagents, led to the conclusion that the most promising methods for the synthesis of aldehydes from Grignard reagents, as far as yields and general applicability were concerned, were the syntheses from ethyl orthoformate, from ethoxymethyleneaniline, and from the dithio acids. Accordingly, a series of eight methylated aromatic aldehydes was prepared by each of the three methods, and the yields of aldehydes, together with the difficulties involved in each method, were compared. The halides—all bromo compounds—used were: *o*- and *p*-bromotoluene, 3- and 5-bromopseudocumene, bromomesitylene, bromodurene, bromoisodurene, and bromopentamethylbenzene. All of the aldehydes, except pentamethylbenzaldehyde, were isolated and weighed either as the sodium bisulfite compounds or as semicarbazones. This was thought advisable since most of the aldehydes are liquids and the mechanical losses involved in handling small amounts of liquids might be great enough to vitiate the results of the comparisons. Pentamethylbenzaldehyde, a high-melting solid, was readily handled as such. The formation of bisulfite compounds and especially of semicarbazones is not a quantitative reaction; likewise, recovery of the aldehydes from these derivatives is not quantitative. Some data with respect to the recovery of aldehydes from their semicarbazones are shown in Table I; the yields of recovered aldehydes were between 80 and 94%. Hence yields of aldehydes figured

in this way represent values appreciably lower than the true ones and if one were interested in the preparation of an aldehyde for subsequent use as such, the most efficient procedure would involve a simple distillation of the aldehyde after it had been steam distilled from the reaction-mixture. Many aromatic aldehydes undergo autooxidation fairly rapidly; losses from this source can be considerable, but the bisulfite compounds and semicarbazones are quite stable and once obtained, can be handled without fear of deterioration.

TABLE II

YIELDS OF ALDEHYDES OBTAINED FROM GRIGNARD REAGENTS BY THREE METHODS

HALIDE	ALDEHYDE	YIELD OF GRIGNARD REAGENT, %	YIELD OF ALDEHYDE, %, FROM:		
			Ethyl orthoformate	Ethoxymethyleneaniline	Dithio acids
p-Bromotoluene	*p*-Tolualdehyde	94	74.4	82.2	23.3
o-Bromotoluene	*o*-Tolualdehyde	94	73.2	80.8	59.6 54.6
[redacted]					
5-Bromopseudocumene	2,4,5-Trimethylbenzaldehyde	90	71.5	80.5	43.9
Bromomesitylene	2,4,6-Trimethylbenzaldehyde	91	57.3	63.8	2.2
Bromodurene	2,3,5,6-Tetramethylbenzaldehyde		61.4	70.4	0
Bromopentamethylbenzene	Pentamethylbenzaldehyde		43.1	60.1	0
3-Bromopseudocumene	2,3,6-Trimethylbenzaldehyde		61.2	65.4	—
Bromoisodurene	2,3,4,6-Tetramethylbenzaldehyde		60.2	64.3	—

p-Tolualdehyde, *o*-tolualdehyde, 2,4,5-trimethylbenzaldehyde and 2,3,5,6-tetramethylbenzaldehyde were obtained in the form of their sodium bisulfite addition products.

2,4,6-Trimethylbenzaldehyde, 2,3,6-trimethylbenzaldehyde and 2,3,4,6-tetramethylbenzaldehyde were obtained in the form of their semicarbazones.

Pentamethylbenzaldehyde was obtained as the pure aldehyde.

SUMMARY OF RESULTS

Yields of aldehydes obtained by the three methods are given in Table II. With regard to the actual procedures used, certain observations were made which are of importance, and these will be discussed briefly.

A. The ethyl orthoformate synthesis. A complete review of this synthesis has been given in the previous paper (4) but the procedure used in the work reported there has been modified and improved. Bodroux (20)

reported that it was necessary to reflux the reaction-mixture after adding ethyl orthoformate, and it was found previously (4) that a period as long as fifteen hours was necessary. When the ester was added to the Grignard reagent, there was no immediate evidence of a reaction. In the present work, it was found that the reaction-mixtures, during the period in which they were refluxed, varied in behavior. In some instances a marked color change occurred, or a precipitate formed; in other cases there was little change in appearance throughout. Experiment showed that the best results were obtained when the reaction-mixture was refluxed for five hours; this was followed by the cautious removal of the ether on the steam-bath. During this process a point was reached at which a vigorous reaction set in; this point had to be watched for carefully, for it was necessary that this reaction should start, and at the same time not become uncontrollable. The instant the vigorous reaction started, the vessel was plunged into an ice-bath; the reaction then proceeded quietly to completion. At the end of the reaction, the cooling bath was removed and the product was processed. In the synthesis of *p*- and *o*- tolualdehyde, yields of 74 and 73%, respectively, were obtained when this procedure was followed; when the ether was partially removed, but not so far as to cause the vigorous reaction to set in, the yields were 51 and 47%, respectively. In view of these results, the hypothesis advanced by Wood and Comley (21) that the reaction proceeds in two stages, appears to be correct.

The reaction-product separated as a viscous, brown material which set to a hard solid mass on standing. It was decomposed by ice and 5 *N* hydrochloric acid, and then the whole mixture—ether and aqueous layers—was refluxed on the steam-bath for a short time in order to decompose the acetal.

The great evolution of heat which occurs when the vigorous reaction sets in renders control of the reaction very difficult except when small amounts of material (0.1–0.2 moles) are involved, and this fact reduces somewhat the value of the ethyl orthoformate synthesis, at least for preparation of the aldehydes described in this paper. Otherwise, it is an admirable synthesis: the materials are cheap, the yields are excellent, the procedure is simple, and the synthesis is to be highly recommended for preparation of aldehydes from rare and costly aromatic halogen compounds, especially when the "entrainment" method has to be used for preparation of the Grignard reagent.

B. The ethoxymethyleneaniline synthesis. The yields of aldehydes obtained by this method were from 4 to 17% higher than those obtained by the orthoformate synthesis. When the reagents were mixed, a reaction ensued immediately. This reaction was not vigorous, but enough heat was evolved to keep the ether boiling gently while the reagents were being

mixed. After addition of all of the reagent, the reaction-mixture was refluxed for a short period of time (usually 30 minutes) and was then decomposed with ice and 5 *N* hydrochloric acid and further processed as described above.

The fact that ethoxymethyleneaniline does not have to be "forced" to react with the Grignard reagent, and that the reaction does not involve sudden liberation of heat as is the case with ethyl orthoformate, no doubt accounts for the higher yields of aldehydes obtained. This, in turn, means that the reaction is adaptable to large quantities of material. The main difficulty with the synthesis, however, arises in the preparation and cost of the reagent, ethoxymethyleneaniline. This must be prepared from ethyl iodide and the silver salt of formanilide, and the silver salt must be carefully dried before it is used in the reaction with ethyl iodide. Monier-Williams (10) showed that if any moisture were present in the salt, the resulting ethoxymethyleneaniline undergoes more or less complete decomposition into alcohol and diphenylformamidine and is useless for the aldehyde synthesis. When operating with large quantities of material it is especially difficult to obtain the silver salt perfectly dry. In this work, the silver salt was dried in the air, then washed thoroughly with petroleum ether and finally dried over phosphorus pentoxide in a vacuum desiccator. Ethoxymethyleneaniline when properly prepared can be obtained in 74% over-all yield from formanilide and is a colorless liquid with a strong aromatic odor, boiling at 87–88° under 10 mm Monier-Williams states that his product was a light yellow oil, and he implies that it cannot be kept pure for more than a few days. The reagent used in this work was kept in a well stoppered bottle in the dark for eight days with no noticeable change; it could probably have been kept for a much longer period without deterioration, provided it was kept dry and in the dark. Comstock and Clapp (22) first prepared this substance; it was later prepared in 50% yield by Claisen (23) from ethyl orthoformate and aniline. The quality of the reagent is very important and the low yields of aldehydes obtained by previous investigators (2, 10) are doubtless due to use of an impure reagent. Monier-Williams (10) obtained *o*-tolualdehyde in 54% yield; Gattermann (2) obtained it in 55% yield. Gattermann did not distill his reagent and reports it as "golden yellow." In this work, using a colorless reagent, *o*-tolualdehyde was obtained in 81% yield.

C. The dithio acid synthesis. In this synthesis, three separate steps are involved:

(a) preparation and purification of the thio acid: $RMgX + CS_2 \rightarrow RCSSH$

(b) reaction of the thio acid in pyridine solution with semicarbazide

$$RCSSH + H_2NCONHNH_2 \cdot HCl \rightarrow RCH{=}NNHCONH_2 + H_2S + S$$

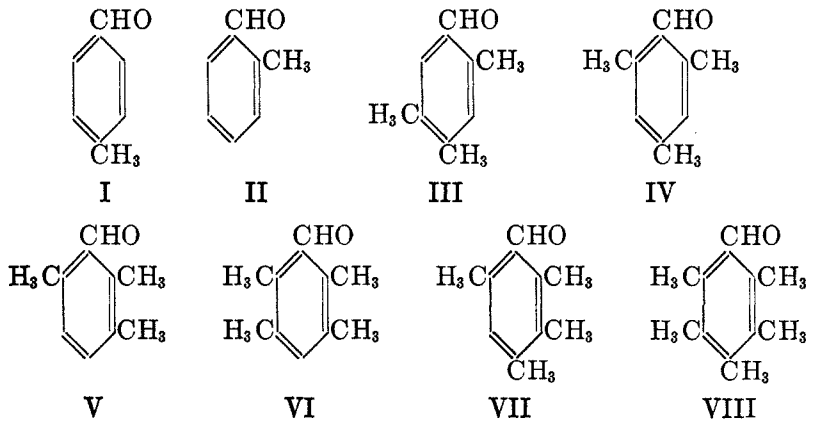
(c) hydrolysis of the semicarbazone to the aldehyde. The reaction of the Grignard reagent with carbon disulfide took place readily. The dithio acid was purified by extraction from the ether solution by 10% aqueous sodium hydroxide, followed by acidification of the alkaline solution. That purification of the thio acid was necessary was shown in the preparation of the aldehyde from 5-bromopseudocumene. When the crude thio acid was used, the yield of aldehyde was 31%; when the purified thio acid was used, the yield of aldehyde was 44%. The thio acids were all dark red oils; when the Grignard complex was decomposed some hydrogen sulfide was liberated, hence it is likely that the reaction between carbon disulfide and a Grignard reagent is accompanied by side reactions. The exact yields of thio acids were not determined in this investigation, nor did Wuyts, the originator of the method, report any yields (11, 12, 13, 14) except *p*-bromodithiobenzoic acid, where the yield was 46%. When the pyridine solution of the dithio acid was boiled with semicarbazide hydrochloride, hydrogen sulfide and sulfur were gradually eliminated and a precipitate of the semicarbazone formed. The pyridine solution was diluted with water and the mixture of sulfur and semicarbazone was removed and washed free of sulfur with a mixture of benzene and carbon disulfide.

The yields of aldehydes obtained in this investigation by use of the thio acid method are in some respects difficult to explain. *o*-Tolualdehyde resulted in 59% yield, but the best yield of *p*-tolualdehyde was but 23%. Yet the yield of Grignard reagents in the two cases was the same—94%. The aldehyde from 5-bromopseudocumene, having one free ortho position, was obtained in 44% yield, but the one from bromomesitylene, with no free ortho position, was obtained in only 2% yield. It appears that the position of the methyl groups in the benzene ring has a great effect in this synthesis, and that not only is the ortho position of importance, but likewise the para position. Bromodurene and bromopentamethylbenzene could not be converted into aldehydes by this method.

When compared with the orthoformate synthesis and that from ethoxymethylene aniline, the dithio acid synthesis of aldehydes is distinctly inferior and in most cases is not to be recommended.

The Grignard reagents. Except for *o*- and *p*-bromotoluenes, all of the halides were converted into Grignard reagents using either the "full entrainment" method of Grignard (24) or the "partial entrainment" method (25) using ethyl bromide as the auxiliary halide. The recommendations of Gilman (26) as to the optimum conditions for formation of the reagent from the halides were followed, except that for preparation of the very insoluble Grignard reagents such as those from bromopentamethylbenzene and bromodurene, magnesium powder was used in place of turnings.

Addition of sodium bisulfite. *p*-Tolualdehyde (I), *o*-tolualdehyde (II), and 2,4,5-trimethylbenzaldehyde (duraldehyde) (III) formed bisulfite addition-compounds readily and in a few minutes when shaken with a saturated aqueous solution of sodium bisulfite. That 2,4,6-trimethylbenzaldehyde (IV) formed a bisulfite addition-compound incompletely and with difficulty was noticed by Gatterman (27); in the present work, a 46% yield of bisulfite addition-compound was obtained from this aldehyde after its concentrated ether solution was shaken (intermittently) with saturated aqueous sodium bisulfite for three weeks. On the other hand, 2,3,6-trimethylbenzaldehyde (V), which resembles IV except that it has an open para position, required only one day to form a bisulfite addi-



tion-product and after three days the yield was 82%. 2,3,5,6-Tetramethylbenzaldehyde (VI), again having an open para position but no open ortho position, formed a bisulfite compound in 93% yield after three days standing. The addition-product did not form in short periods of vigorous shaking with the reagent as do the addition-products of the unhindered aldehydes (I, II, III), but given time, it is formed in excellent yield. 2,3,4,6-Tetramethylbenzaldehyde (VII) which has its para as well as ortho positions occupied, did not begin depositing a bisulfite addition-compound until the third day and after standing with the reagent for two weeks (intermittent shaking), gave the addition-compound in but 40% yield. Pentamethylbenzaldehyde (VIII) failed to form any addition-compound even after three weeks.

It thus appears that an unsubstituted position ortho to the aldehyde group allows for ease and rapidity of formation of a sodium bisulfite addition-product, and under these circumstances the presence of a para substituent has little, if any effect. This has long been recognized, but what has not been noticed is that when both ortho positions are occupied,

then the presence or absence of a group in the para position takes on considerable importance. In a *di-ortho* substituted aldehyde having a free para position, the addition-compound will not form rapidly, but given sufficient time, it will form in very good yield. If the aldehyde has both ortho positions and the para position occupied, the bisulfite compound will be formed with difficulty and in very poor yield. With the completely substituted aldehyde (VIII), no addition-product at all is obtained. The activation of the aldehyde group by the free para position, or the deactivation by a substituted para group, is also shown by the ease with which these aldehydes undergo autooxidation. 2,3,5,6-Tetramethylbenzaldehyde (VI) oxidizes in air much more rapidly than the 2,3,4,6-isomer (VII), while pentamethylbenzaldehyde (VIII) is fairly stable in the air, even after long exposure.

Pentamethylbenzaldehyde (VIII) obtained by the orthoformate synthesis and also *via* ethoxymethyleneaniline, melted at 143–148.5° and its oxime melted at 186–188°, in agreement with the values found by Smith, Webster, and Guss (25) and quite contrary to the value reported by Clément (28) who regarded the product (m.p., 130.5°) which he obtained by action of pentamethylphenylmagnesium bromide upon ethyl formate, as this aldehyde.

EXPERIMENTAL PART[2]

The halogen compounds. o-*Bromotoluene* (105 g., 61.4%) b.p., 178–180°, and p-*bromotoluene* (90 g., 37.5%) b.p., 176–178°, were prepared from the corresponding toluidines (107 g. and 150 g., respectively) by the procedure of Bigelow (29). *5-Bromopseudocumene* (136 g., 68%), m.p., 71–72° was prepared from pseudocumene (120 g.) by the procedure of Smith and Moyle (30). *Bromomesitylene* (148 g., 74%), b.p., 105–107° under 16–17 mm., was prepared from mesitylene (120 g.) by the procedure of Smith (31). *Bromodurene* (183 g., 77%), m.p., 59–60°, was prepared from durene (150 g.) by the procedure of Smith and Moyle (32). *Bromoisodurene* (40 g., 76%), b.p., 105–108° under 2 mm., m.p., 7–8° was prepared from isodurene (33 g.) according to the directions of Smith and Moyle (32). *Bromopentamethylbenzene* (192 g., 83%), m.p., 159–160°, was prepared by slow addition of bromine (165 g.) to a solution of pentamethylbenzene (150 g.) in acetic acid (850 cc.) at room temperature. The product, which precipitated from the cooled solution, was removed, washed with water, dried, and recrystallized from chloroform-ethanol. *3-Bromopseudocumene* was prepared by the Jacobsen rearrangement of the 5-bromo isomer (30, 33).

The Grignard reagents. The Grignard reagents were prepared under an atmosphere of nitrogen in a 500 cc. three-necked flask fitted with a stirrer, dropping-funnel, and condenser. All openings to the air were protected by calcium chloride guard tubes, and the nitrogen was passed through a wash bottle containing sulfuric acid before it entered the apparatus, which was carefully dried (baked) before use. The magnesium (powder) was washed well with 0.1 *N* hydrochloric acid, then successively

[2] Microanalyses by E. E. Renfrew and E. E. Hardy.

with water, acetone, and ether. It was dried in an oven and stored in a desiccator over calcium chloride. The yields of Grignard reagent were determined according to the procedure of Gilman and his collaborators (34). In calculating the yields of the reagent when the entrainment method was used, blank runs were made to determine the yield of ethylmagnesium bromide. This was found to be 95%; therefore, when ethyl bromide was used as the auxiliary halide, the yield of Grignard reagent from it was in each case assumed to be 95% and the proper amount was subtracted from the total Grignard reagent as found by titration. The yields are given in Table II. When yields are not given in Table II, it means that the Grignard reagent was insoluble and that a representative aliquot portion, free from magnesium powder, could not be obtained.

Bisulfite addition-compounds. 2,4,6-Trimethylbenzaldehyde (IV) (2.0 g.) in a small amount of ether was added to a concentrated aqueous solution of analytically pure sodium bisulfite and allowed to stand for three weeks with occasional shaking; yield 1.58 g. (46%) of the bisulfite compound. 2,3,6-Trimethylbenzaldehyde (V) (1.0 g.) similarly gave 1.40 g. (82%) of the addition-compound, but the time required was three days. 2,3,5,6-Tetramethylbenzaldehyde (VI) (2.0 g.) in three days gave 3.06 g. (93%) of addition-product. 2,3,4,6-Tetramethylbenzaldehyde (VII) (2.0 g.) gave 1.32 g. (40%) of addition-product in two weeks. Pentamethylbenzaldehyde (VIII) (2.0 g.) gave no addition-compound in three weeks. All of the aldehyde was recovered unchanged.

Procedures. One illustrative procedure will be given for each of the three methods, and any deviations or changes in connection with the other halides will be indicated by brief notes. *A. The orthoformate procedure.* The ethyl orthoformate was fractionated repeatedly and only the material boiling at 143-145° was used.

p-*Tolualdehyde* (I). The Grignard reagent was prepared in the usual way under nitrogen by adding a solution of *p*-bromotoluene (20.8 g., 0.122 moles) in ether (100 cc.) dropwise (45 min.) and with stirring to magnesium powder (3.3 g., 0.136 moles) suspended in ether (20 cc.). The reaction was started by addition of 0.5 cc. of ethyl bromide and a crystal of iodine, and after all the halide was added, the solution was refluxed for two hours. Ethyl orthoformate (22 g., 0.142 moles) in ether (30 cc.) was then rapidly (5 minutes) added and the reaction-mixture was refluxed for 5 hours. The ether was then distilled off on the steam-bath, and when practically all of it was removed, there was a sudden vigorous reaction. At this point the flask was quickly immersed in an ice-bath and allowed to remain there until all evidence of a reaction had disappeared. After standing overnight, ice (50 g.) and cold 5 *N* hydrochloric acid (125 cc.) were added, the small residual amount of ether was evaporated and the reaction-mixture was refluxed for thirty minutes on the steam-bath under an atmosphere of carbon dioxide. The aldehyde was then steam distilled in an atmosphere of carbon dioxide and the distillate was extracted three times with ether (60 cc. each time). The combined ether extracts were evaporated on the steam-bath to remove solvent and propionic aldehyde (b.p., 50°) and the residue of impure *p*-tolualdehyde was taken up in ether (20 cc.). The ethereal solution was then vigorously shaken with a freshly prepared, saturated aqueous solution of sodium bisulfite, the solid was filtered off, and the filtrate was shaken again with fresh bisulfite solution and filtered. The combined solids were washed with ether and dried. The substance weighed 20.3 g. (74.4%).

o-*Tolualdehyde* (II). *o*-Bromotoluene (18.8 g., 0.110 moles) was converted to the Grignard reagent as above, and the latter was then mixed with ethyl orthoformate (18.0 g., 0.123 moles) and processed as above. The bisulfite compound weighed 18.0 g. (73.2%).

2,4,5-Trimethylbenzaldehyde (III). 5-Bromopseudocumene (20 g., 0.10 moles) and ethyl bromide (4.35 g., 0.04 moles) were converted into Grignard reagents by the reaction with magnesium (4.0 g., 0.165 moles) as above, and then orthoformic ester (23 g., 0.155 moles) was added and the procedure was continued as above. The bisulfite compound weighed 18.1 g. (71.5%).

2,4,6-Trimethylbenzaldehyde (IV). Bromomesitylene (20.0 g., 0.10 moles), ethyl bromide (4.35 g., 0.04 moles), magnesium (4.4 g., 0.181 moles), ethyl orthoformate (25.0 g., 0.162 moles). After removing the ether and propionic aldehyde from the crude aldehyde, a solution of semicarbazide hydrochloride (15 g., 0.134 moles) and sodium acetate (20 g.) in the minimum amount of water was added and then enough ethanol was added to the mixture to bring the aldehyde into solution. After heating on the steam-bath for 20 minutes, the mixture was cooled and the semicarbazone (11.8 g., 57.3%) was removed and crystallized from ethanol. It then melted at 185–188°.

Anal. Calc'd for $C_{11}H_{15}N_3O$: C, 64.35; H, 7.37.
Found: C, 64.19; H, 7.17.

2,3,6-Trimethylbenzaldehyde (V). 3-Bromopseudocumene (29 g., 0.146 moles) in ether (50 cc.), magnesium powder (7.7 g., 0.317 moles), and a crystal of iodine were mixed and to the mixture was added dropwise a solution of ethyl bromide (15.9 g., 0.146 moles) in ether (100 cc.). The green Grignard solution was refluxed for three hours and then ethyl orthoformate (44.4 g., 0.30 moles) in ether (30 cc.) was added. The mixture was processed as described above and the aldehyde was isolated as the semicarbazone, which weighed 18.3 g. (61.2%). The semicarbazone was heated for thirty minutes on the steam-bath with 5 *N* hydrochloric acid. Ether extraction removed the aldehyde, which was carefully fractionated under nitrogen. It was a colorless liquid which boiled at 113–114° under 10 mm., 115–116° under 12 mm., and which did not solidify at −15°.

Anal. Calc'd for $C_{10}H_{12}O$: C, 81.03; H, 8.17.
Found: C, 81.19; H, 8.51.

The *oxime*, prepared from 1.5 g. of the aldehyde by the procedure of Shriner and Fuson (35) apparently existed in two forms (syn and anti ?). The crude product was sublimed under reduced pressure and the sublimate was crystallized from dil. ethanol. It melted at 124–126°.

Anal. Calc'd for $C_{10}H_{13}NO$: C, 73.57; H, 8.03.
Found: C, 73.77; H, 8.05.

The *semicarbazone*, prepared from a small sample of the aldehyde and crystallized several times from ethanol, melted at 167–169°.

Anal. Calc'd for $C_{11}H_{15}N_3O$: C, 64.35; H, 7.37.
Found: C, 64.36; H, 7.21.

2,3,4,6-Tetramethylbenzaldehyde (VII). Bromoisodurene (38.8 g., 0.182 moles) in ether (50 cc.), magnesium powder (9.8 g., 0.403 moles), and a crystal of iodine were converted into the Grignard reagent by adding ethyl bromide (19.8 g., 0.182 moles) in ether (130 cc.). Ethyl orthoformate (54.0 g., 0.365 moles) was added and the mixture processed as above. The aldehyde was isolated as the semicarbazone, which weighed 23.9 g. (60.2%). The aldehyde was regenerated from the semicarbazone as described above, and obtained as a colorless liquid which boiled at 136° under 10 mm., and froze at +15°.

Anal. Calc'd for $C_{11}H_{14}O$: C, 81.43; H, 8.71.
Found: C, 81.54; H, 8.87.

The *oxime* was prepared as above, sublimed in vacuum, and crystallized several

times from aqueous ethanol. Apparently two forms were present in the crude oxime; the one obtained by the procedure outlined melted at 136–137°. The lower-melting form was not obtained pure; it melted, however, about 100°.

Anal. Calc'd for $C_{11}H_{15}NO$: C, 74.52; H, 8.54.

Found (form melting at 136–137°): C, 74.67; H, 8.14.

The *semicarbazone,* prepared from a small specimen of the pure aldehyde and crystallized several times from ethanol, melted at 183–185° to a liquid which quickly solidified and then remelted at 218–221° with evolution of gas.[3]

Anal. Calc'd for $C_{12}H_{17}N_3O$: C, 65.71; H, 7.86.

Found: C, 65.53; H, 7.77.

2,3,5,6-Tetramethylbenzaldehyde (VI). Bromodurene (16.0 g., 0.075 moles), ether (20 cc.), magnesium powder (4.0 g., 0.165 moles), a crystal of iodine, and ethyl bromide (8.12 g., 0.0745 moles) in ether (80 cc.) were processed as above and after addition of ethyl orthoformate (24.0 g., 0.162 moles) in ether (30 cc.), the procedure outlined above was followed. The aldehyde was isolated as the bisulfite compound, which weighed 12.27 g. (61.4%). The addition-product was decomposed with dilute hydrochloric acid, and the aldehyde was removed by ether extraction and distilled under nitrogen. It boiled at 135° under 11 mm. and froze at 20°. It was extremely difficult to obtain the pure aldehyde, as it autooxidized with great rapidity.

Anal. Calc'd for $C_{11}H_{14}O$: C, 81.43; H, 8.71.

Found: C, 80.38; H, 8.74.

Found (after redistillation and immediate analysis): C, 80.17; H, 8.73.

The *oxime,* prepared as outlined above and crystallized repeatedly from aqueous ethanol, melted at 124.5–125.5°.

Anal. Calc'd for $C_{11}H_{15}NO$: C, 74.52; H, 8.54.

Found: C, 74.25; H, 8.65.

The *semicarbazone,* prepared from a specimen of redistilled aldehyde and crystallized repeatedly from ethanol, changed to a wax-like substance at 205–210°, and then melted at 268–270° with decomposition.

Anal. Calc'd for $C_{12}H_{17}N_3O$: C, 65.71; H, 7.86.

Found: C, 66.11; H, 7.62.

Pentamethylbenzaldehyde (VIII). Bromopentamethylbenzene (15.0 g., 0.066 moles), ether (20 cc.), magnesium powder (3.7 g., 0.152 moles), and a crystal of iodine were converted into the Grignard reagent with ethyl bromide (7.25 g., 0.066 moles) in ether (100 cc.). Ethyl orthoformate (22 g., 0.141 moles) in ether (30 cc.) was added and the usual procedure was followed. The reaction-mixture, after decomposition with hydrochloric acid, was steam distilled and as soon as the aldehyde began to come over the process was stopped and the aldehyde was filtered from the cooled residue in the distilling flask. After sublimation in vacuum (130–140° under 2 mm.) and crystallization twice from ethanol, the substance weighed 5.0 g. (43.1%) and melted at 143–148.5°. The oxime melted at 187–188°.[4]

B. The ethoxymethyleneaniline procedure. Preparation of the reagent. A solution of sodium hydroxide (37.7 g., 0.942 moles) in water (50 cc.) was added dropwise and with vigorous stirring to a solution of formanilide (114 g., 0.942 moles) and silver

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[3] See Rapson and Shuttleworth (36) who observed a similar phenomenon in the case of the semicarbazone of methyl-*n*-amyl ketone.

[4] These values are in agreement with those previously reported by Smith, Webster, and Guss (25), but the m.p. of the aldehyde does not agree with the value reported by Clement (28).

nitrate (160 g., 0.942 moles) in aqueous ethanol (50%, 800 cc.). It is essential to use pure alkali and to avoid an excess. The precipitate of silver salt was removed and sucked as dry as possible on the filter. The substance, somewhat sensitive to heat and light, holds water tenaciously but it must be thoroughly dried before it is used. The salt was spread out, protected from the light as much as possible, and allowed to dry in the air for three days. It was then stirred with petroleum ether (600 cc.), filtered, washed with dry ethyl ether, and allowed to dry in the air for a day. The washing process with petroleum ether and ethyl ether was then repeated, and the salt was finally dried in a vacuum desiccator over phosphorus pentoxide. The salt (200 g., 0.877 moles) was mixed with dry ether (600 cc.) and ethyl iodide (136.8 g., 0.877 moles) in a flask fitted with a calcium chloride guard tube, and allowed to stand at room temperature for forty-eight hours with occasional shaking. The precipitate of silver iodide was removed and washed with dry ether. The combined filtrate and washings were fractionated, giving 105 g. (74.2%) of ethoxymethyleneaniline, a *colorless* liquid which boiled at 87–88° under 10 mm.

The general procedure for the preparation of aldehydes was as follows: after preparation of the Grignard reagents (as described above), ethoxymethyleneaniline in ether was added dropwise to the solution at room temperature. The brownish-red reaction-mixture was refluxed for thirty minutes and was then decomposed with ice and hydrochloric acid, refluxed thirty minutes to hydrolyze the anil, after which the aldehyde was isolated as described previously.

p-*Tolualdehyde* (I). *p*-Bromotoluene (15.0 g., 0.0877 moles), ether (100 cc.), magnesium powder (2.6 g., 0.107 moles), ethyl bromide (0.5 cc.), and a crystal of iodine were used to form the Grignard reagent. Ethoxymethyleneaniline (13.4 g., 0.0899 moles) in ether (30 cc.) was added and the reaction-mixture was processed as described. The aldehyde bisulfite compound weighed 16.2 g. (82.2%).

o-*Tolualdehyde* (II). Reagents: *o*-bromotoluene (15.0 g., 0.0877 moles), otherwise same as for I above. The aldehyde bisulfite compound weighed 15.88 g. (80.8%).

2,4,5-Trimethylbenzaldehyde (III). Reagents: 5-bromopseudocumene (10 g., 0.0502 moles), magnesium powder (2.5 g., 0.103 moles), ethyl bromide (3.8 g., 0.033 moles), ether (120 cc.). Ethoxymethyleneaniline (13.42 g., 0.090 moles) in ether (20 cc.). The product (bisulfite compound) weighed 10.2 g. (80.5%).

2,4,6-Trimethylbenzaldehyde (IV). Reagents: bromomesitylene (15.0 g., 0.0754 moles), magnesium powder (3.7 g., 0.152 moles), ethyl bromide (5.5 g., 0.0505 moles), ether (120 cc.). Ethoxymethyleneaniline (19.8 g., 0.133 moles) in ether (30 cc.). The product (semicarbazone) weighed 9.8 g. (63.8%).

2,3,6-Trimethylbenzaldehyde (V). Reagents: 3-bromopseudocumene (23.0 g., 0.116 moles), magnesium powder (6.3 g., 0.259 moles), ethyl bromide (12.6 g., 0.116 moles), ether (150 cc.). Ethoxymethyleneaniline (34.6 g., 0.232 moles) in ether (30 cc.). The product (semicarbazone) weighed 15.5 g. (65.4%).

2,3,5,6-Tetramethylbenzaldehyde (VI). Reagents: bromodurene (8.3 g., 0.039 moles), magnesium powder (2.3 g., 0.0946 moles), ethyl bromide (4.3 g., 0.039 moles), ether (100 cc.). Ethoxymethyleneaniline (11.7 g., 0.0785 moles) in ether (20 cc.). The product (bisulfite compound) weighed 7.3 g. (70.4%).

2,3,4,6-Tetramethylbenzaldehyde (VII). Reagents: bromoisodurene (15.0 g., 0.0704 moles), magnesium powder (3.9 g., 0.160 moles), ethyl bromide (7.63 g., 0.070 moles), ether (120 cc.). Ethoxymethyleneaniline (21.0 g., 0.141 moles) in ether (20 cc.). The product (semicarbazone) weighed 9.9 g. (64.3%).

Pentamethylbenzaldehyde (VIII). Reagents: bromopentamethylbenzene (10 g., 0.044 moles), magnesium powder (2.5 g., 0.103 moles), ethyl bromide (4.8 g., 0.044

moles), ether (100 cc.). Ethoxymethyleneaniline (13.2 g., 0.0885 moles) in ether (20 cc.). The product (aldehyde, m.p., 140–146°) weighed 4.66 g. (60.1%).

C. The dithio acid synthesis. The Grignard reagents were prepared as already described. Carbon disulfide (freshly distilled from phosphorus pentoxide) in ether, was added with stirring, to the Grignard reagent at room temperature. After stirring for an hour, the mixture was allowed to stand for three hours and was then decomposed with ice and 5 *N* hydrochloric acid. The ethereal layer was removed, and the aqueous layer was extracted thoroughly with ether. The combined ethereal solutions were then extracted three times with aqueous sodium hydroxide (10%, 75 cc. each time). The dithio acid was immediately liberated with iced dilute hydrochloric acid and taken up in ether. The ethereal solution was washed twice with water and most, but not all, of the ether was distilled off on the steam-bath. The residual ether was removed at room temperature under reduced pressure. All these operations, beginning with the decomposition of the Grignard product, were carried out as quickly as possible in order to minimize the time of contact of the thio acid with the air. The dithio acid was added to semicarbazide hydrochloride dissolved in pyridine and the solution was gradually heated to the boiling point. The original dark red solution became lighter in color, hydrogen sulfide was evolved and a mixture of sulfur and the semicarbazone separated. After refluxing for thirty minutes, the mixture was poured into cold water (600 cc.) and allowed to stand overnight. The solids were removed, dried, and then well stirred with a mixture of carbon disulfide (15 cc.) and benzene (15 cc.). The semicarbazone was then hydrolyzed as described above, and the aldehyde was removed by steam distillation and weighed as such, converted into the bisulfite compound, or reconverted into the semicarbazone. In all the experiments the crude semicarbazone initially formed was accompanied by small amounts of a material which could not be hydrolyzed by the hydrochloric acid. After crystallization from water, this substance melted at 250–252° with decomposition. While not fully identified, it is likely that the substance was hydrazodicarbonamide, frequently obtained in reactions in which semicarbazide is heated, and which Thiele and Stange (37) reported to melt at 244–245° with decomposition.

p-*Tolualdehyde* (I). Reagents: *p*-bromotoluene (20.0 g., 0.117 moles), magnesium powder (3.5 g., 0.144 moles), ethyl bromide (0.5 cc.), ether (120 cc.). Carbon disulfide (9.5 g., 0.125 moles) in ether (30 cc.). Semicarbazide hydrochloride (16.1 g.) in pyridine (80 cc.) and water (15 cc.). The product (bisulfite compound) weighed 6.12 g. (23.3%).

o-*Tolualdehyde* (II). Reagents: *o*-bromotoluene (15.4 g., 0.090 moles), magnesium powder (2.9 g., 0.119 moles), ethyl bromide (0.5 cc.), ether (120 cc.). Carbon disulfide (7.4 g., 0.0972 moles) in ether (30 cc.). Semicarbazide hydrochloride (16.1 g., 0.144 moles) in pyridine (80 cc.) and water (15 cc.). The product (bisulfite compound) weighed 12.03 g. (59.6%).

2,4,5-Trimethylbenzaldehyde (III). Reagents: 5-bromopseudocumene (20 g., 0.100 moles), magnesium powder (4.0 g., 0.165 moles), ethyl bromide (4.75 g., 0.0436 moles), ether (120 cc.). Carbon disulfide (11.0 g., 0.145 moles) in ether (30 cc.). Semicarbazide hydrochloride and pyridine as above. The product (bisulfite compound) weighed 11.13 g. (43.9%).

2,4,6-Trimethylbenzaldehyde (IV). Reagents: bromomesitylene (20.0 g., 0.100 moles), other reagents as for III above. The product (semicarbazone) weighed 0.45 g. (2.2%).

2,3,5,6-Tetramethylbenzaldehyde (VI). Reagents: bromodurene (15 g., 0.0704 moles), magnesium powder (3.9 g., 0.160 moles), ethyl bromide (7.7 g., 0.706 moles),

ether (120 cc.). Carbon disulfide in ether, and other reagents as above. No product (bisulfite compound) was obtained.

Pentamethylbenzaldehyde (VIII). Reagents: bromopentamethylbenzene (15.0 g., 0.066 moles), magnesium powder (3.7 g., 0.152 moles), ethyl bromide (7.25 g., 0.066 moles), ether (120 cc.). Other reagents as above. No product (aldehyde) was obtained.

SUMMARY

1. A series of methylated aromatic aldehydes has been prepared by each of three methods from the halides *via* the Grignard reagents.

2. Synthesis using ethoxymethyleneaniline gave the best yields (65–82%), and these yields were greater by 4–17% than those obtained using ethyl orthoformate (43–74%). Synthesis by way of dithio acids gave the poorest yields and in some cases gave no aldehyde at all.

3. The syntheses using ethoxymethyleneaniline and ethyl orthoformate are to be highly recommended as preparative methods for aromatic aldehydes from the corresponding halides. The former method is the easier to carry out, and is more adaptable to large scale preparations than the latter, but the reagent is expensive and must be carefully prepared and purified. The latter method has the advantage of cheap reagents, but the second stage of the reaction is so exothermic that it is difficult to control when quantities larger than 0.2 molar are used.

4. An important relationship has been found between para position in aromatic aldehydes and the ease and completeness with which bisulfite compounds are formed, as well as the ease with which the aldehydes undergo autooxidation.

5. Three new aldehydes, 2,3,6-trimethyl-, 2,3,4,6-tetramethyl-, and 2,3,5,6-tetramethyl- benzaldehydes, have been prepared and characterized by means of their semicarbazones and oximes.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DUKE UNIVERSITY]

THE ACTION OF POTASSIUM AMIDE ON CERTAIN *syn* AND *anti* ALDOXIMES, THEIR O-METHYL ETHERS AND THEIR ACETYL DERIVATIVES[1]

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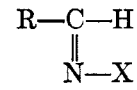
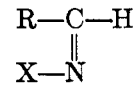
The purpose of this investigation has been to study the action of potassium amide on certain *syn*, and *anti* aldoximes, their O-methyl ethers, and their acetyl derivatives; these compounds may be represented by formulas (I) and (II), in which X is, respectively, OH, OCH_3, and CH_3COO.



(I) syn (α)



(II) anti (β)

The Elimination of Water from Aldoximes. Previously (1) it was shown that certain *anti* aldoximes in 2 *N* sodium hydroxide solution at 97–100° are slowly converted into mixtures of the corresponding carboxylic acids and the isomeric *syn* aldoximes; the latter are more slowly converted to carboxylic acids. The carboxylic acids were assumed to result from the hydrolyses of intermediate nitriles, which were formed by dehydrations of the *anti* aldoximes.

In the present paper it is shown that in the presence of potassium amide in liquid ammonia at room temperature (in a sealed tube), *anti*-4-methoxybenzaldoxime is decomposed completely within nine days. The products isolated were the corresponding amidine (isolated as the picrate, 48%) and amide (15%). Under similar conditions the corresponding *syn* aldoxime appeared to be partly decomposed but the products were not isolated. The formation of amidine from the *anti* aldoxime is probably best accounted for on the basis that the aldoxime eliminates the elements of water to form the corresponding nitrile which is then converted by the potassium amide into the amidine. It has been shown that in the presence

[1] This paper has been constructed from portions of a thesis presented by Gertrude Vermillion in partial fulfilment of the requirements for the Ph.D. degree at Duke University.

of potassium amide in liquid ammonia even at −33°, the nitrile is readily converted to the amidine. The amide was probably formed by hydrolysis of the amidine and possibly also directly from the nitrile by reaction with potassium hydroxide; the latter would result from the reaction of potassium amide with the water that is eliminated from the *anti* aldoxime. The elimination of water from the *anti* aldoxime and the subsequent conversion of the resulting nitrile into the amidine may be represented as follows:

$$\begin{matrix} R{-}C{-}H \\ \| \\ HO{-}N \end{matrix} \xrightarrow{KNH_2} R{-}C{\equiv}N \xrightarrow{KNH_2} R{-}C(=NK)NH_2$$

The fact that the yields of amidine and amide in this reaction, as well as the yields of carboxylic acid and *syn* aldoxime in the reaction reported

TABLE I

PERCENTAGE YIELDS OF PRODUCTS FROM THE O-METHYL ETHERS OF *syn*-, AND *anti*-4-METHOXYBENZALDOXIMES WITH POTASSIUM AMIDE IN LIQUID AMMONIA

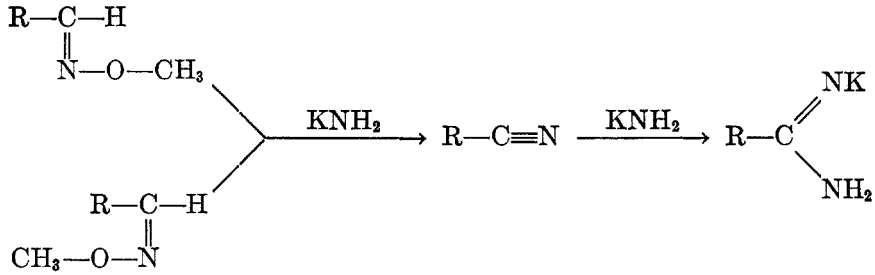
ISOMER	EQUIVALENT OF KNH_2	HOURS	NITRILE			AMIDINE		
			Yield %	M.p. °C. Found[a]	Literature m.p. °C.	Yield %	M.p., °C. Found[a]	Literature m.p. °C.
(A) *anti*	1.28	2	52	58–59	60–61	29	205–206	206–207
(B) *syn*	1.28[b]	2	12	58–59	60–61	24	206–207	206–207
(C) *syn*	3.0	4	0	—	—	88	206–207	206–207

[a] These melting points were raised by recrystallization to those reported in literature.

[b] In this experiment, a portion (10–15%) of the O-methyl ether was recovered.

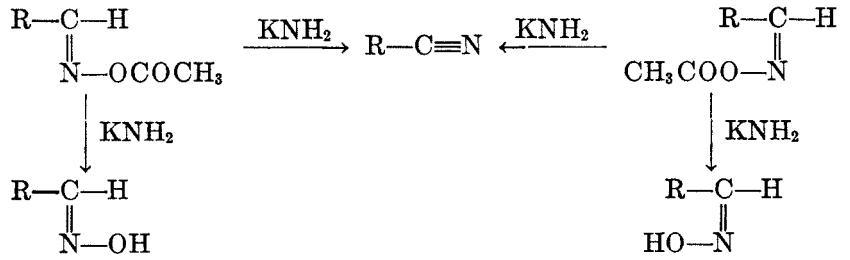
previously (1), were greater than 50%, together with the fact that no other products were found, shows that the results obtained are not to be explained on the basis of a Cannizzaro type of reaction.

The Elimination of Methyl Alcohol from the O-Methyl Ethers of Aldoximes. The O-ethers of *syn* aldoximes have been reported (2) to be stable towards hot sodium hydroxide. We have found that in the presence of potassium amide in liquid ammonia, the O-methyl ethers of both *syn*-, and *anti*-4-methoxybenzaldoximes eliminate the elements of methyl alcohol to form 4-methoxybenzonitrile, which under the conditions used is partly or entirely converted by the potassium amide to the corresponding amidine. The yields and melting points of nitrile and amidine obtained with various proportions of potassium amide are given in Table I. The reactions may be represented as follows:



It can be seen from lines (A) and (B) of Table I that in the presence of 1.28 equivalents of potassium amide within two hours, the *anti* ether is decomposed completely whereas the *syn* ether is not completely decomposed, a portion of it being recovered unchanged. This shows that the elements of methyl alcohol are eliminated from the *anti* ether more readily than from the *syn* ether, as one should expect. Apparently, the reaction of potassium amide with the resulting nitrile competes favorably with the elimination reaction only in the case of the *syn* ether. It seems likely that the elimination reaction with the *anti* ether was practically complete within a few minutes. From line (C) of Table I it can be seen that with 3 equivalents of potassium amide, the *syn* ether is decomposed completely within four hours giving a high yield of the amidine. It seems probable that both the *syn*, and *anti* O-methyl ethers eliminate the elements of methyl alcohol quantitatively in the presence of potassium amide in liquid ammonia.

The Action of Potassium Amide on Aldoxime Acetates (Acetyl Derivatives of Aldoximes). It has been shown previously (3) that *syn*-benzaldoxime acetates react with potassium amide in liquid ammonia to form both nitriles and *syn* aldoximes. In the present paper it is shown that *anti*-benzaldoxime acetates also react with potassium amide to form both nitriles and aldoximes, the *anti* aldoximes being obtained in this case. The reactions may be represented as follows:



Both the *syn*-, and the *anti*-benzaldoxime acetates have been allowed to react with 1.2 equivalents of potassium amide in liquid ammonia for ten minutes. The excess potassium amide was then destroyed by means of

ammonium chloride, and the nitriles and oximes isolated. The yields and melting points of these products are given in Table II.

It can be seen from Table II that both of the *syn* acetates studied give considerable nitrile in addition to the corresponding *syn* aldoxime; in fact, with the acetate of *syn*-3,4,-methylenedioxybenzaldoxime, the yield of nitrile is even slightly higher than that of the aldoxime. As anticipated, the yields of nitrile from the *anti* acetates are higher and the yields of the aldoximes lower than those obtained from the isomeric *syn* acetates.

It is rather remarkable that even the *syn* acetate is decomposed completely by potassium amide within ten minutes at −33°. The formation of nitrile from the *syn* acetate very probably involves the direct elimination of the elements of acetic acid without a preliminary isomerization to the *anti* acetate as has sometimes been assumed (4) in similar reactions.

TABLE II

PERCENTAGE YIELDS OF PRODUCTS FROM THE ACETYL DERIVATIVES OF SUBSTITUTED *syn*-, AND *anti*-BENZALDOXIMES WITH POTASSIUM AMIDE IN LIQUID AMMONIA

SUBSTITUENT	ISOMER	NITRILE			ALDOXIME		
		Yield %	M.p., °C. Found[a]	Literature m.p. °C.	Yield %	M.p., °C. Found[a]	Literature m.p. °C.
4-Methoxy-	*syn*	25	58–60	60–61	61	63–64	64
4-Methoxy-	*anti*	87	58–60	60–61	4	123–125	133
3,4-Methylenedioxy-	*syn*	48	90–92	94–95	44	110	110
3,4-Methylenedioxy-	*anti*	71	93–94	94–95	4	140–142	146

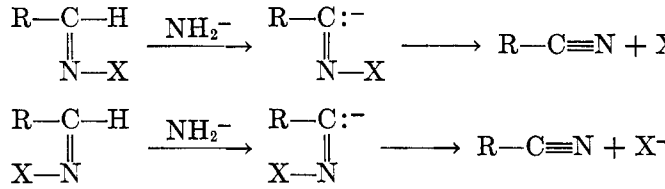
[a] The melting points of products were raised by recrystallization to those reported in the literature.

The fact that the *syn* acetate also gives *syn* aldoxime rather than the *anti* aldoxime (as is obtained with the *anti* acetate) shows that the *syn* acetate is not isomerized to the *anti* isomer by potassium amide in liquid ammonia.

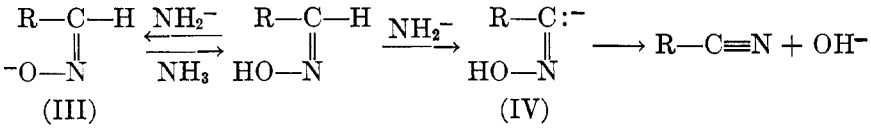
These results illustrate clearly the view held for some time in this laboratory that in the presence of bases both *syn* and *anti* aldoxime esters are capable of eliminating the elements of acids to form nitrile and of undergoing a hydrolytic type of reaction giving aldoximes. In comparison with sodium hydroxide, which reacts with most *syn* acetates to form practically only the *syn* aldoxime, potassium amide favors the elimination reaction more and the hydrolytic type of reaction less, giving considerable nitrile even with the *syn* acetates.

Mechanism of Removal of HX from Compounds of types (I) and (II) by means of Potassium Amide. The removal of the elements of HX from *syn* and *anti* aldoximes, their O-methyl ethers, and their acetyl derivatives by

means of potassium amide is considered to involve an attack by the base on the aldehydic hydrogen atom which is removed as a proton; this is accompanied or followed by the release of X as an anion to form nitrile, thus[2]



When X is hydroxyl the base undoubtedly reacts with the hydroxyl hydrogen to form the aldoxime salt, but this is in equilibrium with unchanged aldoxime. The mechanism of removal of the elements of water from *anti* aldoximes by means of potassium amide may be represented as follows:



(III) (IV)

Anion (IV) might be formed also by the secondary ionization of anion (III) if the resulting doubly charged anion acquires a proton on the oxygen; also, it might be possible, although unlikely, for the doubly charged anion to release oxygen ion ($\overline{\overline{O}}$) to form the nitrile directly.

Such dehydrations by means of bases are of particular interest because they involve the removal of the proton attached to carbon even though this proton is less active than the one attached to oxygen. According to the mechanism assumed, this is possible because the removal of the hydroxyl hydrogen is a reversible process, whereas the removal of the hydrogen attached to carbon, although possibly being reversible also, is, however, accompanied or followed by the irreversible release of hydroxyl ion. Other dehydrations effected by bases are known; for example, the dehydration of the aldol, ethyl β-phenyl-β-hydroxypropionate, is effected by means of triphenylmethylsodium in ether solution at room temperature (5).

EXPERIMENTAL

Reaction of anti-*4-methoxybenzaldoxime with potassium amide.* Preliminary experiments showed that *anti*-4-methoxybenzaldoxime (m.p. 132-133°) is quite stable

[2] Essentially this mechanism has been proposed by Mills [*J. Soc. Chem. Ind.*, **51**, 755 (1932)] for the elimination of acetic acid from *anti* aldoxime acetates, but apparently he considered that *syn* aldoxime acetates could not follow a similar course. See also Hauser and Jordan (3).

in the presence of potassium amide in liquid ammonia at −33°. After fifteen hours in the presence of 1.2 equivalents of potassium amide, 95% of the unchanged *anti*-aldoxime (m.p. 132–133°) was recovered, and after eight days in the presence of 7 equivalents of potassium amide, 87% of the unchanged *anti* aldoxime (m.p. 130–131°) was recovered.

To 1 g. of *anti*-4-methoxybenzaldoxime in a Carius tube was added 5.5 equivalents of potassium amide dissolved in liquid ammonia. The tube was sealed and allowed to stand at room temperatures for nine days. It was then placed in a mixture of solid carbon dioxide and acetone and opened. The reaction mixture was poured into a flask, the solid remaining in the tube being removed by means of 50 cc. of liquid ammonia to which had been added 10 cc. of water. The water served to convert the excess potassium amide to potassium hydroxide. The tube was finally washed with 15 cc. of cold water, the washing being added to the reaction mixture in the flask. The ammonia was evaporated from the solution *in vacuo*, and the aqueous alkaline solution extracted three times with 20-cc. portions of ether. The aqueous solution was made up to 100 cc. in a volumetric flask and a 10 cc. aliquot, after acidifying with acetic acid, treated with 10 cc. of a saturated aqueous solution of picric acid. The yellow precipitate of anisamidine picrate obtained weighed 0.12 g. and melted at 205–206°. After recrystallization from 50% aqueous alcohol solution the substance melted at 206–207°, as did also an authentic sample of anisamidine picrate prepared from 4-methoxybenzonitrile and potassium amide in liquid ammonia according to a modification of the procedure (6) used with other nitriles; a mixed melting point was also the same.

Anal.[3] Calc'd for $C_{14}H_{13}N_5O_8$: N, 18.47. Found: 18.60.

The total yield of the amidine picrate was 1.2 g. or 48%. The combined ether solutions obtained from the extraction of the aqueous alkaline solution, gave on evaporation 0.24 g. of material melting at 105–110°. This was shown to consist of anisamide (m.p. 161–162°) mixed with a little anisamidine (m.p. 112°) (7). From this material was isolated 0.15 g. or 15% yield of anisamide melting at 158–160°. A mixed melting point with an authentic sample of anisamide (m.p. 161–162°) was 158–160°. It should be mentioned also that on standing the aqueous solution of the amidine described above gradually deposited crystals of anisamide.

Reaction of syn-*4-methoxybenzaldoxime with potassium amide. syn*-4-Methoxybenzaldoxime (1 g.) was allowed to stand with 5.6 equivalents of potassium amide in liquid ammonia in a sealed tube at room temperature. After three weeks the tube was opened, the mixture treated with ammonium chloride and then worked up essentially as described above. Twenty per cent of the original *syn* aldoxime was recovered. Some anisamidine appeared to be formed but the substance was not isolated.

Preparation of the O-methyl ethers of syn-, *and* anti-*4-methoxybenzaldoximes.* The O-methyl ethers of *syn*-, and *anti*-4-methoxybenzaldoximes have been prepared previously (8) by treating the oximes in methanol with methyl iodide and silver oxide, but the yield was not reported. In the present investigation these ethers have been prepared by applying a modification of the general Purdie methylation procedure (9). *syn*-4-Methoxybenzaldoxime (9.5 g.) was placed in a three-necked bolt-headed flask fitted with a mechanical stirrer, mercury seal, and a reflux condenser. The third neck of the flask, fitted with a solid cork stopper, was used for introducing the reagents. To the *syn* oxime in the flask was added 32 g. (approximately 15 cc.) of methyl iodide and the mixture refluxed until the oxime was dissolved completely.

[3] Microanalysis by Saul Gottlieb, Columbia University, New York, N. Y.

The flask was then cooled in an ice-bath. One-tenth (approximately 0.14 g.) of the five equivalents of silver oxide that were to be used for the methylation was added, and the mixture stirred vigorously. After a few minutes the ice-bath was replaced by a water-bath, whose temperature was raised to 46° and maintained at 35–46° during the remainder of the reaction. The remaining nine-tenths of the silver oxide was added in one-tenth portions every half-hour. After the addition of the last portion of silver oxide the mixture was stirred for one-half hour. Chloroform was added and the stirring continued for another half-hour. The mixture was cooled, filtered, and the solid washed thoroughly with chloroform. Since the O-methyl ether is strongly adsorbed by silver salts, the solid was refluxed with three separate portions of chloroform for 20 minutes each, filtering after each extraction. The combined chloroform extracts were dried with "Drierite" and the solvent removed *in vacuo* at 30–45°. The oily residue of the *syn* O-methyl ether was cooled to a solid and recrystallized from petroleum ether (b.p. 30–60°). It melted at 39–40°; yield, 4 g. or 40%. Recrystallization gave plates melting at 42–43°. This melting point agrees with that previously reported (8).

The *anti* O-methyl ether of 4-methoxybenzaldoxime was prepared in a similar manner from 4 g. of *anti*-4-methoxybenzaldoxime in 70 cc. of dry ether, 15 cc. of methyl iodide, and 7.5 g. of silver oxide. The temperature of the bath was kept below 45° and the stirring continued for thirty-four hours after all of the silver oxide had been added, additional methyl iodide (two 10-cc. portions) being added during this time. After recrystallization from petroleum ether (b.p. 30–60°) one gram of the *anti* O-methyl ether was obtained melting at 36°. This melting point agrees with that reported previously (8).

Reaction of the O-methyl ethers of syn-, *and* anti-*4-methoxybenzaldoximes with potassium amide in liquid ammonia.* To 1.28 equivalents of potassium amide (prepared from 0.14 g. of potassium) in 200 cc. of liquid ammonia contained in a Dewar flask fitted with a mechanical stirrer was added one equivalent (0.46 g.) of the O-methyl ether of *anti*-4-methoxybenzaldoxime dissolved in 15 cc. of anhydrous ether. A pale yellow color developed in the mixture, followed almost immediately by a pale pink color which persisted to the end of the reaction. After two hours the stirring was stopped and 0.24 g. of solid ammonium chloride added to the mixture, which was then poured into a beaker. The residue remaining in the beaker after the ammonia and ether had evaporated, together with that in the Dewar flask, was treated with 50 cc. of ice cold water and the mixture extracted with three 40-cc. portions of ether. The combined ether solutions after extracting with cold 2 *N* sodium hydroxide, drying, and evaporating, gave 4-methoxybenzonitrile; none of the O-methyl ether was recovered. No aldoxime could be isolated. The original aqueous solution, which had been extracted with ether, was shaken with an equal volume of a saturated aqueous solution of picric acid; a yellow precipitate of the picrate of anisamidine was obtained. After recrystallization from 50% aqueous alcohol solution the substance melted at 206–207° as did also the product prepared from a known sample of 4-methoxybenzonitrile and potassium amide in liquid ammonia according to a modification of the procedure used with other nitriles (6); a mixed melting point was also the same. The yields of products obtained in the above experiment and the melting points on which the yields are based are given in line (A) of Table I.

The reaction of the O-methyl ether of *syn*-4-methoxybenzaldoxime (0.59 g.) with potassium amide was carried out as described above for the *anti* isomer, using 1.28 equivalents of potassium amide to one of the O-methyl ether. The potassium amide was used up at the end of the two hour period, since the addition of a crystal of tri-

phenylmethane failed to produce the deep red color of triphenylmethylpotassium. On working up the reaction mixture, both nitrile and amidine (isolated as picrate) were obtained; also an appreciable amount (10–15%) of unchanged O-methyl ether was recovered. The yields of products are given in line (B) of Table I.

The reaction of the O-methyl ether of *syn*-4-methoxybenzaldoxime was carried out also using three equivalents of potassium amide to one equivalent of the O-methyl ether. After stirring four hours, ammonium chloride (0.3 g.) was added to the mixture and the products isolated. No nitrile or unchanged O-methyl ether was obtained. The aqueous solution, which had been extracted with ether, was made up to 100 cc. in a volumetric flask and a 10 cc. aliquot treated with 7 cc. of saturated aqueous picric acid solution. A yellow precipitate of anisamidine picrate was obtained. The yield of this product is given in line (C) of Table I.

Reactions of syn-, *and* anti-*benzaldoxime acetates with potassium amide in liquid ammonia.* Jordan's procedure (1) for the reaction of acetyl *syn* aldoximes with potassium amide has been modified considerably. Freshly cut potassium (0.207 g. or 0.005 mole) was dissolved in 150 cc. of freshly distilled liquid ammonia in a Dewar flask and a piece of rusty iron gauze suspended in the solution until the blue color had disappeared. The solution of potassium amide was transferred by means of pressure to a second Dewar flask containing 1 g. (0.0048 mole) of acetyl-*syn*-3,4-methylenedioxybenzaldoxime dissolved in 100 cc. of dry ether. The mixture, which acquired a yellow color, was shaken for ten minutes. Solid ammonium chloride (0.3 g.) was then added, and the color disappeared. The mixture was poured into a beaker and the ammonia and ether allowed to evaporate. To the solid remaining was added 50 cc. of ice-cold water and the mixture extracted three times with 40-cc. portions of ether. The combined ether extracts were washed three times with 20-cc. portions of cold 2 *N* sodium hydroxide and then once with 20 cc. of cold water. Evaporation of the ether solution gave 3,4-methylenedioxybenzonitrile and saturation of the aqueous alkaline solution with carbon dioxide gave 3,4-methylenedioxybenzaldoxime.

The following experiments were carried out in a similar manner. One gram (0.005 mole) of acetyl-*syn*-4-methoxybenzaldoxime in 21 cc. of dry ether was treated with 1.18 equivalents of potassium amide prepared from 0.209 g. (0.0053 mole) of potassium in 75 cc. of liquid ammonia. One gram (0.005 mole) of acetyl-*anti*-4-methoxybenzaldoxime dissolved in 26 cc. of dry ether was treated with 1.18 equivalents of potassium amide prepared from 0.209 g. (0.0053 mole) of potassium in 100 cc. of liquid ammonia. One gram (0.0048 mole) of acetyl-*anti*-3,4-methylenedioxybenzaldoxime dissolved in 88 cc. of dry ether was treated with 0.29 g. (1.1 equivalent) of potassium amide prepared from 0.209 g. (0.0053 mole) of potassium in 125 cc. of liquid ammonia.

The yields of nitrile and aldoxime obtained in these experiments together with the melting points on which the yields are based are given in Table II. After recrystallization, the products were identified by their melting points; mixed melting points with authentic samples were taken in certain cases.

SUMMARY

1. In the presence of potassium amide in liquid ammonia at room temperature (sealed tube), *anti*-4-methoxybenzaldoxime presumably eliminates the elements of water to form the corresponding nitrile, which is converted by the potassium amide into the amidine, the latter being isolated as the picrate; also, the corresponding amide was isolated.

2. In the presence of potassium amide in liquid ammonia at −33°, *syn*-, and *anti*-4-methoxybenzaldoxime O-methyl ethers give 4-methoxybenzonitrile apparently quantitatively.

3. In the presence of potassium amide in liquid ammonia at −33°, *syn*-, and *anti*-benzaldoxime acetates give nitrile and the corresponding *syn*, and *anti* aldoxime. These reactions appear to be complete within ten minutes. The *anti* acetates give higher yields of nitrile and lower yields of aldoxime than the *syn* isomers.

4. The mechanisms of the elimination reactions are discussed.

DURHAM, N. C.

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(1) JORDAN AND HAUSER, *J. Am. Chem. Soc.*, **58**, 1304 (1936).
(2) BRADY AND KLEIN, *J. Chem. Soc.*, **1927**, 877.
(3) HAUSER AND JORDAN, *J. Am. Chem. Soc.*, **57**, 2450 (1935).
(4) See, for example, GILMAN'S "Organic Chemistry," John Wiley and Sons, New York, N. Y., **1938**, p. 387.
(5) HAUSER AND BRESLOW, *J. Am. Chem. Soc.*, **62**, 3344 (1940).
(6) See CORNELL, *J. Am. Chem. Soc.*, **50**, 3311 (1928).
(7) See LOSSEN AND GRABOWSKI, *Ann.*, **297**, 385 (1897).
(8) LINDEMANN AND TSCHANG, *Ber.*, **60**, 1729 (1927).
(9) PURDIE AND IRVINE, *J. Chem. Soc.*, **83**, 1028 (1903).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE REACTIONS AND ENOLIZATION OF CYCLIC DIKETONES. V. (1) SOME CARBONYL REACTIONS

C. F. KOELSCH AND C. D. LECLAIRE[1]

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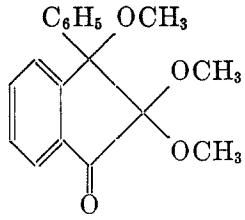
α-Diketones derived from cyclopentane have two features of special interest: their enolizability and the reactivity of their carbonyl groups. During previous investigations of the factors most noticeably affecting enolizability (1), isolated observations of the heightened reactivity of one of the carbonyl groups have been made; but these observations have not been correlated and interpreted. The present paper is a report on a study of this reactivity, undertaken in order to answer the questions: which of the carbonyl groups in a cyclic α-diketone of given structure is more prone to undergo additive reactions, and how does the activity of this carbonyl group compare with that of a carbonyl group in an acyclic diketone?

The activation of a carbonyl group by an adjacent negative (electron attracting) group appears to be quite general. Only brief reference to a few of the numerous examples of this activation in acyclic carbonyl compounds need be made. Chloral, glyoxalic acid (2), mesoxalic ester (3), mesityl glyoxal (4), 2,3,4-triketopentane (5) all show peculiarities in behavior, especially a tendency to add alcohols or water, which can be ascribed to the activation under discussion. Acyclic α-diketones apparently are not quite active enough to add alcohols or water, but this type of reactivity is pronounced with α-keto aldehydes and with triketones.

The same effects are found among the cyclic dicarbonyl compounds. While cyclopentanedione-1,2 (6) and diosphenols (7), perhaps because of their existence in enolic forms, do not add hydroxylated substances, some cyclic α-diketones have this property in a marked degree. The first case of this sort was noted by Perkin, Roberts, and Robinson (8), who found that while indandione-1,2 in keeping with its α-diketone structure formed yellow solutions in non-polar solvents, it gave colorless solutions in alcohols. Attempts to isolate acetals or hemiacetals from such solutions, however, were entirely unsuccessful. When the colorless alcoholic solutions were evaporated or chilled, the original yellow diketone separated (9).

[1] Abstracted from a Thesis by C. D. LeClaire, presented to the Graduate Faculty of the University of Minnesota in partial fulfilment of the requirements for the Ph.D. degree, March 1939.



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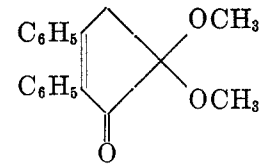

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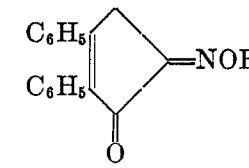

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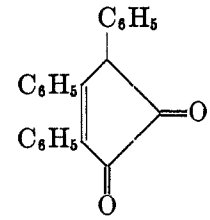

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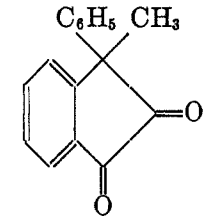


V

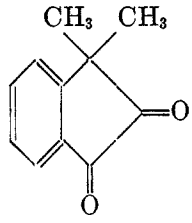
A still more pronounced activity has been observed in 3-bromo-3-phenylindandione-1,2 and in 3-methoxy-3-phenylindandione-1,2 (10). These substances are both deeply colored, but their solutions in alcohol are nearly colorless. From these solutions were isolated colorless crystalline acetals of the probable structure I. The parent substance from which these derivatives were obtained, 3-phenylindandione-1,2 did not form acetals; but since this diketone exists entirely in the enolic state, the lack of this type of reactivity is not surprising.

4,5-Diphenylcyclopentane-4-dione-1,2, a compound which exists wholly in the ketonic state, readily formed a methyl acetal (II), and it has been shown that the reaction involves the carbonyl group adjacent to the methylene carbon (9). This same diketone reacted with two equivalents of phenylmagnesium bromide under all conditions, but it was converted into a monoxime (III), reaction again involving the carbonyl group adjacent to the methylene carbon.

3,4,5-Triphenylcyclopentene-3-dione-1,2 (IV) (1), like the diketone discussed in the preceding paragraph, does not enolize; but it formed no acetal when treated with alcohols. It reacted with two equivalents of phenylmagnesium bromide, but unfortunately its behavior towards hydroxylamine was not studied.

Still another diketone, 3-methyl-3-phenylindandione-1,2 (V) (11) which would be expected to show heightened reactivity of one of its carbonyl groups has been prepared. Contrary to expectation, however, this diketone did not react with alcohols; its behavior towards hydroxylamine was not studied.

Three diketones were studied in the present research: 3,3-dimethylindandione-1,2 (VI), 3,3-dimethyl-6-nitroindandione-1,2 (VII), and 3,3-diphenylindandione-1,2 (VIII). Diketones in which carbon-3 was quaternary were selected so that complications due to possible enolization could not arise.



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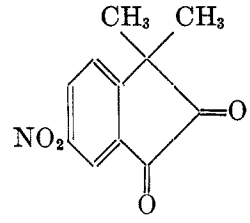

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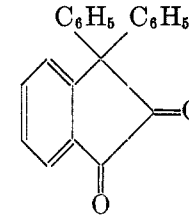
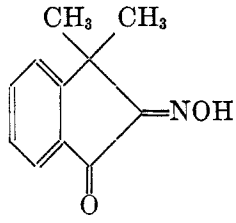
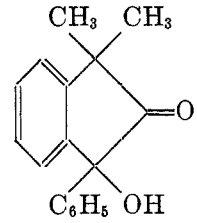


VIII

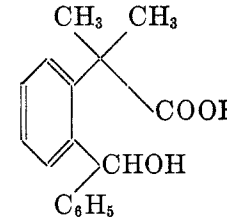
3,3-Dimethylindandione-1,2 (VI) showed many properties characteristic of reactive carbonyl compounds, such as an ability to add sodium bisulfite or potassium cyanide. When treated with an excess of hydroxylamine, the diketone formed a dioxime, but if only one equivalent of hydroxylamine was used a mono-oxime was formed, identical with the compound (IX) obtained by the nitrosation of 3,3-dimethylindanone-1.



IX



X



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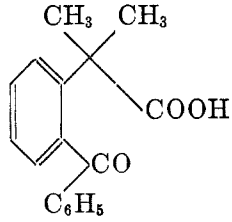
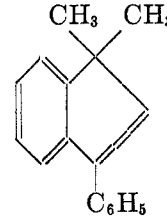


XII



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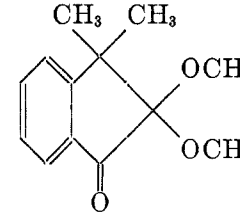


XIV

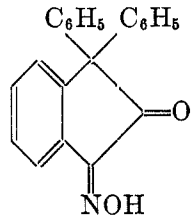
The formation of this mono-oxime indicated that the 2-carbonyl of the diketone was more reactive than the 1-carbonyl. It was therefore at first surprising to find that the 1-carbonyl was attacked preferentially by phenylmagnesium bromide. Treated with one mole of this reagent, the

diketone yielded 1-phenyl-3,3-dimethylindanol-1-one-3 (X) a compound whose structure was proved by cleavage with sodium hydroxide to the acid (XI) and oxidation of this in the form of its lactone to *o*-benzoylphenyldimethylacetic acid (XII). The structure of this degradation product was established by an independent synthesis. Treatment of 3,3-dimethylindanone-1 with phenylmagnesium bromide followed by dehydration of the resulting carbinol yielded 1,1-dimethyl-3-phenylindene (XIII) and this on oxidation gave *o*-benzoylphenyldimethylacetic acid (XII) identical with the acid obtained from the indanolone.

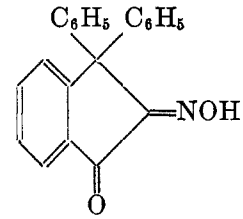
3,3-Dimethylindandione-1,2 dissolved in alcohols to give solutions whose yellow color was markedly different from the orange of solutions of the diketone in non-polar solvents; but cooling the alcoholic solutions caused the separation of the unchanged diketone. When hydrogen chloride was added to a methanol solution of the diketone and the mixture was allowed to stand, a colorless acetal (XIV) was formed. That the acetal formation involved the 2-carbonyl was shown by treatment of the acetal with an excess of phenylmagnesium bromide and hydrolysis of the oily product. This procedure led to the keto alcohol (X) which had been obtained previously by the action of one mole of phenylmagnesium bromide on the diketone itself.

6-Nitro-3,3-dimethylindandione-1,2 (VII) behaved in much the same way as the un-nitrated diketone, although its reactions were not investigated fully. It yielded pink solutions in non-polar solvents, yellow solutions in alcohols; it reacted with sodium bisulfite and with potassium cyanide.

3,3-Diphenylindandione-1,2 (VIII) did not show properties of a very reactive carbonyl compound: it did not add sodium bisulfite, nor did it form an acetal with acidified methanol. Treated with hydroxylamine, the diketone yielded a monoxime (XV) which, since it was different from the product (XVI) obtained by the nitrosation of 3,3-diphenylindanone-1, had the oxime group on carbon-1.



XV



XVI

The data concerning the additive reactions involving one carbonyl group of the cyclic diketones pertinent to the present discussion are

TABLE I

MONO-ADDITION REACTIONS OF CYCLIC α-DIKETONES

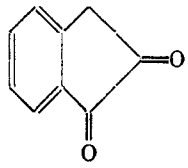
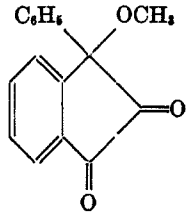
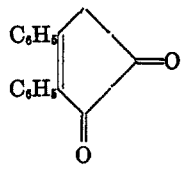
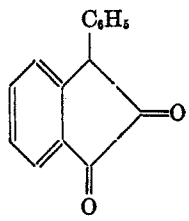
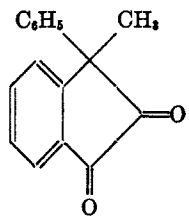
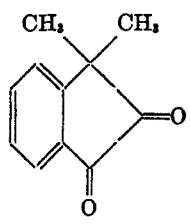
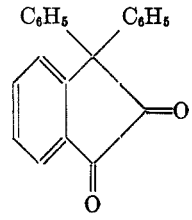
	ROH	1 EQ. NH_2OH	1 EQ. C_6H_5MgBr
	Unstable hemi-acetal formed (?)	Carbonyl-2 oximated	—
	Carbonyl-2 gives acetal	—	—
	Carbonyl-2 gives acetal	Carbonyl-2 oximated	Both carbonyls react
	No reaction	—	Both carbonyls react, carbonyl -2 as enol
	No reaction	—	—
	Carbonyl-2 gives acetal	Carbonyl-2 oximated	Carbonyl-1 reacts

TABLE 1—*Concluded*

	ROH	1 EQ. NH_2OH	1 EQ. C_6H_5MgBr
	No reaction	Carbonyl-1 oximated	—

summarized in Table I. It is apparent here that in compounds bearing no phenyl group on carbon-3, carbonyl-2 shows an additive tendency greater than that of a carbonyl group in an acyclic α-diketone. When carbon-3 bears a phenyl group, this additive tendency is diminished, and two phenyl groups on carbon-3 remove it completely. In the case of 3-phenyl-3-methoxyindandione-1,2, it may be assumed that the deactivating effect of the phenyl group is overcome by the methoxyl also present.

That the 2-carbonyl usually shows a greater tendency than the 1-carbonyl to be involved in reactions with hydroxylamine or alcohols may be explained by considering that the double bond conjugated with the 1-carbonyl tends to lessen the polarization of the latter. Hence in the reversible reactions of oxime or hemiacetal formation, any reagent attacking the 1-carbonyl even if this is the major original point of attack, is subsequently given up to the 2-carbonyl.[2]

The exceptional formation of the 1-oxime and not the 2-oxime from 3,3-diphenylindandione-1,2 is probably due in small part to steric hindrance of the 2-carbonyl by the adjacent phenyl groups, mainly, however, to the ability of the phenyl groups to deactivate the 2-carbonyl through electron donation. Steric hindrance could diminish only the rate of oximation, while the other process, also acting in preventing acetal formation from *e.g.* 3-methyl-3-phenylindandione-1,2, would detract from the stability[3] of the 2-oxime.

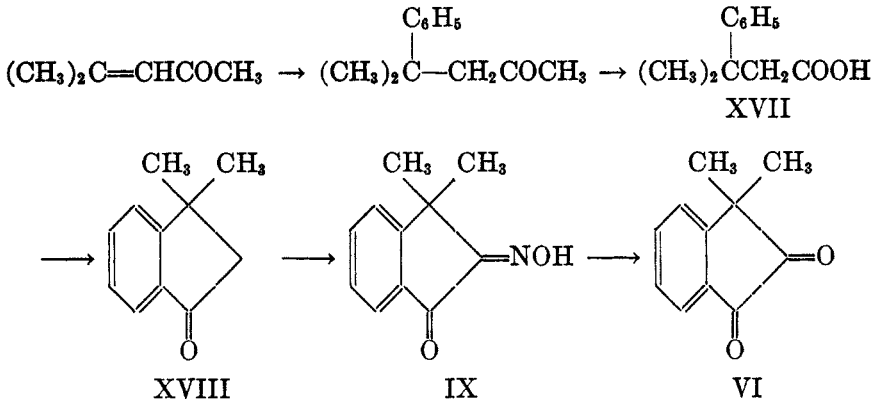
Phenylmagnesium bromide, like hydroxylamine, attacks the more exposed rather than the more polar carbonyl group of 3,3-dimethylindandione-1,2. But unlike hydroxylamine, the Grignard reagent adds

[2] It must be acknowledged that if this explanation is true, little weight can be attached to the method used for determining the structures of the mono-oximes. The structure determination used is thus offered only for lack of an alternative.

[3] This stability would be described by the hydrolysis constant of the oxime or acetal. See CONANT AND BARTLETT, *J. Am. Chem. Soc.*, **54**, 2896 (1932).

irreversibly, so that the 2-carbonyl is involved only if a second mole of phenylmagnesium bromide is available.

A number of points in connection with the preparations and incidental reactions of the diketones used in this study should be mentioned. 3,3-Dimethylindandione-1,2 was prepared through the following series of reactions:



β-Phenylisovaleric acid (XVII) has been prepared previously by the aluminum chloride catalyzed addition of benzene to β,β-dimethylacrylic acid (12). It was found much more convenient in the present work to carry out the reactions in the order shown (13), since β-phenylisovaleric acid was more easily extracted than was β,β-dimethylacrylic acid from the large volume of water required in the hypochlorite oxidations of the corresponding ketones. It was also found that cyclization of the acid to 3,3-dimethylindanone-1 (XVIII) did not require the isolation and purification of the acid chloride (12).

Nitrosation of 3,3-dimethylindanone-1 was carried out both by the action of butyl nitrite and hydrochloric acid and by the action of butyl nitrite and sodium methoxide on the ketone. Although less convenient, the latter procedure is to be recommended, since the acid method sometimes led to the oxime, and sometimes under apparently identical conditions to dimethylhomophthalimide (14).

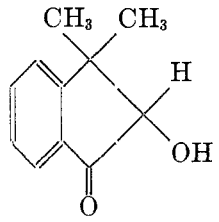
Acid hydrolysis of the oxime to the diketone proceeded smoothly when formaldehyde was used as a hydroxylamine acceptor in the procedure originated by Perkin (8).

In addition to the reactions already described, 3,3-dimethylindandione-1,2 showed the usual characteristic reactions of α-diketones. It reacted with excess hydroxylamine to give a dioxime (also obtained from the nitroso compound IX and hydroxylamine), it formed a quinoxaline with

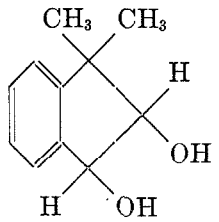
o-phenylenediamine, and it yielded dimethylhomophthalic anhydride on treatment with alkaline hydrogen peroxide.

In addition to its property of forming acetals, 3,3-dimethylindanedione-1,2 showed another interesting behavior. When an acid-free alcoholic solution of the diketone was illuminated it lost its deep yellow color, the alcohol was oxidized (formaldehyde was isolated from a methanol solution), and the diketone was converted into a colorless dihydro compound. This reaction is analogous to the photochemical reduction of quinone by alcohols discovered by Ciamician and Silber (15).

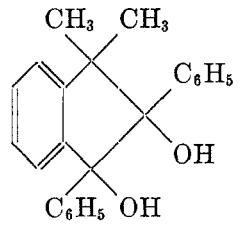
The dihydro compound from 3,3-dimethylindandione was very unstable towards many reagents, and no crystalline product other than the original diketone could be obtained from it when it was treated with aqueous alkali, with benzoyl chloride, acetyl chloride, or acetic anhydride, alone or in aqueous alkali or in pyridine. With phenylmagnesium bromide the dihydro compound yielded an oil and 1,2-diphenyl-3,3-dimethylindandiol-1,2 (XXI), a glycol also obtainable by the action of phenylmagnesium bromide on the original diketone. The dihydro compound could be titrated with aqueous permanganate, yielding thus the diketone almost quantitatively. On melting, the dihydro compound became orange, but no gas was evolved; from the melt was isolated 3,3-dimethylindandione-1,2 in a yield of 50%, and a faintly yellow oil which benzoyl chloride converted into a solid that analyzed for 1,2-dibenzoyloxy-3,3-dimethylindene. The most likely explanation for these data is that the dihydro compound was 3,3-dimethylindanol-2-one-1 (XIX), and that it readily underwent disproportionation to 3,3-dimethylindandione-1,2 and 3,3-dimethylindandiol-1,2 (XX).



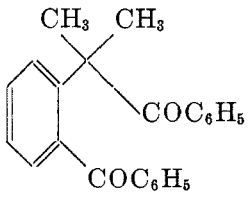
XIX



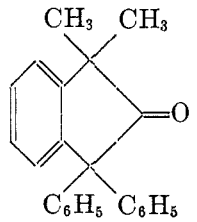
XX



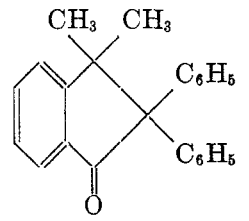
XXI



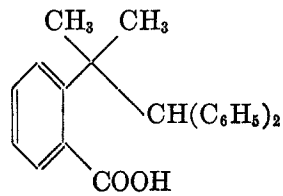
XXII



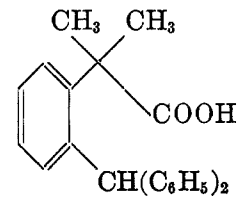
XXIII



XXIV



XXV



XXVI

When 3,3-dimethylindandione was treated with an excess of phenylmagnesium bromide, both of its carbonyl groups were attacked and a glycol (XXI) was formed. This glycol was characterized by its behavior towards lead tetraacetate, whereby it was converted into *o*-α-dibenzoylcumene (XXII), and by its behavior towards sulfuric acid in acetic acid. The latter reagent brought about a pinacol rearrangement, but whether the resulting ketone was XXIII or XXIV could not be ascertained definitely. Fusion of the ketone with sodium hydroxide converted it into an acid (XXV) or (XXVI), but when the sodium salt of this acid was distilled with soda-lime it lost sodium hydroxide instead of sodium carbonate and gave back the ketone (XXIII or XXIV). Such a ring closure would involve the intermediate formation of a C–Na derivative, and this type of compound would be more likely to be formed from the Ar_3CH group in XXVI than from the Ar_2RCH group in XXV. Thus formula XXIII is the preferred one for the pinacolone.

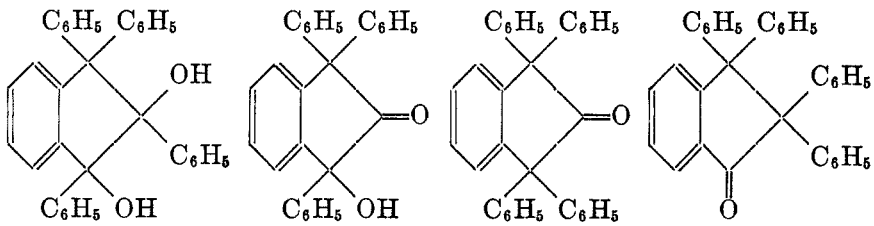
3,3-Dimethylindanone-1 was readily converted into a mononitro derivative by the action of fuming nitric acid. The structure of the product could not be proved definitely, since oxidation led either to a nitrodimethylhomophthalic acid of unknown orientation or to complete destruction. There is little doubt, however, that the nitro ketone was the 6-nitro compound, since it has been shown that while nitration of hydrindone leads to the formation of one part of 4-nitrohydrindone to five parts of 6-nitrohydrindone (16), the nitration of 3-methylhydrindone yields only 3-methyl-6-nitrohydrindone (17).

3,3-Dimethyl-6-nitrohydrindone-1 was nitrosated by treatment with butyl nitrite and acetyl chloride, and the oximino compound so produced was hydrolyzed using hydrochloric acid and formaldehyde. The resulting orange-yellow α-diketone was characterized through its ability to form a quinoxaline with *o*-phenylenediamine, and through its reaction with alkaline hydrogen peroxide, which led to 6-nitrodimethylhomophthalic anhydride.

An unsuccessful attempt to hydrolyze 2-isonitroso-3,3-diphenylindanone-1 has been reported (18), but it was found in the present work that with formaldehyde and hydrochloric acid this hydrolysis could be carried

out easily. As noted previously in this paper the resulting 3,3-diphenylindandione-1,2 did not react with potassium cyanide or with sodium bisulfite. In some other reactions characteristic of α-diketones, however, it took part readily. Thus with *o*-phenylenediamine it formed a quinoxaline, and with alkaline hydrogen peroxide it yielded diphenylhomophthalic anhydride.

When 3,3-diphenylindandione-1,2 was treated with an excess of phenylmagnesium bromide and the addition-product was hydrolyzed, a non-crystalline product was obtained. Since this product, on dehydration with sulfuric acid in acetic acid yielded a substance $C_{33}H_{24}O$ (XXX), together with a small amount of oil, it was probably a mixture of the two forms of 1,2,3,3-tetraphenylindandiol-1,2 (XXVII). In support of this conclusion a separate synthesis of the substance $C_{33}H_{24}O$ was carried out. 1,3,3-Triphenylindanol-1-one-2 (XXVIII) (19) with phenylmagnesium bromide yielded only one form of 1,2,3,3-tetraphenylindandiol-1,2 (XXVII), obtained here as a crystalline substance. When this crystalline glycol was dehydrated, it yielded a mixture of compounds, both $C_{33}H_{24}O$. One of these, comprising about 25% of the mixture, melted at 218–219°; the other, comprising some 75% of the mixture, melted at 185–186° and was identical with the dehydration product of the non-crystalline glycol mixture. The higher-melting dehydration product was probably the symmetrical ketone (XXIX), while the lower-melting dehydration product probably had the unsymmetrical structure (XXX). An attempt to cleave the lower-melting substance by fusion with sodium hydroxide led only to a resin, a result which might be expected in view of the known instability of pentaphenylethanes in air (20).



XXVII XXVIII XXIX XXX

EXPERIMENTAL

Preparation and Reactions of 3,3-Dimethylindandione-1,2

Addition of benzene to mesityl oxide. Mesityl oxide (350 g.) was added slowly to a well-stirred suspension of aluminum chloride (630 g.) in benzene (1400 ml.) at 10°. After the mixture had stood for three hours it was decomposed with iced hydrochloric acid; the 4-phenyl-4-methylpentanone-2 obtained (541 g.) boiled at 115° at 11 mm. [literature (13), 134° at 22 mm.].

Hypochlorite oxidation. 4-Phenyl-2-methylpentanone-2 (350 g.) was added to a stirred sodium hypochlorite solution (4 liters of 3.3 *N*) while the whole was heated on a steam-bath. The chloroform produced was allowed to distil during the initial exothermic reaction, and stirring was continued as long as any hypochlorite remained (18–25 hours). The unused ketone was then separated, the aqueous layer was acidified, and the solid β-phenylisovaleric acid was removed. It was purified by distillation (b.p. 155° at 10 mm.) and crystallization from petroleum ether; it melted at 58–59° [literature (13) 58–58.5°]. Yields from such runs averaged 163 g. or 73% calculated on the basis of the ketone not recovered.

Ring closure to 3,3-dimethylindanone-1. To a solution of β-phenylisovaleric acid (237 g.) in 750 ml. of benzene was added 320 g. (1.15 eq.) of phosphorus pentachloride, and the mixture was heated until no more hydrogen chloride was evolved (20 minutes). Then 180 g. of aluminum chloride was added with stirring, and heating was continued for an additional twenty minutes. The mixture was decomposed by pouring onto ice, and the benzene layer was washed with dilute hydrochloric acid and then with dilute sodium carbonate to remove unchanged acid. The 3,3-dimethylindanone-1 (180 g. = 84%) distilled at 110° at 8 mm. [literature (12), 119° at 13 mm.].

Nitrosation of 3,3-dimethylindanone-1. A mixture of butyl nitrite (50 g.) and 3,3-dimethylindanone-1 (50 g.) was added to 250 g. of methanol in which had been dissolved 11.2 g. of sodium. The mixture was allowed to stand in the ice-box for two days, then water and dilute acid were added and the butyl alcohol and unchanged ketone were removed by steam distillation. The remaining pale yellow oil (54 g.) solidified on cooling and was used directly for the preparation of the diketone. Recrystallized from water, the nitroso compound was obtained in the form of white scales that melted at 138–141°, while when it was crystallized from ethanol it formed white hexagonal plates that melted at 145–147°. The higher-melting modification was analyzed.

Anal. Calc'd for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.9.
Found: C, 70.0; H, 5.7.

The nitroso compound was soluble in aqueous sodium carbonate; with benzoyl chloride in ether it gave a benzoate that melted at 169–171° after crystallization from acetic acid.

Hydrolysis of the nitroso compound. The crude oxime described above (50 g.) was boiled for three hours in a mixture consisting of 150 ml. of acetic acid, 50 ml. of 40% formaldehyde, and 30 ml. of concentrated hydrochloric acid. The solution became deep red, and on cooling the diketone precipitated; water was added to complete the precipitation, giving an almost pure product in nearly quantitative yield. After distillation under reduced pressure and crystallization from acetic acid, the 3,3-dimethylindandione-1,2 formed orange crystals that melted at 106–107°.

Anal. Calc'd for $C_{11}H_{10}O_2$: C, 75.9; H, 5.8.
Found: C, 75.4; H, 5.9.

The diketone gave a colorless crystalline addition-product when it was added to a concentrated aqueous solution of sodium bisulfite. This addition-product was quite soluble in water and was useful in experiments where the diketone had to be removed from other substances inert towards bisulfite, since the diketone could be regenerated from it by warming with dilute hydrochloric acid.

Anal. Calc'd for $C_{11}H_{11}NaO_5S$: Na, 8.3.
Found: Na, 8.7.

The diketone also gave a colorless crystalline addition-product with concentrated

aqueous potassium cyanide. This substance was easily soluble in water; it gave oily products when its aqueous solution was acidified or when its solution in alcoholic hydrogen chloride was boiled for some time.

Anal. Calc'd for $C_{11}H_{10}O_2 \cdot KCN \cdot H_2O$: K, 15.2.
Found: K, 15.0.

Oximation of 3,3-dimethylindandione-1,2. (*Monoxime*). To a solution of hydroxylamine hydrochloride (0.2 g.) and hydrated sodium acetate (0.43 g.) in 5 ml. of water and 2 ml. of ethanol was added 0.5 g. of the diketone. The solid gradually dissolved and an oil separated which later became partly crystalline. The product was recrystallized from water (charcoal), and shown to be identical with the previously described nitroso compound of m.p. 138–141° by a mixed melting point determination.

(*Dioxime*). One gram of the diketone was added to a solution of hydroxylamine hydrochloride (2.5 g.) in a mixture of 10 ml. of ethanol and 10 ml. of 10% sodium hydroxide. The diketone rapidly disappeared when the mixture was warmed and the dioxime (1.07 g.) separated. After recrystallization from dilute ethanol it melted at 191–193° with decomposition. The dioxime gave a yellow solution in aqueous sodium hydroxide, but it was not soluble in sodium carbonate.

Anal. Calc'd for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9.
Found: C, 64.8; H, 5.9.

The same dioxime (0.88 g.) was obtained from the nitroso compound (1.0 g.), but the reaction was much slower than that between hydroxylamine and the diketone, requiring four days for practical completion.

Anal. Found: C, 64.8; H, 6.0.

The dioxime gave a dibenzoyl derivative that melted at 192–193°.

Anal. Calc'd for $C_{25}H_{20}N_2O_4$: C, 72.8; H, 4.9.
Found: C, 72.9; H, 4.9.

Quinoxaline from 3,3-dimethylindandione-1,2. Mixed with *o*-phenylenediamine in hot alcohol, the diketone was converted rapidly into its quinoxaline (11,11-dimethyl-11-indeno[1,2-b]quinoxaline, Ring Index 2517) which was sparingly soluble in hot alcohol. Crystallized from acetic acid, it melted at 146°.

Anal. Calc'd for $C_{17}H_{14}N_2$: C, 82.9; H, 5.7.
Found: C, 83.0; H, 5.7.

Cleavage of 3,3-dimethylindandione-1,2 by hydrogen peroxide. To a solution of the diketone (2 g.) in ethanol (25 ml.) was added 25 ml. of 3% hydrogen peroxide in which had been dissolved 0.5 g. of sodium hydroxide. When the slightly exothermic reaction was over and the diketone color had faded, the solution was acidified. Since no satisfactory analysis could be obtained on the resulting dimethylhomophthalic acid (2.4 g.), the compound was converted into its anhydride by heating. Crystalized from acetic acid, the anhydride melted at 81–82° [literature (21) 82–83°].

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.4; H, 5.3.
Found: C, 69.4; H, 5.5.

Acetal formation by 3,3-dimethylindandione-1,2. The diketone was dissolved in methanol which had been nearly saturated with hydrogen chloride. After the solution had been allowed to stand for ten hours, it was poured into water and ether. The ether layer was removed, washed with aqueous sodium bisulfite to remove unchanged diketone (about 50% of this substance was recovered), and dried with sodium sulfate. The acetal was precipitated with ligroin (30–60°), and was recrystallized from ether-ligroin. The 2,2-dimethoxy-3,3-dimethylindanone-1 so obtained formed colorless prisms that melted at 75–76°.

Anal. Calc'd for $C_{13}H_{16}O_3$: C, 70.8; H, 7.3.
Found: C, 70.2; H, 7.3.

On warming with dilute hydrochloric acid the acetal was converted into the diketone.

Reaction of the acetal with phenylmagnesium bromide. To a solution of the acetal (1.03 g.) in ether was added with stirring 5 ml. of 2.65 *M* phenylmagnesium bromide (1.8 ml. required). The mixture was allowed to stand for fifteen minutes at 35° and then was decomposed with iced ammonium chloride. The biphenyl and bromobenzene from the Grignard solution were steam distilled, but no crystalline product could be isolated from the non-volatile oil. The oil was boiled with hydrochloric acid in water and methanol, but this treatment failed to yield a solid product. The oil was then boiled for eight hours with methyl alcoholic sodium hydroxide. This procedure resulted in the formation of two substances, an acid and a neutral compound, the former probably benzohydrol-*o*-dimethylacetic acid since it gave the lactone of this substance (see below) on crystallization, and the latter certainly 3,2-dimethyl-1-phenylindanol-1-one-2, since it melted at 126–128° alone or mixed with an authentic sample (see below) of this hydroxy ketone. The neutral and acid fractions were separately oxidized with chromic acid in acetic acid. The acid fraction was not completely oxidized, and yielded 0.34 g. of unoxidized lactone as well as some *o*-benzoylphenyldimethylacetic acid. The neutral fraction gave 0.21 g. of *o*-benzoylphenyldimethylacetic acid which sintered at 188° and melted at 196–198° alone or mixed with a sample of the acid obtained by the oxidation of 1,1-dimethyl-3-phenylindene.

Reaction of 3,3-dimethylindandione-1,2 with one equivalent of phenylmagnesium bromide. To an ether-toluene solution of 6 g. of the diketone at −18° was added with stirring 1.3 equivalents of phenylmagnesium bromide in a concentration of 2.65 *M*. The yellow product which formed was decomposed by the addition of aqueous ammonium chloride, and the mixture was steam distilled. The residue was dried in ether, and the 3,3-dimethyl-1-phenylindanol-1-one-2 (4.2 g.) was precipitated by the addition of ligroin. Recrystallized from dilute ethanol, the hydroxy ketone formed white plates that melted at 128–129°.

Anal. Calc'd for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4.
Found: C, 80.6; H, 6.3.

When it was boiled for six hours with 25% aqueous-alcoholic potassium hydroxide the hydroxy ketone (1 g.) was partly recovered unchanged (0.67 g.) and partly converted into benzohydrol-*o*-dimethylacetic acid. The latter precipitated as its lactone (0.33 g.) when the alkaline solution was acidified. The lactone was insoluble in aqueous sodium carbonate, slowly soluble in aqueous sodium hydroxide, and rapidly soluble in alcoholic sodium hydroxide. Acidification of its alkaline solutions precipitated it unchanged in the form of needles that melted at 126–127°.

Anal. Calc'd for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4.
Found: C, 80.9; H, 6.2.

The lactone of benzohydrol-*o*-dimethylacetic acid (0.12 g.) in acetic acid was oxidized by adding twice the required amount of chromic acid in acetic acid and warming the solution on a steam-bath. Water was added, whereupon the *o*-benzoylphenyldimethylacetic acid (0.11 g.) separated in compact crystals. Recrystallized from acetic acid, it sintered at 188° and melted at 196–198° alone or mixed with a sample prepared as described below.

o-*Benzoylphenyldimethylacetic acid from 1,1-dimethyl-3-phenylindene.* 1,1-Dimethyl-3-phenylindene was prepared by the addition of an excess of phenylmagne-

sium bromide to 3,3-dimethylindanone-1 in ether and dehydration of the resulting carbinol by boiling it with acetic acid containing a drop of sulfuric acid. After crystallization from methanol the hydrocarbon melted at 49–51° [literature (12) 50–51°]. The indene (0.8 g.) was oxidized by boiling it with twice the calculated amount of chromic acid in acetic acid, giving *o*-benzoylphenyldimethylacetic acid (0.63 g.) which sintered at 188° and melted at 196–198°.

Anal. Calc'd for $C_{17}H_{16}O_3$: C, 76.1; H, 6.0; Neut. equiv., 268.
Found: C, 76.1; H, 6.0; Neut. equiv., 265.

Reaction of 3,3-dimethylindandione-1,2 with two equivalents of phenylmagnesium bromide. Four times the calculated quantity of phenylmagnesium bromide in standardized solution was added to the diketone (8 g.) in ether (200 ml.). The reaction-mixture was allowed to stand for a short time at room temperature and was then worked up in the same way as has been described for the reaction with one equivalent of Grignard reagent. The resulting 3,3-dimethyl-1,2-diphenylindandiol-1,2 (10.1 g.) melted at 125–126° after crystallization from ether-ligroin.

Anal. Calc'd for $C_{23}H_{22}O_2$: C, 83.6; H, 6.7.
Found: C, 83.7; H, 6.8.

Treated with an excess of lead tetraacetate in benzene, the glycol gave *o*-α-dibenzoylcumene in good yield. Recrystallized from acetic acid this diketone formed colorless needles or prisms that melted at 115–116°.

Anal. Calc'd for $C_{23}H_{20}O_2$: C, 84.1; H, 6.1.
Found: C, 83.7; H, 6.2.

Pinacol rearrangement of 3,3-dimethyl-1,2-diphenylindandione-1,2. When the glycol was warmed in acetic acid containing a few drops of sulfuric acid, an exothermic reaction took place and a new compound separated in nearly quantitative yield. This substance melted at 125–126° (a mixture with the original glycol of the same melting point melted below 100°), and analyzed for 3,3-dimethyl-1,1- (or 2,2-)diphenylindanone-2 (or -1).

Anal. Calc'd for $C_{23}H_{20}O$: C, 88.4; H, 6.5.
Found: C, 88.5; H, 6.6.

The ketone was not attacked by alcoholic alkali, but when it was stirred with a eutectic mixture of sodium and potassium hydroxides at 300° it melted and then solidified. The excess alkali was dissolved by adding water in small amounts, the alkali salt being insoluble in the strongly basic solution. The salt was then dissolved in a large amount of hot water (1 g. was soluble in about 500 ml. at 100°), filtered, and acidified with hydrochloric acid. The acid crystallized from acetic acid in fine needles that melted at 185–186°.

Anal. Calc'd for $C_{23}H_{22}O_2$: C, 83.6; H, 6.7.
Found: C, 83.6; H, 6.5.

The acid was recovered unchanged after it had been boiled with copper acetate in quinoline. When it was mixed with a large excess of soda-lime and strongly heated a solid distillate was obtained in poor yield. Crystallized from methanol this substance (Found: C, 88.6; H, 6.2) melted at 121–123°; a mixture with dimethyldiphenylindanone melted at 124–126°.

Photochemical reduction of 3,3-dimethylindandione-1,2. A solution of the diketone (0.2 g.) in isopropyl alcohol (12 ml.) retained its deep yellow color indefinitely when kept in the dark, but it was completely decolorized after it had been exposed to direct sunlight for twenty-five minutes. A colorless product was then precipitated by water.

A more concentrated solution of the diketone (9.4 g. in 150 ml.) became pale

yellow on illumination for three and one-half hours, and a slightly pink product was precipitated by water. Crystallization from ether-ligroin gave 3,3-dimethylindanol-2-one-1 in the form of colorless prisms (8.25 g.) that melted to an orange liquid at 111–115°.

Anal. Calc'd for $C_{11}H_{12}O_2$: C, 74.9; H, 6.9.
Found: C, 74.9; H, 6.6.

The preparation of the hydroxy ketone succeeded equally well in methanol or ethanol. After illumination of 1 g. of the diketone in methanol, the hydroxy ketone was precipitated and the solution was shaken out with ether. The addition of dimedon to the aqueous solution gave a precipitate (0.08 g.) that melted at 189° and was identical with the dimedon derivative of formaldehyde. A similar treatment of methanol in the absence of the diketone gave no precipitate.

Titrated in acetone solution at room temperature, the hydroxy ketone (1 g.) decolorized 7.35–7.40 ml. of 0.52 *M* potassium permanganate in acetone (calc'd 7.27 ml.). The resulting solution yielded 3,3-dimethylindandione-1,2 in nearly the theoretical amount together with a trace of dimethylhomophthalic acid.

Disproportionation of 3,3-dimethylindanol-2-one-1. The hydroxy ketone (1.5 g.) was melted and boiled for a few minutes. The melt was treated with ether, giving a part (0.62 g.) of the resulting 3,3-dimethylindandione-1,2 directly; the rest of this compound (0.13 g.) was obtained by extracting the ether solution with sodium bisulfite. Remaining in the ether was a faintly yellow oil which could not be crystallized. It was treated in ether with benzoyl chloride, and the resulting benzoyl derivative was crystallized from ligroin. This derivative, 3,3-dimethyl-1,2-dibenzoyloxyindane, formed white needles that melted at 86–87°.

Anal. Calc'd for $C_{25}H_{22}O_4$: C, 77.7; H, 5.7.
Found: C, 77.3; H, 6.0.

Preparation and Reactions of 3,3-Dimethyl-6-nitroindandione-1,2

Nitration of 3,3-dimethylindanone-1. Five grams of the ketone was cooled to −10° and added to 25 g. of nitric acid (*d.* 1.5) at the same temperature. A small amount of urea was added and the mixture was allowed to warm to 15° and to stand at this temperature for thirty minutes. It was then poured on ice; the separated solid was filtered and washed with ligroin (30–60°) to remove un-nitrated ketone (used in a subsequent nitration). If the mixture became red during the nitration through the formation of nitrous acid, the nitro ketone was accompanied by a brown alkali-soluble oil, but in satisfactory experiments this was not formed, the yield of pure 3,3-dimethyl-6-nitroindanone-1 being 2.5–4.0 g. Crystallized from methanol the compound formed colorless prisms that melted at 133–134°.

Anal. Calc'd for $C_{11}H_{11}NO_3$: C, 64.4; H, 5.4.
Found: C, 64.2; H, 5.4.

When it was boiled for one hour with aqueous potassium permanganate, the nitro ketone gave nitrodimethylhomophthalic acid in good yield, but no other compound could be isolated when the time of boiling was greatly increased.

Nitrosation of 3,3-dimethyl-6-nitroindanone-1. To a solution of the nitro ketone (1 g.) in ether was added butyl nitrite (1 g.) and acetyl chloride (0.4 g.). The reaction was slow at the start, but soon became vigorous. The product was crystallized from acetic acid, giving faintly yellow prisms (1.05 g.) that melted at 210–222°.

Anal. Calc'd for $C_{11}H_{10}N_2O_4$: C, 56.4; H, 4.3.
Found: C, 56.3; H, 4.5.

Hydrolysis of the nitroso compound. A mixture of the above nitroso compound

(1 g.), acetic acid (10 ml.), formalin (2 ml.), and conc'd hydrochloric acid (2 ml.) was boiled for three to five hours and then cooled. The resulting 3,3-dimethyl-6-nitroindandione-1,2 crystallized in almost the calculated amount. Recrystallized from acetic acid, it formed bright orange prisms that melted at 172–174°. It gave yellow solutions in alcohols and pink solutions in non-polar solvents.

Anal. Calc'd for $C_{11}H_9NO_4$: C, 60.3; H, 4.1.
Found: C, 60.1; H, 4.3.

With an excess of hydroxylamine, the nitro diketone gave a substance that crystallized in white needles melting at 171–180°. Analysis indicated that it was an impure dioxime.

Anal. Calc'd for $C_{11}H_{11}N_3O_4$: C, 53.0; H, 4.0.
Found: C, 53.9, 54.7; H, 4.8, 4.8.

Treated in alcohol with a slight excess of 3% hydrogen peroxide to which had been added a little sodium hydroxide, the nitro diketone gave α,α-dimethyl-5-nitrohomophthalic acid. The acid was recrystallized from acetic acid containing a small amount of sulfuric acid, which converted it into the corresponding anhydride; small white prisms that melted at 163–165°.

Anal. Calc'd for $C_{11}H_9NO_4$: C, 56.1; H, 3.9.
Found: C, 55.7; H, 4.0.

When the nitro diketone (70 mg.) was warmed in ethanol (5 ml.) with *o*-phenylenediamine (50 mg.), the corresponding quinoxaline separated in long white needles (91 mg.). This compound, 3-nitro-11,11-dimethyl-11-indeno[1,2-b]quinoxaline (R.I. 2517), melted at 269–271° after crystallization from acetic acid.

Anal. Calc'd for $C_{17}H_{13}O_2N_3$: C, 70.1; H, 4.5.
Found: C, 70.1; H, 4.7.

Preparation and Reactions of 3,3-Diphenylindandione-1,2

3,3-Diphenylindanone-1. Phosphorus pentachloride (18 g.) was added to β,β,β-triphenylpropionic acid (25 g.) [prepared in 56% yield by the method of Gagnon (22)] in 100 ml. of dry benzene, and the mixture was warmed until no more hydrogen chloride was evolved. Then aluminum chloride (11 g.) was added and the mixture was boiled for thirty minutes longer. The product, worked up in the usual way, melted at 130–131° [literature (22) 131–132°] and weighed 22.5 g.

Nitrosation of 3,3-diphenylindanone-1. To a solution of sodium (2 g.) in absolute ethanol (200 ml.) was added a mixture of diphenylindanone (8 g.) and butyl nitrite (8 g.). After it had stood at room temperature for three days, the solution deposited the sodium salt of the isonitroso compound in orange-red crystals. This was filtered and acidified, giving 4.5 g. of the isonitroso compound. The remainder of the product (4 g.) was obtained by adding dilute hydrochloric acid to the filtrate from the sodium salt, and steam distilling the butyl alcohol. The product crystallized from acetic acid in the form of yellow prisms that melted at 206–209° [literature (18), 220°].

Hydrolysis of the isonitroso compound. A mixture of 3,3-diphenyl-2-oximinoindanone-1 (7.8 g.), 60 ml. of acetic acid, 30 ml. of 40% formaldehyde, and 15 ml. of conc'd hydrochloric acid was boiled for sixteen hours. On cooling, the solution deposited 3,3-diphenylindandione-1,2 in orange prisms that melted at 150–151°.

Anal. Calc'd for $C_{21}H_{14}O_2$: C, 84.6; H, 4.7.
Found: C, 84.3; H, 5.0.

Treated in alcohol with a slight excess of 3% hydrogen peroxide containing a little sodium hydroxide, the diketone (1 g.) was rapidly decolorized, and then diphenylhomophthalic acid was precipitated on acidification. The acid was recrystallized

from acetic acid containing a small amount of sulfuric acid, which converted it into diphenylhomophthalic anhydride (0.9 g.), small white prisms that melted at 227–228°.

Anal. Calc'd for $C_{21}H_{14}O_3$: C, 80.0; H, 4.6.
Found: C, 80.2; H, 4.6.

Warmed in alcohol with a slight excess of *o*-phenylenediamine, the diketone was converted quantitatively into its nearly insoluble quinoxaline. This compound, 11,11-diphenyl-11-indeno[1,2-b]quinoxaline (R.I. 2517), crystallized from ethyl acetate in faintly tan prisms that melted at 244–245°.

Anal. Calc'd for $C_{27}H_{18}N_2$: C, 87.6; H, 4.9.
Found: C, 87.5; H, 4.8.

Treated with one equivalent of hydroxylamine, the diketone was transformed into 3,3-diphenyl-1-oximinoindanone-2. This substance formed pale yellow prisms that melted at 215–217° and showed a great lowering in melting point when mixed with 3,3-diphenyl-2-oximinoindanone-1.

Anal. Calc'd for $C_{21}H_{15}NO_2$: C, 80.5; H, 4.8.
Found: C, 80.1; H, 4.9.

Reaction of 3,3-diphenylindandione-1,2 with phenylmagnesium bromide. To a benzene solution of the diketone was added a large excess of phenylmagnesium bromide in ether. The mixture was boiled for thirty minutes and then decomposed with iced ammonium chloride. Volatile substances were removed by steam distillation, leaving an oil which became glassy on cooling, but which could not be crystallized. This substance was boiled with acetic acid containing a few drops of sulfuric acid, when it was converted into 2,2,3,3-tetraphenylindanone-1. This ketone crystallized from acetic acid in the form of small white prisms that melted at 185–186°.

Anal. Calc'd for $C_{33}H_{24}O$: C, 90.8; H, 5.5.
Found: C, 90.8; H. 5.6.

Reaction of 1,3,3-triphenylindanol-1-one-2 with phenylmagnesium bromide. To a solution of the hydroxy ketone (19) (0.5 g.) in xylene was added an excess (5 ml. of 2.65 *M* phenylmagnesium bromide. The mixture was distilled to 100° and kept at this temperature for fifteen minutes, and then decomposed with iced ammonium chloride. The volatile substances were removed by steam distillation, and the residue was crystallized from ether-ligroin. 1,2,3,3-Tetraphenylindandiol-1,2 obtained in this way in good yield, melted at 177–178°.

Anal. Calc'd for $C_{33}H_{26}O_2$: C, 87.2; H, 5.8.
Found: C, 87.3; H, 6.2.

The crystalline glycol was boiled for a few minutes with acetic acid containing a few drops of sulfuric acid. The product was separated by crystallization from ether into two substances, 2,2,3,3-tetraphenylindanone-1 (75%) which melted at 185–186° and 1,1,3,3-tetraphenylindanone-2 (25%) which melted at 218–219°. The lower-melting substance was identified by direct comparison with a sample of the ketone obtained by the dehydration of the glassy glycol; the higher-melting compound was analyzed.

Anal. Calc'd for $C_{33}H_{24}O$: C, 90.8; H, 5.5.
Found: C, 89.3, 89.8; H, 5.4, 5.9.

SUMMARY

The mutual activating effect of the carbonyl groups in some derivatives of indandione-1,2 is greater than that in acyclic α-diketones. Although

carbonyl-1 of the indandiones is more available for reaction, carbonyl-2 is more polar. The polarization of carbonyl-2 is cut down when aromatic nuclei are substituted on carbon-3. These conclusions are reached through a consideration of data already published and through a study of the reactions of 3,3-diphenyl-, 3,3-dimethyl-, and 3,3-dimethyl-6-nitro-indanione-1,2 towards a number of carbonyl reagents.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE PYROLYSIS OF α,α,γ-TRIPHENYLPROPYLENE

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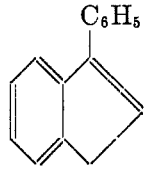
3-Phenylindene (I) rearranges (1) to 2-phenylindene (II) (2) when it is distilled over pumice at a red heat. Little is known concerning the mechanism of this reaction except that an intermediate of structure III is not involved. Similarly 1-phenylnaphthalene, 1-ethylnaphthalene, and 1,6-dimethylnaphthalene passed over silica gel at 350–430° yield the corresponding 2-naphthalene derivatives (3).



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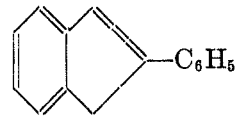

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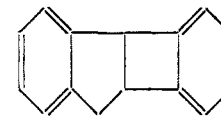
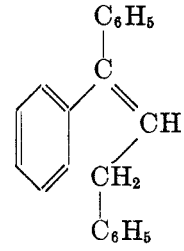


III



IV

Sometimes similarities can be found between rearrangements taking place in cyclic compounds and those in acyclic substances. Thus, aside from numerous cases of well known pinacol rearrangements, the behavior of 1,1,3-triphenylindene towards sodium (4) may be compared with that of $\alpha,\alpha,\gamma,\gamma$-tetraphenylpropylene towards lithium (5). The first hydrocarbon is transformed into a sodium derivative of 1,2,3-triphenylindene, the latter into a lithium derivative of 1,2,3-triphenylhydrindene, and both reactions involve the migration of a phenyl group.

[1] Abstracted from a thesis by P. R. Johnson, presented to the Graduate Faculty of the University of Minnesota in partial fulfilment of the requirements for the Ph.D. degree 1938.

The research described in the present paper was undertaken to determine whether a cyclic nucleus was essential in the thermal rearrangements referred to above. The behavior of α,α,γ-triphenylpropylene (IV), an acyclic compound analogous to 3-phenylindene, was studied, since if α,β,γ-triphenylpropylene could be found in the pyrolysis products from this substance, a type of reaction similar in the acyclic and the cyclic series would be indicated. Unfortunately no α,β,γ-triphenylpropylene was isolated; rearrangement took place, but cyclization also occurred, and as shown below, it was probable that cyclization was the primary process.

Five pyrolyses were carried out at 450–460° using the reduced pressure technique devised by Mayer, Sieglitz, and Ludwig (1) for 3-phenylindene. In these runs a little toluene was formed, but even when the condensate was put through the furnace several times most of the product consisted of unchanged α,α,γ-triphenylpropylene. Five more pyrolyses were then run at the same temperature but at atmospheric pressure. In these cases, probably because the propylene could be passed more slowly over the heated contact substance, more significant results were obtained; they are summarized in Table I.

As a typical experiment run 10 may be described in detail. The pyrolysis of 20.7 g. of the propylene gave a product which was separated by distillation into five parts. The first fraction (b.p. 100–110°) weighed 2.6 g. and was identified as toluene by converting it into 2,4-dinitrotoluene.

The second fraction (b.p. 105–130° at 10 mm.) weighed 3.5 g. and was found to contain 66% of α,α-diphenylethylene by titration with bromine. The ethylene was isolated and identified in the form of diphenylvinyl bromide. The remainder of the second fraction was nitrated, yielding α,α-di-*p*-nitrophenylethane and di-*p*-nitrophenylmethane. The isolation of these nitro derivatives indicated the presence of α,α-diphenylethane and diphenylmethane, but since nitration of the two hydrocarbons in pure states could not be carried out quantitatively, no exact estimate could be made as to the relative quantities of them present in the second fraction.

The third fraction (b.p. 130–200° at 10 mm.) weighing 2.0 g. was not investigated, but it was considered unlikely that it contained any substance not present in fractions two and four.

The fourth fraction (b.p. 200–220° at 10 mm.) weighed 8.65 g. From it was isolated 4.35 g. of a mixture of 1,2-diphenylindene and 2,3-diphenylindene, identified by conversion into pure 2,3-diphenylindene by warming with alcoholic potash (6), and into 1-benzal-2,3-diphenylindene by treatment with benzaldehyde and alkali (7). Chromic acid oxidation of the oil remaining after the crystalline indenes had been removed yielded benzoic acid, phenylacetic acid, *o*-benzoylbenzoic acid, benzophenone, and *o*-dibenzoylbenzene. The formation of these substances indicated the

TABLE I

PYROLYSIS OF α,α,γ-TRIPHENYLPROPYLENE

NO.	CONTACT AGENT	RATE OF ADD'N, G./HR.	PROPYLENE USED, G.	FRACT. 1 100–110° (ATM.)	FRACT. 2 105–130° (10 MM.)	FRACT. 3 INTERMEDIATE	FRACT. 4 200–220° (10 MM.)	RESIDUE	TOTAL RECOVERY
6	Clay plate	2	11	Not isol.	2 g. No products identified	—	5 g. 1.5 g. of 2,3-diphenylindene isol.	3 g.	10 g.
7	Used in run 6	4	30	0.5 g. In ice-HCl trap. No attempt to obtain toluene from material in first receiver	6.5 g. Diphenyl methane and ethylene identified. 63% Unsat. by bromine titration	4 g.	10.5 g. 4 g. of 2,3-diphenylindene isolated. α,α,γ-Triphenylpropylene ident. as bromo comp.	4 g. Some indene isolated	25.5 g.
8	Used in runs 6 and 7	4	28	Not isol.	5.5 g. Products same as in 7	4 g.	13.5 g. 1.5 g. of 2,3-diphenylindene isolated. 0.25 g. of 1,2-diphenylindene isolated and identified	4 g. Not investigated	27 g.
9	Pumice	8	21	0.6 g. Toluene	2.65 g. No products identified. 30% Unsat.	In fract. 4	11.9 g. No indenes isol. Oxidation indicated 1,3-diphenylindene	5.5 g.	20.65 g. Not fully investigated
10	Clay plate	4	20.7	2.6 g. Toluene, 0.3 g. in CO_2 trap, remainder in first receiver. No benzene	3.5 g. Same as in 7 and 8, plus α,α-diphenylethane. Bromine titration showed 66% unsat.	2 g.	8.65 g. 4.35 g. of a mixture of 1,2- and 2,3-diphenylindenes shown by oxidation. Original propylene shown by oxidation to benzophenone	2.5 g. 0.7 g. of indene isol. Oxidation showed 1,3-diphenylindene	20 g.

presence in fraction four of 1,3-diphenylindene and of the original triphenylpropylene; the presence of the latter compound was also shown in other runs by isolating its monobromo derivative.

The distillation residue weighed 2.5 g., and on standing in ether gave a few milligrams of crystals that melted at 280°. This substance was not identified, but it could not be tetraphenylethylene (m.p. 221°) or tetraphenylethane (m.p. 209°) or α,δ-diphenyl- (m.p. 152°) or $\alpha,\alpha,\delta,\delta$-tetraphenyl-butadiene (m.p. 202°). Treatment of the remaining oil with ligroin led to the isolation of 1,2- and 2,3-diphenylindene, and oxidation of the uncrystallizable material gave *o*-dibenzoylbenzene (showing 1,3-diphenylindene), benzoic acid, and a small amount of anthraquinone. The isolation of anthraquinone was not necessarily due to the presence of unusual rearrangement products of the propylene, since the same substance was isolated from the oxidation products of pure synthetic 2,3-diphenylindene. How anthraquinone was formed in this oxidation cannot be explained; benzoylbenzoic acid gave none of it under conditions identical with those used in the oxidations.

A complete understanding of the mechanisms of the pyrolysis might be reached only through a quantitative knowledge of the products formed, but some conclusions can be drawn from the data available. The substances shown to be present in the pyrolysis products, toluene, diphenylmethane, α,α-diphenylethane, α,α-diphenylethylene, 1,2-diphenylindene, 1,3-diphenylindene, 2,3-diphenylindene, and α,α,γ-triphenylpropylene are formed by cracking, rearrangement, and ring closure.

Cracking during pyrolysis is generally assumed to involve the formation of free radicals (8), the radicals separating being those of low electron attraction (9). Thus, α,α,γ-triphenylpropylene should yield benzyl and diphenylvinyl, and since an allyl shift is also probable (10), benzohydryl and styryl. Of the ten compounds possible through coupling of these radicals only one, the original α,α,γ-triphenylpropylene, was isolated. But this is not evidence against the formation of free radicals, since coupling between two energy-rich fragments probably requires the assistance of a third body for the dissipation of the energy (8). Furthermore the concentration of radicals in any volume is low, so that their most likely fate is to become hydrogenated at the expense of the relatively abundant α,α,γ-triphenylpropylene.

Cyclization of α,α,γ-triphenylpropylene probably results from the dehydrogenation of the acyclic hydrocarbon by the free radicals formed through cracking. In support of this hypothesis a semi-quantitative survey of all the pyrolysis products shows that for every molecule cracked one is cyclized. In run 10 where 0.075 moles of the propylene was pyrolyzed, if fraction three was divided equally between fractions two and four,

then 4.5 g. was the total weight of mixed diphenyl -methane, -ethane, and -ethylene. Of this 66% or 0.0165 mole was diphenylethylene. The rest of this mixture, calculated as diphenylmethane, amounted to 0.0093 mole. The quantity of substances arising from hydrogenation of benzohydryl and decomposition or hydrogenation of diphenylvinyl was thus 0.026 mole, approximately equal to the quantity of toluene (0.028 mole) isolated, and not greatly different from the amount of indenes (0.021 mole) found.

Direct cyclization would lead either to 1,1-diphenylindene which was not found, or to 1,3-diphenylindene, whose presence in small amounts was indicated. The main cyclization products were 1,2- and 2,3- diphenylindene, easily interconvertible (7) substances whose formation from the propylene requires the migration of a phenyl group. It is probable that migration occurs after and not before cyclization, since rearrangement before cyclization would lead to α,β,γ-triphenylpropylene, and either this substance or its cracking products, stilbene or α,β-diphenylethane, would have been isolated.

It must be concluded, as it was in the case of the non-rearrangement of $\alpha,\gamma,\gamma,\gamma$-tetraphenylpropylene by sodium (11), that the breaking of an open propylene chain is more readily brought about than is the displacement of a phenyl group. To avoid the cleavage, the carbon chain along which the phenyl group migrates must be part of a ring, and it thus appears that a cyclic structure is essential for the type of rearrangement in question.

One statement can be made concerning the mechanism of the rearrangement. Since no benzene is formed in a medium where free radicals are hydrogenated, the migrating phenyl group does not separate as a free radical.

EXPERIMENTAL

α,α,γ-Triphenylpropylene. Methyl β-phenylpropionate treated with an excess of phenylmagnesium bromide gave α,α,γ-triphenylpropanol which melted at 87° [literature (12), 87°]. This alcohol was dehydrated by boiling with acetic acid containing a little sulfuric acid; the resulting α,α,γ-triphenylpropylene, obtained in yields averaging 78%, melted at 32° and boiled at 225° under 12 mm. or at 214° under 7 mm. [literature (13), b.p. 222° under 10 mm.].

A convenient derivative, prepared from the hydrocarbon and bromine in warm acetic acid, was α,α,γ-triphenyl-β-bromopropylene, which melted at 96-97° [literature (14), 97-98°].

Pyrolysis apparatus. The pyrolyses were carried out in the apparatus illustrated in Fig. 1. The triphenylpropylene was introduced from a dropping-funnel, jacketed so that high-melting solids might be accommodated, whose stopcock rotated on a vertical axis. Purified nitrogen (8 ml./min.) was used as an inert gas to carry the substance through the furnace; calculations indicated that the maximum time for the passage of the pyrolyzed substance through the heated furnace packing was 150 sec., but mist usually appeared in the receiver 70 sec. after the first drop of substance

had been introduced. The pyrolysis took place in a porcelain tube 10 mm. inside diameter and 47 cm. long, packed with pumice stone or chips of unglazed clay plate. The tube was heated over 26 cm. of its length by a resistance furnace, Nichrome wire wound over an insulated iron tube, jacketed with asbestos. Pyrolysis temperatures were read by means of a thermocouple and its associated apparatus and were controlled by an adjustable resistance. Most of the pyrolysis products were condensed in a receiver at room temperature; the more volatile substances were removed from the nitrogen stream by a second receiver cooled in acetone-dry ice.

Pyrolysis 10. α,α,γ-Triphenylpropylene (20.7 g.) was dropped into the pyrolysis tube over a period of five hours. The temperature of the tube was about 450°, the

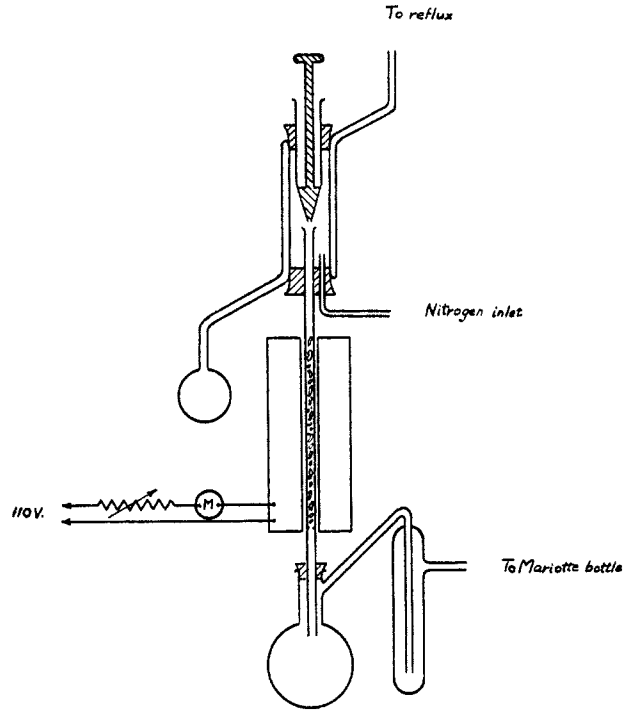


FIG. 1. THE PYROLYSIS APPARATUS

tube was packed with porous clay plate, and the flow of nitrogen through the system was 10 ml./minute.

The greater portion (19.5 g.) of the products collected in the first receiver, and about 0.3 g. of liquid was found in the dry ice trap. The slight loss of material during the run was due to some condensation of the products in the lower end of the porcelain tube. The material in the first receiver was then distilled, giving the following fractions: 1. 2.3 g. of b.p. 80–115°/atm.; 2. 3.5 g. of b.p. 120–130°/10 mm.; 3. 1.9 g. of b.p. 130–180°/9 mm.; 4. 8.65 g. of b.p. 200–225°/9 mim.; 5. 2.5 g. of residue.

Characterization of fraction 1. Six drops of fraction 1 was added to 0.5 ml. of a mixture of equal volumes of concentrated nitric and sulfuric acids. After the first reaction had subsided, the mixture was heated gently for a few minutes and then

poured on ice. The solid product (m.p. 64–66°) was filtered and crystallized from methanol. It then melted at 69.5–70.5° alone, or at 69.5–71° when mixed with 2,4-dinitrotoluene.

Since previous runs had shown that a phenyl group migrated during the pyrolysis, special efforts were made to find benzene in fraction 1. But no evidence for the presence of even small amounts of this substance was obtained.

Characterization of fractions 2 and 3. Semi-quantitative bromination of fraction 2 showed it to contain 64–66% of unsaturation calculated as diphenylethylene. Fractions 2 and 3 were combined and redistilled, giving 4.1 g. boiling at 124–127° under 9 mm. This was treated with a slight excess of bromine in carbon tetrachloride, and the reaction-mixture was steam distilled. The nonvolatile oil (3.3 g.) solidified on seeding with β,β-diphenylvinyl bromide. It was recrystallized from ligroin, giving 2.5 g. of solid which melted at 48–48.5°; a portion of this recrystallized from methanol melted at 49–49.5°, alone or mixed with an authentic sample of β,β-diphenylvinyl bromide.

The steam distillate from the bromination contained carbon tetrachloride and an oil (1.0 g.) which on redistillation boiled at 124–127° under 9 mm. (0.7 g.). This was shaken in chloroform for thirty minutes with a mixture of 0.6 ml. of nitric acid and 2 ml. of sulfuric acid. The product was removed and crystallized from ether and then benzene, giving a few milligrams of p,p'-dinitrodiphenylmethane which melted at 181–182°, alone or mixed with a known sample.

The benzene and ether were removed from the mother liquors. The oil remaining was dissolved in a mixture of 1 ml. of acetic acid with 1 ml. of nitric acid, and the whole was warmed on a steam-bath for five hours. From this nitration there was obtained a small amount of α,α-di-*p*-nitrophenylethane, which crystallized from methanol in the form of yellow needles that melted at 145–148°. Mixed with an authentic sample of the same compound of melting point 147–149°, the product melted at 145–147°.

Characterization of fraction 4. Treatment of fraction 4 with ether-petroleum ether gave 4.35 g. of a mixture of 1,2- and 2,3- diphenylindenes which melted at 94–110°, and after recrystallization from ethanol at 104–106°. In pyrolysis 8 (Table I) these components were separated by extended fractional crystallization and identified by direct comparison with synthetic samples of 1,2-diphenylindene (m.p. 177–178°) and of 2,3-diphenylindene (m.p. 108–109°). In the present pyrolysis the mixture was identified as described in the theoretical section.

Titration of a portion of the oil from which the indenes had been crystallized indicated the presence of 60–70% of unsaturated substances, but the only crystalline material which could be isolated by treatment with bromine was a small amount of 1-bromo-2,3-diphenylindene, identified by direct comparison with a known sample of this compound. A portion (0.5 g.) of the oil was then warmed with chromic acid (0.5 g.) in acetic acid. In the acidic products of this oxidation only benzoic acid was accurately identified, but indications were had of the presence of phenylacetic acid and of *o*-benzoylbenzoic acid. The neutral oxidation products consisted of a small amount of benzophenone and 0.1 g. of *o*-dibenzoylbenzene, separated by steam distillation and identified by mixed melting points.

Control experiments on the oxidation of pure 1,3-diphenylindene with a 5% excess of chromic acid gave approximately 50% yields of *o*-dibenzoylbenzene. Inasmuch as the above oxidation was carried out with less than the theoretical amount of oxidizing agent, and as only small amounts of acidic products were obtained, fraction d contained a fairly large percentage of 1,3-diphenylindene.

Characterization of the residue. The residue from the fractionation of the pyrolysis products was allowed to stand for several days in ether, when it deposited a few milligrams of a colorless crystalline compound (m.p. 280°) which was not identified. Concentration of the mother liquor and dilution with petroleum ether yielded 0.7 g. of 2,3-diphenylindene. The oil remaining (1.5 g.) was divided into two equal parts. One of these, oxidized by warming with 0.75 g. of chromic acid in acetic acid, gave a few milligrams of anthraquinone, some benzoic acid, and 0.1 g. of *o*-dibenzoylbenzene. The other, allowed to stand in ether solution, slowly deposited a small amount of 1,2-diphenylindene, identified by a mixed melting point determination and by conversion into 1-benzal-2,3-diphenylindene.

Synthesis of 1,3-diphenylindene. The addition of an excess of phenylmagnesium bromide to 3-phenylindanone, followed by distillation of the resulting carbinol gave 1,3-diphenylindene in a yield of 70%; the hydrocarbon melted at 69–70° [literature (12) 71–72°] after it had been crystallized from acetic acid.

Oxidation of 1,3-diphenylindene. To a solution of 1,3-diphenylindene (0.502 g.) in acetic acid (10 ml.) was added slowly 0.635 g. of chromic acid in 5 ml. of acetic acid. The mixture was heated on a steam-bath for four hours, then poured into water and steam distilled to remove acetic and benzoic acids. The residue was taken up in ether and washed with an excess of dilute sodium carbonate; the acidic products so removed (0.240 g.) were not investigated. The ether solution was then evaporated to dryness, leaving 0.294 g. (51%) of pure *o*-dibenzoylbenzene which melted at 145–146°.

Synthesis of 2,3-diphenylindene. α-Phenylcinnamic acid [m.p. 170°, literature (15) 172°] was prepared in a yield of 85% by heating a mixture of sodium phenylacetate (172 g.), benzaldehyde (120 g.), and acetic anhydride (400 g.) at 150–170° for nine hours. Electrolytic reduction (16) of this substance (200 g.) gave α,β-diphenylpropionic acid, purified by distillation [b.p. 215–220° under 18 mm., m.p. 85–92°; literature, m.p. (17) 82°, 88–89°, 95–96°; b.p. (18) 330–340°].

A solution of α,β-diphenylpropionic acid (110 g.) in benzene (500 ml.) was treated with phosphorus pentachloride (110 g.); conversion to the acid chloride was completed by warming. Then aluminum chloride (100 g.) was added in portions, the mixture was boiled for thirty minutes and worked up in the usual way. There was obtained 46 g. (45%) of 2-phenylindanone which boiled at 210–215° under 10 mm. and melted at 74–76° [literature (19), 77–78°].

This ketone was treated with an excess of phenylmagnesium bromide and the resulting carbinol was dehydrated by warming with acetic acid containing a little sulfuric acid. 2,3-Diphenylindene so obtained in good yield melted at 108.5–109.5° [literature (20) 108–109°].

Oxidation of 2,3-diphenylindene. The hydrocarbon (0.486 g.) in acetic acid was treated with chromic acid (0.631 g.) and the products were worked up as described for 1,3-diphenylindene. On standing in ethanol, the neutral products (0.183 g.) deposited a small amount of anthraquinone and later 0.1 g. of *o*-benzoylbenzil which melted at 94°, alone or mixed with a known sample (21).

From the acidic products there was obtained 0.120 g. of *o*-benzoylbenzoic acid.

SUMMARY

The products obtained by pyrolysis of α,α,γ-triphenylpropylene are formed through cracking, cyclization, and rearrangement. It is suggested that dehydrogenation of α,α,γ-triphenylpropylene by the free radicals

formed in its cracking is the cause of the cyclization, that the cyclization precedes the rearrangement, and that the rearrangement does not involve free radicals.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

ATTEMPTED SYNTHESIS OF 1,2,3-TRIPHENYL-1,3-BUTADIENE. SYNTHESIS AND PROPERTIES OF 1,2,3-TRIPHENYLALLYL ALCOHOL

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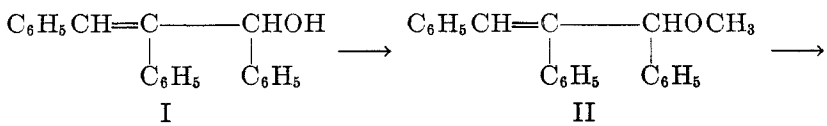
Received February 12, 1941

Among the already known phenyl-substituted 1,3-butadienes the following have been shown to give addition compounds with philodienic components: 1-phenylbutadiene (1), 2-phenylbutadiene (2), 1,2-diphenylbutadiene (3), 2,3-diphenylbutadiene (4), 1,4-diphenylbutadiene (1), and 1,2,4-triphenylbutadiene (3). The only exception in this series appears to be the 1,2,3,4-tetraphenyl-substituted product (5, 6), and by comparison with phenyl-substituted 9-vinylphenanthrenes we submitted the hypothesis (3), that 1,2,3-triphenylbutadiene (V) also should be inert in the Diels-Alder reaction, because it contains three neighboring carbon atoms, each of which is linked to an aromatic group. In these open-chain dienes the phenyl groups must be arranged in a way which does not favor the approaching of philodienic molecules, in contrast to the behavior of polyphenyl cyclopentadienones (7). So far, the synthesis of the diene V has failed, but some of the observations we made on the intermediary stages may be of general interest and are therefore dealt with in this paper.

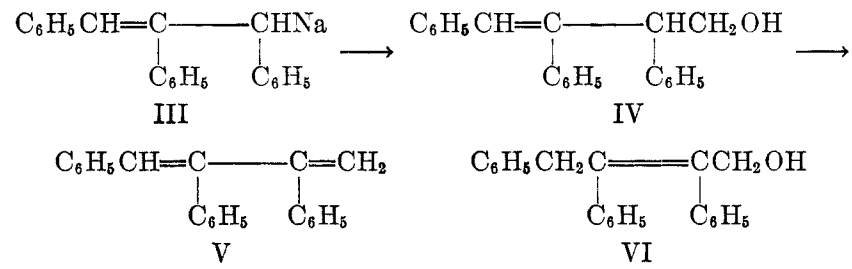
Kohler and co-workers (8) have shown that α-phenylbenzalacetophenone reacts with Grignard reagents mainly in the 1,4-position to give substituted benzyldesoxybenzoins, $C_6H_5CHCHCOC_6H_5$. On the other hand, α-phenyl-

cinnamic aldehyde behaves "normally" (9) and yields the carbinols $C_6H_5CH{=}CCHOHR$ by 1,2-addition. By interaction of this aldehyde

with phenylmagnesium bromide, we prepared 1,2,3-triphenylallyl alcohol (I), identical with the reduction product obtained from benzaldesoxybenzoin with aluminum isopropoxide. We then intended to proceed along the following scheme:



I II



III IV

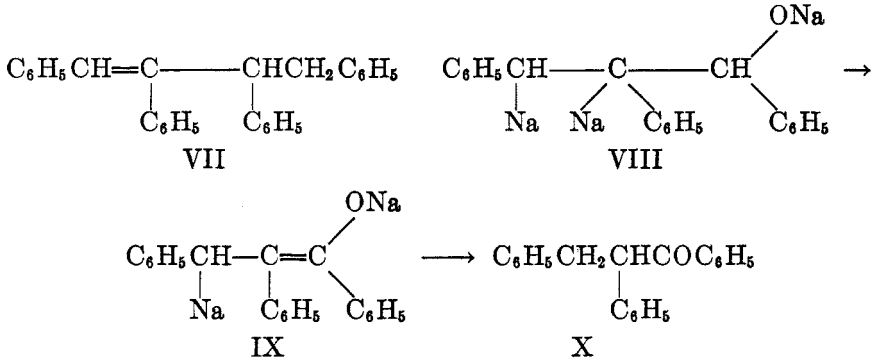
V VI

Compound I was easily methylated in cold methanol with a few drops of concentrated sulfuric acid. After a few minutes the methyl ether (II) began to crystallize out. II reacts smoothly with sodium powder in ether, and the product III, when decomposed with paraformaldehyde, is converted into 2,3,4-triphenyl-3-buten-1-ol. However, it proved impossible to dehydrate IV to the desired butadiene (V). Acetyl chloride, *e.g.*, formed the acetate of IV, which was stable even on heating to 350°. Tschugaeff's method yielded a yellow oil, which was sensitive to air and did not give satisfactory analytical figures. It may be that this oil consisted partly of the required diene, because it decolorized bromine, whereas I and IV did not. Anyhow, condensation of this impure material with maleic anhydride was unsuccessful. The failure to dehydrate IV satisfactorily, raised the question whether this carbinol had really the structure ascribed to it, or was the product (VI) of an allylic rearrangement. To decide this point, the sodium compound III was brought into reaction with benzyl chloride, because all the possible reaction products are known (6). A hydrocarbon of m.p. 147–148° was obtained, which most probably represents 1,2,3,4-tetraphenyl-1-butene (VII), although direct comparison with an authentic sample could not be carried out. The synthesis of VII proves that no rearrangement has occurred. Therefore the conclusion seems justified that also in the reaction product with formaldehyde the double bond remains in its original position.

With triphenylallyl alcohol we observed a very curious reaction. In ethereal solution, it reacts with sodium, not in the usual way to form an alcoholate, but to establish apparently a metal-to-carbon bond, since the solution acquired a deep wine-red color. After decomposition with ethanol, two substances could be isolated from the reaction mixture: benzyldesoxybenzoin, m.p. 120° (X), and a dihydro product of m.p. 92°, which was identified with the α form of 1,2,3-triphenylpropanol (10). The preparation of an authentic sample of this compound is described below.

The formation of benzyldesoxybenzoin, which resembles an intramolecular oxidation-reduction process, may be explained in various ways: Sodium metal may add to the ethylenic linkage and at the same time

form an alcoholate, so that the trisodium compound (VIII) becomes the intermediate.



When NaH is split off from VIII, the enolate is obtained which, when sodium is replaced by hydrogen, is tautomerized to benzyldesoxybenzoin.

TABLE I

	TRIPHENYLALLYL ALCOHOL	α-TRIPHENYLPROPANOL
Triphenylallyl alcohol (93°)	93°	97–98°
α-Triphenylpropanol (92°)	97–98°	92°
β-Triphenylpropanol (87°)	87–89°	76–85°

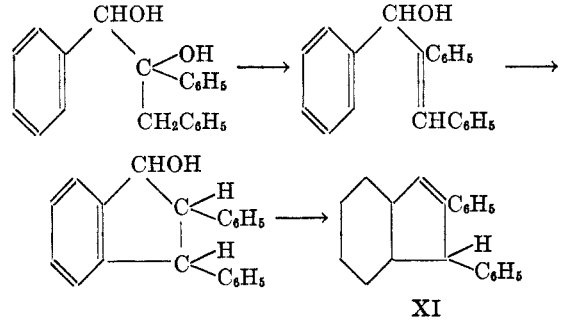
VIII may give the triphenylpropanol directly by replacement of sodium by hydrogen. It is also possible that sodium effects an allylic rearrangement into the enol form of X. In this case, triphenylpropanol owes its formation to a special addition reaction. Experiments are now under way to clear up the mechanism of this reaction.

For the synthesis of α-triphenylpropanol, required for comparison with the above product, we reduced I catalytically, whereby a mixture of the α and β forms was obtained. As only the β form is produced by reduction of benzyldesoxybenzoin with sodium amalgam (11), the result of the various reduction processes apparently depends on the sequence in which the two unsaturated linkages are hydrogenated. The accompanying table shows the mixed melting points of I and the stereoisomeric triphenylpropanols: A mixture of the α form and I (which melt at about the same temperature) shows an elevation of the melting point.

In the Grignard synthesis of I we observed that on working up the reaction mixture with dilute acid, 1,2-diphenylindene (XI) is formed in place of triphenylallyl alcohol. The compound I was already assumed (12) to

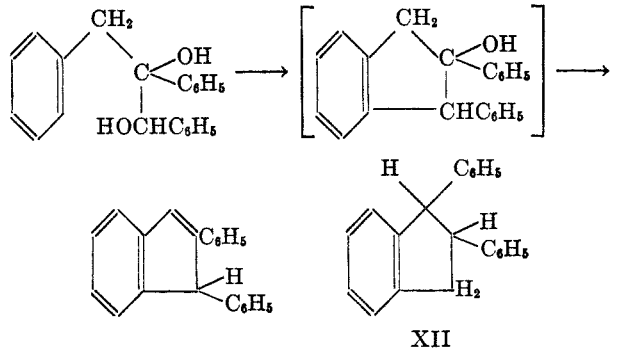
be the intermediary stage in the cyclization of α-benzylhydrobenzoin according to the scheme A, in preference to the alternative scheme B (13).

A.



XI

B.



XII

Our experience with triphenylallyl alcohol supports the first reaction mechanism; namely, (a) heating the methyl ether II with concentrated sulfuric acid to 90° immediately produces XI by splitting off methanol; (b) when acetylation of I is attempted with acetyl chloride, the liberated hydrochloric acid also causes simultaneous cyclization and deacetylation; (c) the acetate of I can be isolated by the use of acetic anhydride and is readily converted into XI by sulfuric acid at 100°; (d) when hydriodic acid is used, all the above mentioned substances yield directly the higher-melting form of 1,2-diphenylhydrindene (XII) (14), which is best prepared in this way.

It is obvious that cyclization always occurs by way of the intermediary indanol derivatives. These easily split off a molecule of ROH (R = H, CH_3, $COCH_3$) and yield the indene system. Indanol derivatives have already been shown to be very unstable (15). On the other hand, it is not understandable, how the acetate of I or its methyl ether could suffer direct "cyclodehydration" with elimination of ROH. It may be noted also, that triphenylallyl alcohol is thermally stable and can be distilled *in vacuo* without cycloisomerization.

EXPERIMENTAL

1,2,3-Triphenylallyl alcohol (I). To a Grignard solution, produced from bromobenzene (10 g.) and magnesium (1.6 g.), α-phenylcinnamic aldehyde (4.5 g.) was added. When decomposed with ammonium chloride, the reaction mixture yielded directly a crystalline product, which was recrystallized from ligroin; prisms, m.p. 93°, yield 3.5 g.

Anal. Calc'd for $C_{21}H_{18}O$: C, 88.1; H, 6.3.
Found: C, 87.8; H, 6.2.

With hot conc'd sulfuric acid, the substance gives an olive-green solution. Bromine is not decolorized.

When the above reaction mixture is treated with dilute sulfuric acid and the residue distilled *in vacuo* at 125° and 0.2 mm., a thick, yellow syrup is obtained, which is induced to crystallize upon trituration with petroleum ether. Recrystallization from high-boiling petroleum ether yielded needles of m.p. 177°, which did not depress the melting point of an authentic sample of 1,2-diphenylindene.

Anal. Calc'd for $C_{21}H_{16}$: C, 94.0; H, 6.0.
Found: C, 93.85; H, 6.3.

1,2,3-Triphenylallyl alcohol was also obtained from benzaldesoxybenzoin (27.5 g.) and aluminum isoproproxide (41 g.) in isopropanol (200 cc.). On decomposing the solution with potassium hydroxide, an oil separated, which crystallized after a few hours. It was identical with the product from the Grignard reaction; yield, 25 g.

Triphenylallyl acetate. Triphenylallyl alcohol (0.5 g.) was boiled in acetic anhydride (5 cc.). The solution was poured into ice-water and the precipitate recrystallized from butanol (tetragonal plates) or high-boiling petroleum ether (rods); m.p. 129°.

Anal. Calc'd for $C_{23}H_{20}O_2$: C, 84.1; H, 6.1.
Found: C, 84.35; H, 6.1.

In contact with conc'd sulfuric acid, the crystals stain first red-brown, but immediately change to green, the reaction becoming exothermic. After heating the mixture on a steam-bath for two minutes, water was added, and the white precipitate was identified as 2,3-diphenylindene.

When triphenylallyl alcohol, its acetate, or its methyl ether were boiled for one hour with hydriodic acid, and the solution poured into water, a brown syrup was obtained. It was dissolved in carbon tetrachloride, washed with soda and thiosulfate solution and distilled, b.p. 180-200° at 5 mm. The bright yellow distillate was triturated with petroleum ether. Recrystallization from isopropanol yielded long, glistening rods, m.p. 126°, which did not depress the melting point of 1,2-diphenylhydrindene.

Reaction with sodium. I (5.7 g.) was shaken with sodium powder (2 g.) in ether for 48 hours. The residue obtained after decomposition with ethanol and evaporation of the solvent, crystallized on trituration with petroleum ether. It was twice recrystallized from ligroin, whereby a mixture of prisms and needles settled down. These were separated mechanically. (a) Needles, from alcohol, m.p. 119°; mixed melting point with benzyldesoxybenzoin, 120°. (b) Prisms, from ligroin, m.p. 92°; mixed melting point with the α form of 1,2,3-triphenylpropanol, 92°.

Anal. Calc'd for $C_{21}H_{20}O$: C, 87.5; H, 7.0.
Found: C, 87.0; H, 7.3.

Catalytic reduction. A solution of I (11 g.) in glacial acetic acid (50 cc.) was hydrogenated in the presence of 1 g. of catalyst (palladium on barium sulfate). In one hour, 950 cc. (754 mm., 26°) was absorbed; calc'd, 950 cc. After evaporation of the

solvent, the residue was triturated with petroleum ether and recrystallized from methanol. The mixture of needles and prisms so obtained was separated mechanically. The needles had the m.p. 92°, after recrystallization from ethanol. They proved to be the α form of 1,2,3-triphenylpropanol. The β form was obtained from ligroin as prisms, m.p. 86–87°. A mixture of the two stereoisomers melted between 76° and 85°.

2,3,4-Triphenyl-3-buten-1-ol (IV). I (5.7 g.) was dissolved in methanol (50 cc.), and 5 drops of conc'd sulfuric acid added. After a few minutes at room temperature, the methyl ether (II) began to separate; it was recrystallized from ligroin, m.p. 96°, mixed melting point with I, 80–85°.

Anal. Calc'd for $C_{22}H_{20}O$: C, 88.0; H, 6.7; OCH_3, 10.3.
Found: C, 87.85; H, 6.7; OCH_3, 10.3.

An ethereal solution of the methyl ether (10 g.) was shaken with sodium (8 g.) for 48 hours, whereby the solution acquired a deep red color. The sodium compound (III) was then decomposed with paraformaldehyde (1.5 g.). The residue from the ethereal solution was distilled *in vacuo*, b.p. 205° at 2.0 mm., and then triturated with petroleum ether. The product crystallized from dilute ethanol in long lancets, m.p. 106°, which became green in contact with conc'd sulfuric acid, and dissolved in it with red-brown color when heated. This substance (IV) did not decolorize bromine.

Anal. Calc'd for $C_{22}H_{20}O$: C, 88.0; H, 6.7.
Found: C, 88.1; H, 6.7.

When 1.5 g. of the carbinol (IV) was refluxed for two hours with acetyl chloride (5 cc.), a crystalline acetate was obtained, which formed rods from ethanol, m.p. 94°. After heating this substance to 350° under normal pressure, or after distillation *in vacuo* (b.p. 280° at 0.03 mm.), it was recovered unchanged.

Anal. Calc'd for $C_{24}H_{22}O_2$: C, 84.2; H, 6.4.
Found: C, 83.9; H, 6.4.

With conc'd sulfuric acid the acetate of IV gives a deep violet color.

The alcohol (IV) (2.5 g.) was boiled with 1 g. of sodium powder in xylene for 6 hours, the solution filtered, and treated first with carbon disulfide (5 cc.), then boiled for two hours with methyl iodide (5 cc.). After filtering off the sodium iodide, the solution was shaken with silver powder and then distilled, b.p. 155° at 0.2 mm. A thick, yellow syrup was obtained, which decolorized bromine strongly. No picrate could be isolated from the alcoholic solution of this substance, nor any addition product with maleic anhydride.

Anal. Calc'd for $C_{22}H_{18}$: C, 93.6; H, 6.4.
Found: C, 88.9; H, 6.2.

The addition compound III, prepared from II (2 g.) and sodium powder (1 g.) in ether, was decolorized with benzyl chloride (1 g.), and the residue which remained after evaporation of the solvent was recrystallized first from methanol, then twice from acetic acid; m.p. 147–148°.

Anal. Calc'd for $C_{28}H_{24}$: C, 93.3; H, 6.7.
Found: C, 93.0; H, 6.7.

The author wishes to thank Mr. A. Löffler for his technical assistance in carrying out this work.

SUMMARY

1. 1,2,3-Triphenylallyl alcohol and its derivatives are easily cyclized to 1,2-diphenylindene.

2. The synthesis of 1,2,3-triphenylbutadiene by dehydration of 2,3,4-triphenyl-3-buten-1-ol failed.

3. The abnormal reaction of 1,2,3-triphenylallyl alcohol with sodium is described.

4. Catalytic reduction of this alcohol yields a mixture of the stereoisomeric triphenylpropanols.

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SPECTRA OF PORPHYRINS AND THEIR ACID SALTS

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INTRODUCTION

H. Fischer's work confirmed without doubt, more than a decade ago, Küster's conception of the porphyrin nucleus as that of a tetrapyrrole ring, the pyrroles being joined by methine carbons. The precise nature of the inner ring is, however, in doubt and has been the subject of considerable speculation. The present investigation was undertaken in an attempt to determine spectroscopically the existence of various acid porphyrin forms.

The Fischer-Küster formula could make possible a molecule with four basic dissociation constants, *i.e.*, the nitrogens being secondary or tertiary and adding H^+ according to: $NH + H^+ = NH_2^+$, and $N + H^+ = NH^+$

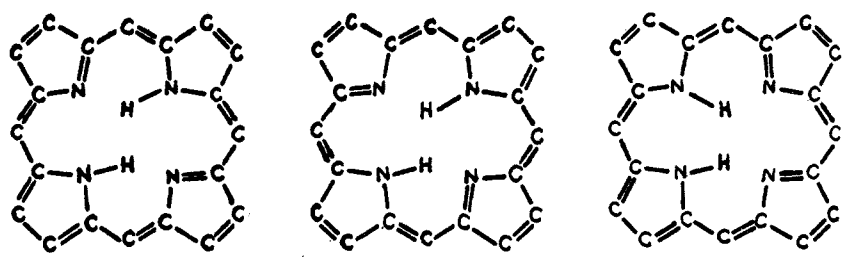


FIG. 1

With few exceptions, however, porphyrin salts have been of the composition P·2HCl as shown by both potentiometric methods (1) and chemical analyses (2, 9). The usual method of obtaining porphyrin salts does not involve high acidity (*i.e.*, greater than concentrated HCl). Some of the nitrogens involved in salt formation may be of extremely weak basicity and their behavior may be shown in concentrated acid spectroscopically (3). It has generally been presumed that each acid form will display its own characteristic spectrum. Thus a compound capable of tetrasalt formation should display five spectral forms, one for each of the salts, and one for the free base. Similarly, a compound capable of disalt formation should show three forms, etc.

Disalt formation as well as color and equivalence of the pyrrole rings,

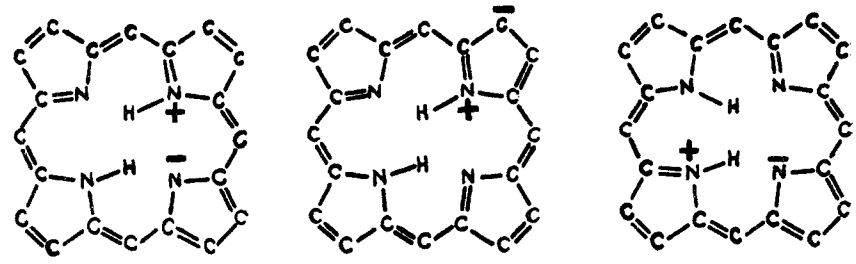
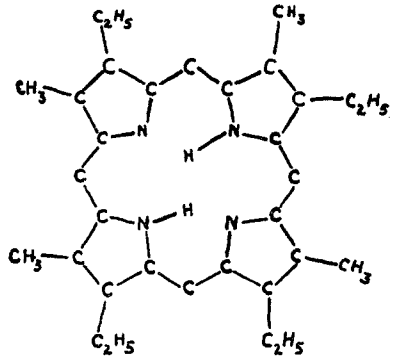
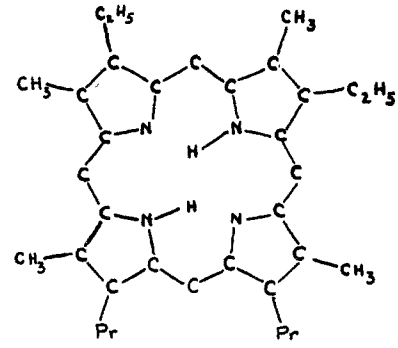


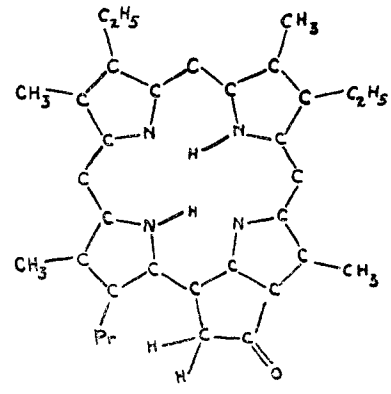
FIG. 2



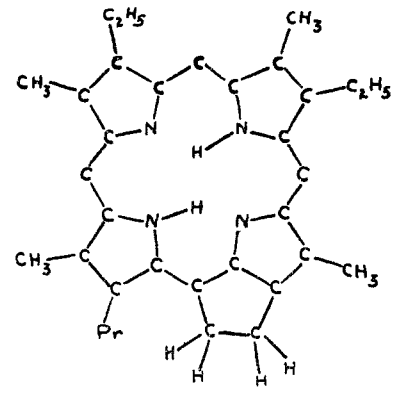
Etioporphyrin III



Mesoporphyrin IX



Phylloerythrin



Desoxophylloerythrin

FIG. 3

are readily explained by Fischer's formula. The free base is assumed to resonate among eight homopolar structures (Fig. 1) etc., and forty-eight ionic structures, *e.g.*, Fig. 2. It is, of course, possible that the tautomerism

indicated (conceivably a resonance because of the small distance to be traversed) does not exist (6, 4), and the number of structures would be halved. Both the x-ray analyses of phthalocyanines (5) and infra-red studies of porphyrins (10), however, indicate N—H—N bonding. Forms containing a double charge-separation could also be written, but their contribution is of much smaller magnitude than those with single charge-separation. The different homopolar formulas readily show the equivalence of the β-positions of the pyrroles, while the charge-separated structures promote color formation. We believe that in acid solution the charge-separated forms predominate, that is, approximate more closely the true state of the resonating structure, showing the interaction of the nitrogens with the rest of the system and explaining the acid spectra.

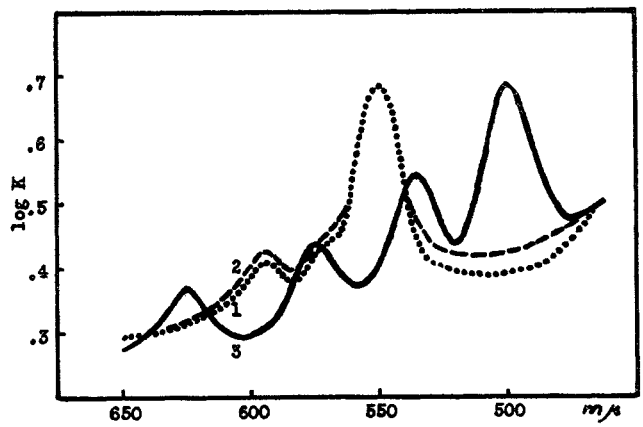


FIG. 4. ETIOPORPHYRIN III
1. 96% H_2SO_4. 2. Pyridine-H_2SO_4 mixture. 3. Pyridine

Four porphyrins were studied, three of which displayed two spectral curves and one, three spectral curves. The compounds used were: etioporphyrin III, mesoporphyrin IX, desoxophylloerythrin, and phylloerythrin; their skeletal structural relationships are shown in Fig. 3 [Pr = $-(CH_2)_2COOH$].

EXPERIMENTAL

Etioporphyrin III was obtained as a sublimation product by the decarboxylation of mesoporphyrin IX. This was accomplished by heating mesoporphyrin in a potassium nitrate bath at 350° in a high vacuum (10^{-5} mm. Hg).[1] Mesoporphyrin itself was obtained by hemin reduction by the method of Fischer (2), except for the

[1] Courtesy of Dr. H. J. Almquist, Division of Poultry Husbandry, University of California.

use here of 57% hydriodic acid (Merck's reagent sp. g. 1.7). Hemin was prepared by the usual method of Schalfejeff from defibrinated cow blood. Desoxophylloerythrin

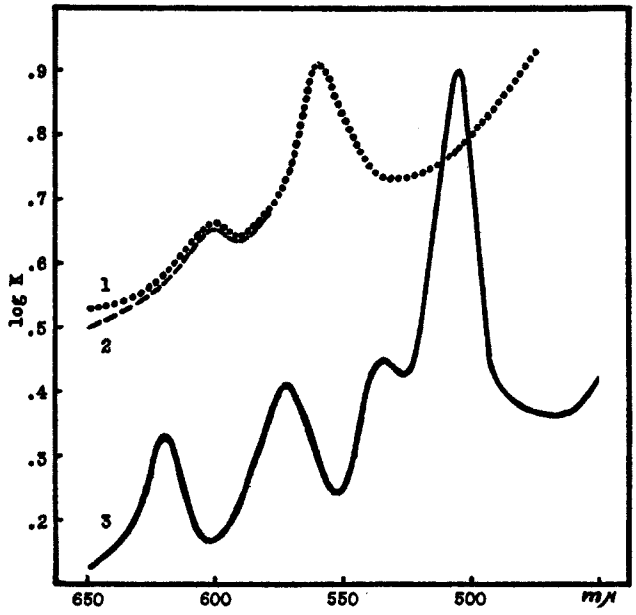


FIG. 5. DESOXOPHYLLOERYTHRIN
1. 96% H_2SO_4. 2. 48% H_2SO_4. 3. Pyridine

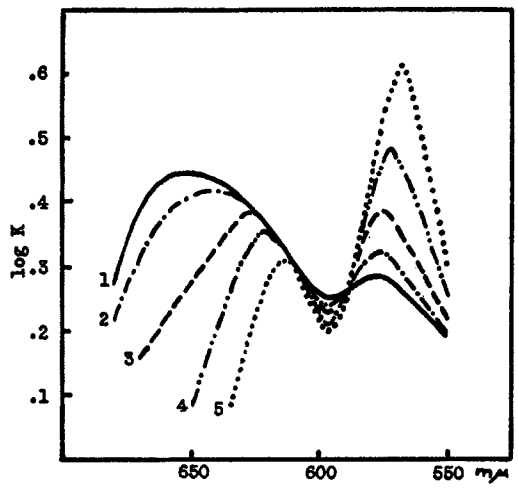


FIG. 6. PHYLLOERYTHRIN
1. 96% H_2SO_4. 2. 22.8% HCl. 3. Pyridine. 4. 11.4% HCl

was prepared from a chlorophyll mixture with hydrobromic-acetic acid, and phylloerythrin by hydriodic-acetic acid reduction.

Absorption measurements were made visually with a Bausch and Lomb Universal Spectrophotometer.

As the acid solvent, 96% sulfuric acid was utilized, in which all the compounds were stable. Acidity was decreased by addition of pyridine down to a 1:1 ratio of pyridine-sulfuric acid, (with further dilution, insoluble pyridine-H_2SO_4 is formed). Pyridine-hydrochloric acid mixtures were therefore substituted for the lower acidities. The results are shown in figures 4, 5, and 6. To avoid confusion, the curves for lower acidities are not included. They were in all cases practically identical with the lowest acid spectra shown.

It is seen that except for phylloerythrin there is no significant form change in concentrated acid solution apart from solvent effects (band maxima shift and volume contraction), *cf.* figure 7.

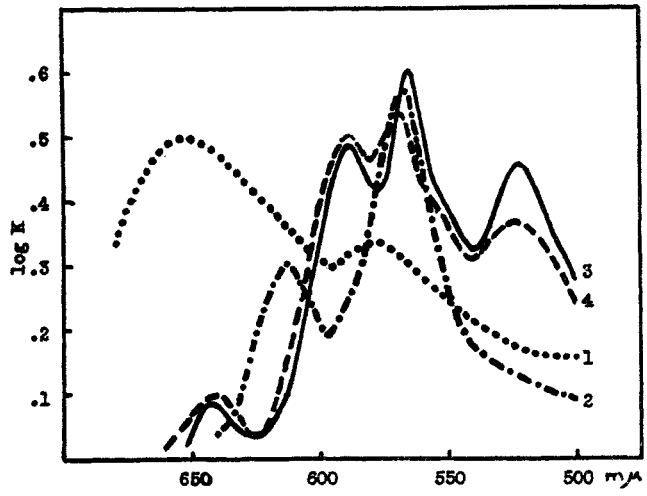
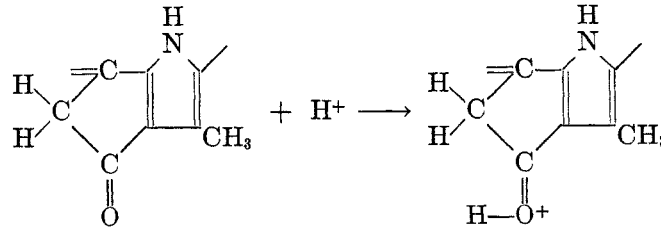


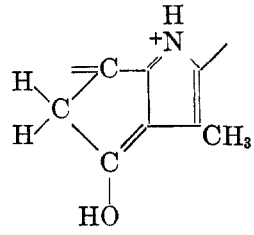
FIG. 7. PHYLLOERYTHRIN
1. 96% H_2SO_4. 2. 86.4%. 3. 76.7%. 4. 67.3%. 5. 48% H_2SO_4

DISCUSSION

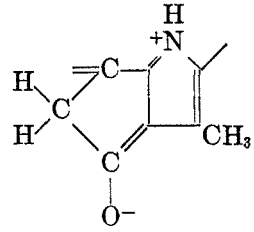
The change of the acid spectrum of phylloerythrin in concentrated sulfuric acid may be correlated with the oxygen on the isocyclic ring. This oxygen is capable of oxonium formation, *viz.*,



The latter structure can then resonate with one of the ring nitrogens, *e.g.*,



resulting in a spectral shift toward the red. The keto group of the free base involves the resonance:



resulting in significant effect on the free base spectrum, but this charge-separation involves more work than that occasioned by the oxonium resonance. In the enolic free base, a resonance similar to the ketonic is not possible, and thus the ketonic form probably predominates.

Treibs (9) has cited evidence (7) that various degrees of porphyrin-acid compounds exist, the ratio of porphyrin:acid varying from 1:1 to 1:5, types greater than 1:2 being addition compounds. He concludes that there are two acid spectral types, the highest and normally observed type being a disalt. The existence of a higher type, however, has been demonstrated here in phylloerythrin, and may be expected in similar compounds such as pheoporphyrin a_5, etc.

In an attempt to find the intermediate type (monosalt) of a typical porphyrin (mesoporphyrin), pyridine-acetic acid spectra have been measured. It is seen (Fig. 8) that the intermediate forms may be calculated by the assumption of a salt/free base ratio, and the addition of the proportionate amount of the corresponding acid and free base curves. (To avoid confusion with the calculated values, the ordinates of the observed mixture have been displaced vertically.) Spectroscopic evidence of an intermediate type has, therefore, not been found. The monosalt must then be formed in such a manner as to have a spectrum identical with that of the free base or the disalt, or its existence must be limited within an extremely short range of acidity. We believe the latter to be more probable for

three reasons. Representing the porphyrin, its mono- and di-salts by structures 1, 2 and 3 respectively (Fig. 9),

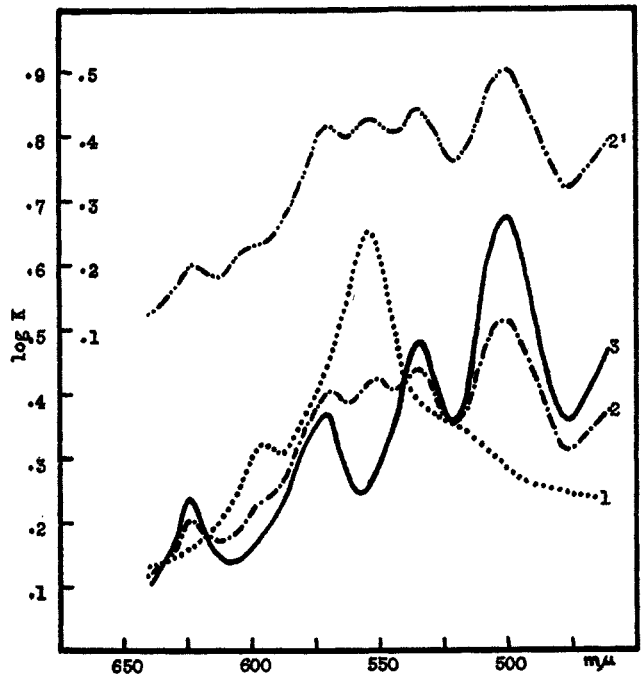


FIG. 8. MESOPORPHYRIN IX

1. Glacial acetic acid. 2. Mixture, calculated, Pyridine-acetic acid (6:4). 2' Mixture, observed. (To avoid confusion with the calculated values, the ordinates of the observed mixture have been displaced vertically.) 3. Pyridine.

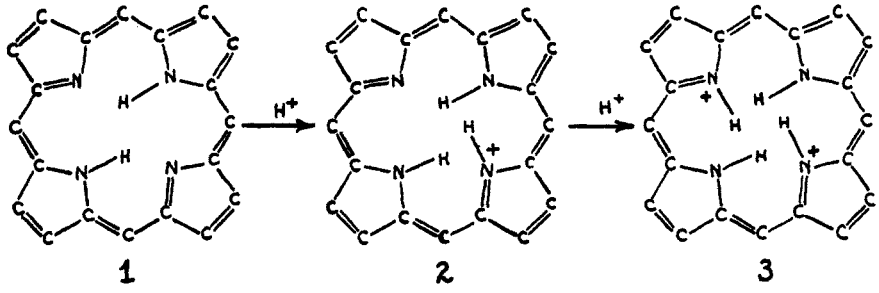


FIG. 9

(a) the spectrum of the monosalt cannot be identical with that of the free base because the addition of the first hydrogen (structure 2) should result in an increase in color (shift to the red) owing to the ease of charge-migration (without charge-separation),

(b) nor can the spectrum of the monosalt be identical with that of the disalt (structure 3) because nitrogen-carbon charge-separated resonance structures and H-tautomers cannot exist in the latter, though they may in the former,

(c) because of the unsymmetrical nature of the monosalt, its existence should be limited to a short range of acidity, on the basis of the work of Schwarzenbach and co-workers (8).

The monosalt spectrum may possibly be determined by appropriate calculations in the narrow region where, by virtue of its presence, the salt/free base curve deviates from calculated values.

SUMMARY

Four porphyrins, etioporphyrin III, mesoporphyrin IX, phylloerythrin and desoxophylloerythrin were studied.

1. Spectroscopic investigation reveals no change in acid form with increasing acidity up to 96% sulfuric acid, except where additional structures may be formed and the resonances increased, as oxonium formation on the ketonic oxygen of phylloerythrin.

2. "Intermediate" types of porphyrin spectra are shown to be mathematically deducible by the addition of the acid and free base curves, assuming a salt/free base ratio.

3. The existence of porphyrin monosalts must be limited within a narrow range of acidity.

The authors wish to acknowledge the criticism and numerous helpful suggestions of Drs. M. Calvin and G. Mackinney.

BERKELEY, CALIF.

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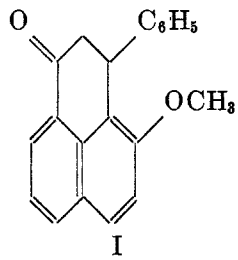
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

STUDIES IN THE PERINAPHTHENE[1] SERIES. IV[2]. SOME ATTEMPTS TO SYNTHESIZE 9-PHENYL-PERINAPHTHANONE-7

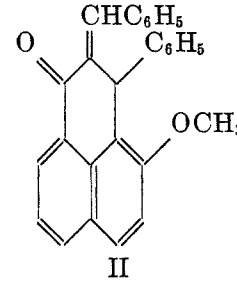
C. F. KOELSCH AND J. A. ANTHES[3]

Received February 24, 1941

Some time ago it was reported (1) that cyclization of β-phenyl-β-(2-methoxynaphthyl)propionyl chloride with aluminum chloride led to 1-methoxy-9-phenylperinaphthanone (I). Although the analytical figures for the product and for its derivatives were in agreement with this formula, other considerations made it possible that the cyclization was accompanied by dehydrogenation and that the product might be a perinaphthenone derivative. The compound has now been found to yield a benzal derivative (II) when treated with benzaldehyde and alkali, and accordingly its structure is definitely that indicated by the analyses.



I



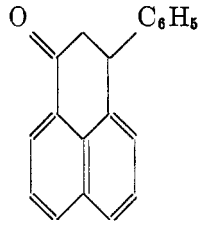
II

With the perinaphthanone structure (I) established, it was desirable to investigate the chemical behavior of the parent ketone III to discover if certain peculiarities of I were also found in the methoxyl-free substance. But none of the syntheses attempted for the preparation of III have yielded this compound. Some attempts which gave results of general interest are described in the present paper.

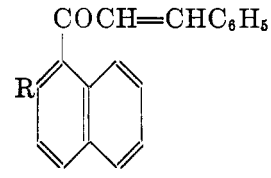
[1] The general title for the papers in this series and the naming and numbering of the compounds concerned have been changed in accordance with recent suggestions on nomenclature (9).

[2] Paper III, KOELSCH AND ROSENWALD, *J. Org. Chem.*, **3**, 462 (1938).

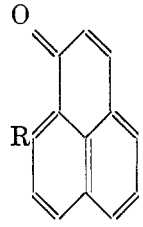
[3] Abstracted from a thesis by J. A. Anthes presented to the Graduate Faculty of the University of Minnesota in partial fulfilment of the requirements for the Ph.D. degree, January, 1939.



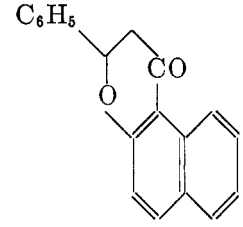
III



IV, R = H
VI, R = OCH_3



V, R = H
VII, R = OH

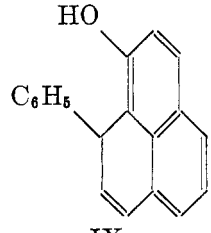


VIII

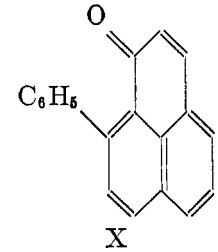
Treatment of cinnamoylnaphthalene (IV) with aluminum chloride has been reported (2) to yield III, but it is now shown that the substance obtained in this way is actually perinaphthenone-7 (V). The synthesis appears to hold some promise as a general method for preparing perinaphthanones, since 1-cinnamoyl-2-methoxynaphthalene (VI) can be converted through an intermediate (VIII) in satisfactory yield into 6-hydroxynaphthenone-7 (VII).

Considered in analogy with the results of Fuson (3) on the reversibility of the Friedel-Crafts reaction and with those of Koelsch and Richter (4) on aromatization through elimination of hydrocarbons from hydroaromatic rings, the elimination of benzene in the present instance is not surprising. However no reasonable hypothesis can be advanced to explain why benzene is not eliminated from I either when this substance is formed or when it is heated with an excess of aluminum chloride.

Another reaction which might have led to III is the one between phenylmagnesium bromide and perinaphthenone-7 (V).



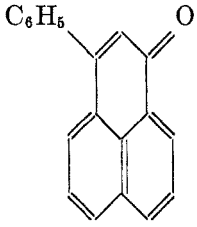
IX



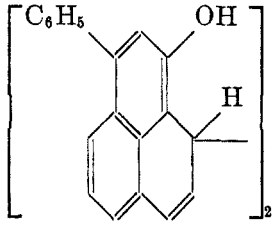
X

The product here, however, is IX, since its dehydrogenation by distillation leads to a phenylperinaphthenone (X) which can be oxidized to the known (5) 2-phenylnaphthalic anhydride. The Grignard reaction thus, in spite of the absence of substituents in the 8 and 9 positions of V, involves the 6,6a rather than the 8,9 double bond of this ketone. It is of the same type as a number of previously studied (5) Grignard additions to perinaphthenones.

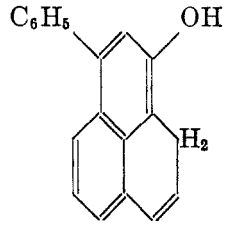
Finally it was hoped that III could be prepared by reduction of 9-phenylperinaphthenone (XI), a ketone which was obtained from 1-benzoylnaphthalene through β-(1-naphthyl)cinnamic acid. The reduction, however, does not involve the 8,9 double bond; it proceeds in two separate stages, in each of which one atom of hydrogen is taken up. The first product (XII), a crystalline red substance, shows a molecular weight in



XI



XII



XIII

melted camphor corresponding to a monomeric radical or semiquinone. But this low molecular weight is considered to be due to disproportionation into XI and XIII, for a solution made from XII in acetic acid has a color whose depth is inversely proportional to dilution. As pointed out by Michaelis (6), such colorimetric measurements can be used to distinguish between semiquinone and dimer formation, since in the former case $K = \frac{(S)^2}{(T)\ (R)}$ and in the latter $K = \frac{D}{(T)\ (R)}$ where T represents an oxidized form, R a reduced form, S a semiquinone, and D a dimer.

The second product (XIII) is a colorless solid. It reacts readily with oxygen to give XII and later XI, but this reconversion to XI is not quantitative; non-crystalline by-products are formed, and more oxygen is taken up than is necessary for oxidation to XI. 9-Phenylperinaphthenone-7 (XI) reacts with an equivalent amount of XIII in ligroin to give XII quantitatively.

At the dropping mercury electrode,[4] XI is reduced, the two reduction potentials found corresponding to the two stages in the process. The curve obtained (Fig. 1) coincides with the one obtained similarly for peri-

[4] We are indebted to Dr. James Lingane for assistance in experiments involving the dropping electrode.

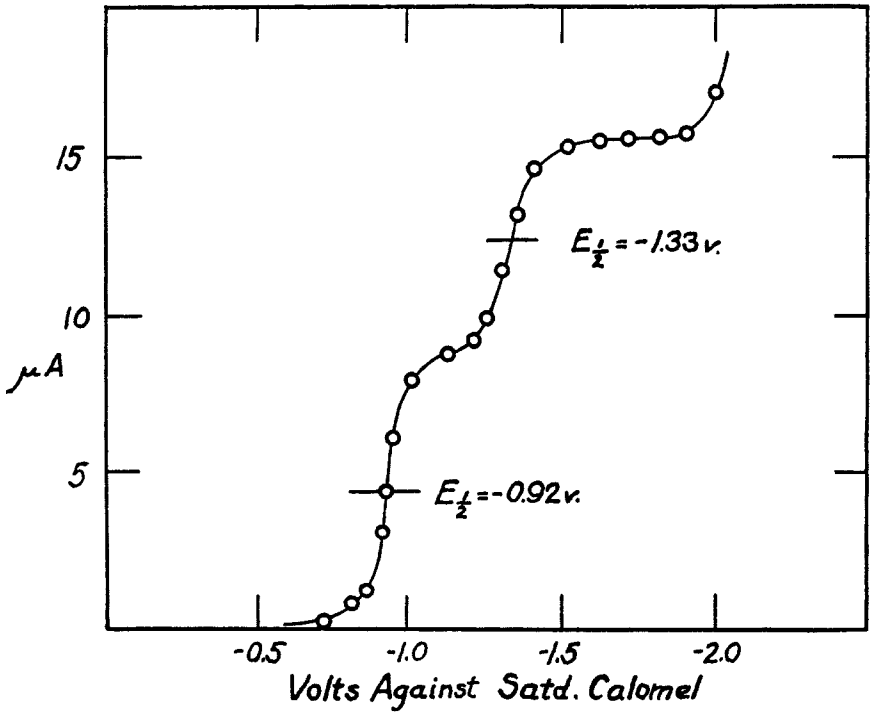


FIG. 1. REDUCTION OF 9-PHENYLPERINAPHTHENONE-7 IN 0.1 *N* LiCl IN 65% ETHANOL, T = 25°, AT THE DROPPING MERCURY ELECTRODE

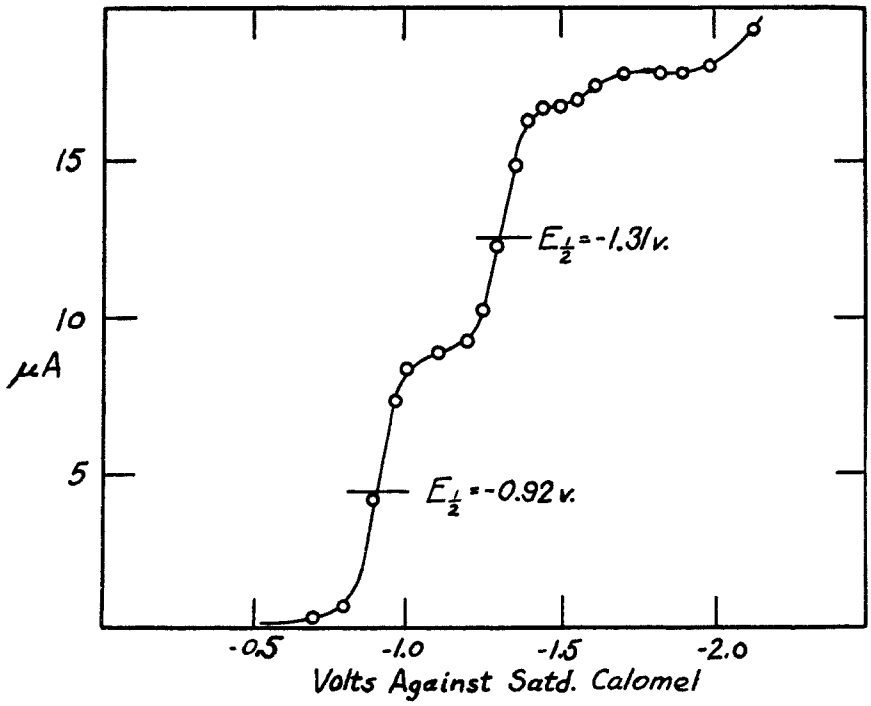


FIG. 2. REDUCTION OF PERINAPHTHENONE IN 0.1 *N* LiCl IN 50% ETHANOL, T = 26°, AT THE DROPPING MERCURY ELECTRODE

naphthenone-7[5] (V) (Fig. 2). This supports the structures already advanced for the reduction products, since if reductioninvolved the 8,9 double bond, thephenylated substances (XI and XII) would have reduc-(ion potentials different from those of the non-phenylated substances tV and its quinhydrone).

EXPERIMENTAL

8-Benzal-1-methoxy-9-phenylperinaphthanone-7 (II). To a solution of benzaldehyde (1 g.), 1-methoxy-9-phenylperinaphthanone-7 (1) (0.2 g.) and sodium hydroxide (5 drops of 40%) in alcohol (15 ml.) was added enough water to cause incipient precipitation. The whole was heated on a steam-bath for twelve hours and then cooled. Treatment of the precipitated oil with alcohol left a solid which was recrystallized from benzene. The product (0.05 g.) formed pale yellow crystals that melted at 168–170°; it gave a deep blue color with concentrated sulfuric acid.

Anal. Calc'd for $C_{27}H_{20}O_2$: C, 86.2; H, 5.4.
Found: C, 86.4; H, 5.4.

Perinaphthenone-7 (V). (*a*) *From 1-cinnamoylnaphthalene.* The Friedel-Crafts reaction between naphthalene (200 g.) and acetyl chloride (200 g.) in carbon disulfide gave a mixture of 1- and 2-acetylnaphthalene boiling at 154–156° (10 mm.), in a yield of 94%. This was separated by treatment with picric acid (7), a yield of 44% of pure 1-acetylnaphthalene being obtained.

A mixture of this ketone (88 g.) and benzaldehyde (64 g.) with a solution of sodium hydroxide (30 g.) in water (270 ml.) and alcohol (190 ml.) was stirred at 15–25° for five hours and finally heated on a steam-bath for a few minutes. On standing, the mixture deposited 1-cinnamoylnaphthalene as a yellow oil which was not obtained crystalline (literature (8), m.p. 105°). A portion of this oil (50 g.) with aluminum chloride (100 g.) in carbon disulfide (200 ml.) was boiled for two hours. The mixture was hydrolyzed with iced hydrochloric acid, and the product was crystallized from benzene-ligroin and then from dilute alcohol. It formed brownish plates (9.4 g.) that melted at 152–154°. An additional crystallization from ligroin gave yellow plates that melted at 153.5–154° alone or mixed with an authentic sample (literature (9), corr. m.p. 156–156.5°).

(*b*) *From cinnamic acid and naphthalene.* A solution of cinnamic acid (40 g.) and naphthalene (40 g.) in benzene (500 ml.) was treated with phosphorus pentachloride (80 g.) and boiled for five minutes. Aluminum chloride (112 g.) was added in portions with cooling, and the whole was then boiled for twenty-five minutes. The aluminum complex was decomposed with iced hydrochloric acid, and the perinaphthenone was extracted from the tarry material in the benzene by washing twice with conc'd hydrochloric acid. It was precipitated by dilution with water and crystallized from benzene; yield, 6 g.

1-Cinnamoyl-2-methoxynaphthalene. A mixture of cinnamic acid (70 g.), 2-methoxynaphthalene (70 g.), phosphorus pentachloride (100 g.), and benzene (400 ml.) was boiled for five minutes, then cooled and treated with aluminum chloride (70 g.) added in small portions. The deep red solution was boiled for ten minutes and then

[5] Reduction of perinaphthenone-7 with zinc and acetic acid was accompanied by color changes similar to those shown by 9-phenylperinaphthenone-7 [*cf.* Fieser and Hershberg, *J. Am. Chem. Soc.*, **60**, 1660 (1938)] but the compounds involved could not be isolated in pure states.

decomposed with iced hydrochloric acid. The benzene was steam distilled and the residue was crystallized from a mixture of chloroform and alcohol. The product (92 g.) formed bright yellow needles that melted at 140–141° (literature (10), 138–140°).

The ketone was also prepared from 1-acetyl-2-methoxynaphthalene and benzaldehyde, but this synthesis was more tedious than that described above.

5,6-Benzoflavanone (VIII). A mixture of 1-cinnamoyl-2-methoxynaphthalene (20 g.), carbon disulfide (150 ml.), and aluminum chloride (10 g.) was stirred at room temperature for four hours, allowed to stand overnight and then worked up in the usual way. The product was separated by crystallization from acetic acid into unchanged cinnamoylnaphthalene (4 g.) and 5,6-benzoflavanone [VIII, 2,3-dihydro-3-phenylnaphtho(2.1-b)pyrone-1, Ring Index No. 2004] (7 g.). The latter substance formed colorless plates that melted at 116–117°. It gave a red color with alcoholic alkali, a brownish-red with ferric chloride, but no test with Folin's reagent.

Anal. Calc'd for $C_{19}H_{14}O_2$: C, 83.1; H, 5.1.
Found: C, 83.0; H, 5.1.

With benzaldehyde and alcoholic alkali, 5,6-benzoflavanone gave a benzal derivative, pale yellow crystals that melted at 164–166°.

Anal. Calc'd for $C_{26}H_{18}O_2$: C, 86.2; H, 5.0.
Found: C, 86.0; H, 5.0.

6-Hydroxperinaphthenone-7 (VII). A mixture of 1-cinnamoyl-2-methoxynaphthalene (20 g.), benzene (300 ml.), and aluminum chloride (18 g.) was stirred and boiled for twenty-five minutes and then decomposed with iced hydrochloric acid. The benzene layer was separated, and hydrogen chloride was passed into it; the hydroxyperinaphthenone hydrochloride which precipitated was filtered and boiled with a mixture of alcohol and chloroform to set free the ketone. The product (8.2 g.) formed golden plates that melted at 200–201°. It formed a sodium salt difficultly soluble in water, and gave a fluorescent green solution in sulfuric acid.

Anal. Calc'd for $C_{13}H_8O_2$: C, 79.6; H, 4.1.
Found: C, 79.3; H, 3.9.

Unsuccessful attempts were made to methylate 6-hydroxyperinaphthenone-7 using the sodium salt and methyl sulfate, the silver salt and methyl iodide, and methanol and hydrogen chloride. Likewise all attempts to acetylate or to benzoylate the compound were unsuccessful.

With aqueous permanganate, first in alkaline then in acidic solution, 6-hydroxyperinaphthenone-7 (1.1 g.) gave the mono-potassium salt of hemimellitic acid (0.7 g.). The acid obtained from this salt melted at 191–192° and with diazomethane gave a methyl ester which melted at 100–102° alone or mixed with an authentic sample of trimethyl hemimellitate.

Addition of phenylmagnesium bromide to perinaphthenone. A solution of perinaphthenone-7[6] (10 g.) in an excess of ethereal phenylmagnesium bromide was boiled for three hours and then decomposed with iced hydrochloric acid. The alkali-soluble oily product was dehydrogenated by distillation under reduced pressure and then crystallized from acetic acid. There was obtained 6.5 g. of 1-phenylperinaphthenone-7 (X) which melted at 145–147°, and on further crystallization at 150–

[6] The ketone used in experiments summarized in this section was prepared both by the method previously described in this paper and by the method of Silberman and Barkov [*J. Gen. Chem. U. S. S. R.*, **7**, 1733 (1937)] using essentially the modifications described by Fieser and Hershberg (9).

152°. It formed orange-yellow crystals which were insoluble in alkali but which gave an orange-yellow solution with green fluorescence in sulfuric acid.

Anal. Calc'd for $C_{19}H_{12}O$: C, 89.0; H, 4.7.
Found: C, 89.1; H, 5.5.

Oxidized in acetone with potassium permanganate (2.5 g.), 1-phenylperinaphthenone-7 (1 g.) was partly recovered unchanged (0.6 g.) and partly converted into 2-phenylnaphthalic anhydride (0.13 g.) which melted at 237–239° alone or mixed with an authentic sample (5).

Synthesis of 9-phenylperinaphthenone-7. A mixture of 1-benzoylnaphthalene (220 g.), ethyl bromoacetate (160 g.), benzene (600 ml.), and granular zinc (60 g.) was warmed to start the reaction, and then boiled for six hours. Dilute hydrochloric acid was added, and the benzene layer was washed and evaporated. A portion of the residue was separated by crystallization from alcohol into 1-benzoylnaphthalene and ethyl β-hydroxy-β-(1-naphthyl)hydrocinnamate. The latter substance formed colorless cubes that melted at 116.5–118° and gave a bright green solution in sulfuric acid.

Anal. Calc'd for $C_{21}H_{20}O_3$: C, 78.8; H, 6.7.
Found: C, 78.5; H, 6.8.

A solution of ethyl β-hydroxy-β-(1-naphthyl)hydrocinnamate (1 g.) in concentrated sulfuric acid (10 ml.) was allowed to stand at room temperature for two hours and then poured into water. The solid was crystallized from ligroin, giving 9-phenylperinaphthenone-7 (0.3 g.) which melted at 142–143° (literature (11), 142–143°).

Anal. Calc'd for $C_{19}H_{12}O$: C, 89.0; H, 4.7.
Found: C, 88.8; H, 4.7.

The bulk of the product from the Reformatsky reaction was boiled with alcoholic potassium hydroxide to recover unchanged 1-benzoylnaphthalene (100 g.). Crude β-hydroxy-β-(1-naphthyl)hydrocinnamic acid was precipitated with hydrochloric acid and was cyclized without further purification. Twenty grams of the substance treated with 180 ml. of cold conc'd sulfuric acid gave 7 g. of 9-phenylperinaphthenone-7.

Reduction of 9-phenylperinaphthenone-7. To a solution of 9-phenylperinaphthenone-7 (2 g.) in acetic acid (25 ml.) and water (5 ml.) was added 0.7 g. of zinc dust. On shaking, the yellow mixture became red and then colorless. The zinc was filtered, and the mother liquor, which rapidly became red, was allowed to stand exposed to air for ten hours, when dark red crystals of 7,7'-bi-(4-phenyl-6-hydroxyperinaphthenyl) (XII) were deposited in good yield. From the mother liquor was recovered a small amount of 9-phenylperinaphthenone-7. Recrystallized from dilute alcohol, the red compound sintered at 124° and melted to a dark red liquid at 127–128°. A solution in melted camphor was orange.

Anal. Calc'd for $C_{38}H_{26}O_2$: C, 88.7; H, 5.1; Mol. wt., 514.
Found: C, 88.3; H, 5.2; Mol. wt. (Rast), 257.

A colorless acetic acid solution obtained by reducing 0.4 g. of 9-phenylperinaphthenone-7 absorbed 15 ml. of oxygen in twenty-two hours and 30 ml. in one hundred hours (calc'd for 1 atom of oxygen per mole, 19.6 ml.). From the dark solution there was then isolated 0.31 g. of pure 9-phenylperinaphthenone-7 and some tarry material.

A column 1 cm. high of an acetic acid solution of XII, sufficiently concentrated that a definite red color was apparent, was placed in each of two colorimeter tubes. To one of these was added acetic acid to a height of 3 cm. The color in the more

dilute solution became orange; viewed through the whole length of the solution, the depth of color was approximately one-third that of the undiluted solution.

4-Phenyl-6-hydroxyperinaphthene (XIII) was obtained by carrying out the reduction of 9-phenylperinaphthenone-7 with zinc and acetic acid in an atmosphere of hydrogen. It was nearly colorless, melted at 136–138° and was soluble in aqueous sodium hydroxide. Since it rapidly became red in air, giving XII, it was not analyzed. Attempts to obtain derivatives by treating XIII with methyl sulfate and alkali, or with diazomethane, or by carrying out the reduction of XI in acetic anhydride-sulfuric acid gave negative results. A ligroin solution of XIII became red on mixing with one containing an equal weight of XI, and the quinhydrone XII was deposited in good yield.

SUMMARY

The structure of 1-methoxy-9-phenylperinaphthanone-7 has been substantiated by conversion of the substance into a benzal derivative, but attempts to synthesize the parent compound, 9-phenylperinaphthanone-7, have been unsuccessful. The attempts were (a) the cyclization of 1-cinnamoylnaphthalene, which gave perinaphthenone-7, (b) the treatment of perinaphthenone-7 with phenylmagnesium bromide, which gave 6-phenylperinaphthenone, and (c) the reduction of 9-phenylperinaphthenone, which gave 4-phenyl-6-hydroxyperinaphthene. The last named compound was of particular interest since it reacted with 9-phenylperinaphthenone-7 to form a quinhydrone.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. V. SYNTHESIS OF 5-ALKYL-α-PYRONES

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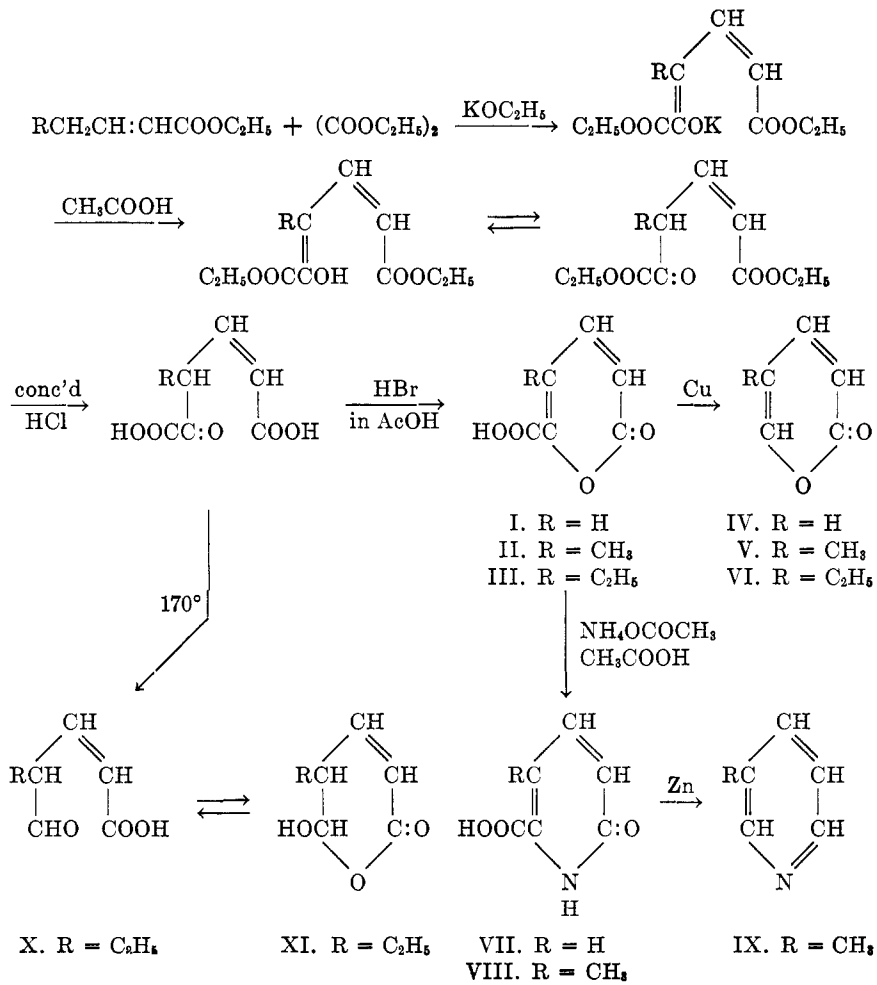
In preceding communications (1) syntheses of model unsaturated lactones related to the digitalis-strophanthus group of cardiac aglycones have been described. While the majority of the cardiac aglycones may be placed in this group on the basis of the structure of the side chain, there exists a smaller group of such drugs the side chain of which consists of an α-pyrone ring carrying the cyclopentanophenanthrene ring system as a substituent in the 5-position of the pyrone ring. This second group is typified by the active principles of the squill (*Scilla maritima*), which are found as glycosides, and of certain toad venoms in which the steroid component is found conjugated with suberylarginine. The elucidation of the structure of scillaridin-A, the aglycone of scillaren-A from the squill is due to the investigations of Stoll and his collaborators (2), while structural studies on the toad venoms have attracted several workers (3, 4, 5). While the presence of the α-pyrone side chain on carbon atom 17 of the cyclopentanophenanthrene ring system has been clearly demonstrated, some doubt remains as to the positions of hydroxyl groups and double bonds in the main ring system of the molecules. The question of relationship between physiological action and structure in the case of scillaridin-A has received some attention from Stoll (2), who showed that, in general, the intact α-pyrone side chain is necessary for full cardiotonic action of the drug. Chen, Chen, and Anderson (6) found that simple lactones related to α-pyrone such as coumarin and dehydracetic acid, were completely devoid of activity. We have, therefore, taken up the question of the synthesis of 5-substituted α-pyrones in the hope that direct synthetic methods may be made available for preparing such derivatives for pharmacological study.

Since the classical investigations of von Pechmann (7) on coumalin and of Hantzsch (8) and Anschütz, Bendix, and Kerp (9) on mesitenlactone, the chemistry of α-pyrone and its substitution products, aside from the coumarins, has met with but occasional interest. The first systematic synthesis of such an α-pyrone derivative, 6-phenylcoumalin, which has been obtained from coto bark, has been described only recently by Kalff (10). Two possible approaches to the synthetic problem are open, *viz.*,

ring-closure of an appropriately substituted open-chain aldehydo acid, or its equivalent, and transformations of an α-pyrone already carrying a reactive group in the 5-position. In the present paper we present the results of an exploration of the first of these general methods. A partial preliminary report dealing with this subject has appeared (11).

Borsche and Manteuffel (12) have described the condensation of ethyl formate with ethyl crotonate in the presence of potassium ethoxide. The expected product of such a reaction would be ethyl γ-formylcrotonate, which in turn can be considered as the ethyl ester of the hydroxy acid arising from saponification of α-pyrone. The product of the reaction was described as a yellow oil, in which the presence of ethyl γ-formylcrotonate



was indicated by a strong ferric chloride color test and by the preparation of a dinitrophenylhydrazone, although the formyl ester was not isolated in the pure state. If one then were to use a γ-substituted crotonic ester in a similar manner, ring-closure of the γ-substituted γ-formyl crotonic acid would lead to a 5-substituted α-pyrone. We have repeated the experiment of Borsche and Manteuffel and conclude that the formyl crotonic ester is present in the yellow oil in such small proportions as to make this synthesis impractical. The small yield of dinitrophenylhydrazone and rapid increase in viscosity of the product on standing indicate that extensive polymerization of the primary reaction product readily occurs. The use of ethyl $\Delta^{\alpha,\beta}$-hexenoate gave equally unpromising results.

The difficulties caused by the ready polymerization of the formylcrotonate were overcome by use of the corresponding oxalyl derivatives. Lapworth (13) and Prager (14) condensed ethyl oxalate with ethyl crotonate, and Lapworth closed the ring in the condensation product by treatment with hydrochloric acid, after hydrolysis of the ester groups. He assigned the structure of α-pyrone-6-carboxylic acid (I) to the product of the ring closure, although rigid proof for this was lacking. Decarboxylation of the pyrone acid yielded only traces of α-pyrone (IV) in amounts too small for identification. Likewise, attempts to prepare a pyridone derivative, a reaction characteristic of α-pyrones, were unsuccessful. We have been able to carry out these two reactions, thus proving the correctness of Lapworth's assumption. Decarboxylation of α-pyrone-6-carboxylic acid was accomplished with satisfactory yields of α-pyrone by the use of copper powder, a reagent which has been used for the similar decarboxylation of γ-pyrone acids by Willstätter and Pummerer (15). The resulting α-pyrone was identified by its maleic anhydride addition compound. This procedure offers a more convenient method for the preparation of α-pyrone than the somewhat cumbersome method of von Pechmann (7). It is interesting to note that coumalic acid could not be decarboxylated under similar conditions. α-Pyrone-6-carboxylic acid was converted into 2-pyridone-6-carboxylic acid (VII) by the method of Leben (16), using ammonium acetate and glacial acetic acid.

The practicality of the general method having been shown, we have applied it to the preparation of 5-methyl- and 5-ethyl-α-pyrone from ethyl $\Delta^{\alpha,\beta}$-pentenoate and ethyl $\Delta^{\alpha,\beta}$-hexenoate respectively. Both unsaturated esters condense with ethyl oxalate in the presence of potassium ethoxide (17), although contrary to Borsche and Manteuffel (12), who used two moles of potassium ethoxide per mole of ester, we find that the use of one mole of condensing agent results in superior yields. When the resulting oxalyl esters were boiled with concentrated hydrochloric acid no ring closure took place in contrast to the behavior of the unsub-

stituted crotonic ester derivative. The ester groups only were eliminated by hydrolysis. The desired ring closure was accomplished by heating the free oxalyl acids with a solution of hydrogen bromide in acetic acid in sealed tubes. Other reagents which normally lactonize γ- and δ-keto acids were without effect on the substituted oxalyl acids. Such resistance to lactonization is not unexpected. The enol form of the acid must be assumed as an intermediate and the substituted acids would be expected to show less enolization, just as a β-keto ester carrying an alkyl substituent on the α-carbon atom is less enolized than an unsubstituted one, since the

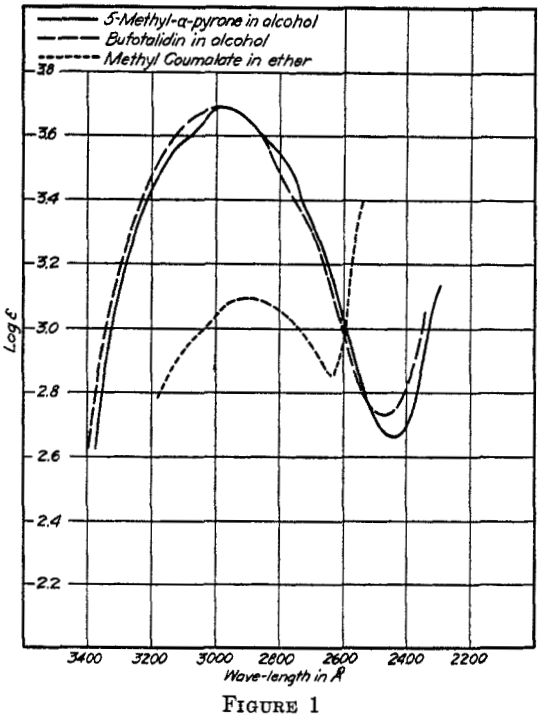


FIGURE 1

compounds under consideration are vinylogs of oxalo-acetic acids. The ultraviolet absorption curve for 5-methyl-α-pyrone is shown in Fig. 1 along with that for bufotalidine (3 g) and methyl coumalate (18), from which the effect of the conjugation of the carboxyl group in the latter with the ring double bonds is apparent and the identity of the pyrone ring of the model substances with that of the natural drugs is evident.

The application of the above synthesis to the preparation of α-pyrones containing a saturated cyclic substituent in the 5-position was not successful. Cyclohexylacetaldehyde was conveniently prepared from cyclo-

hexylmethylmagnesium bromide and ethyl orthoformate with hydrolysis of the acetal first formed. This on condensation with malonic acid readily gave γ-cyclohexylcrotonic acid. However we were unable to accomplish the condensation of the ethyl ester of the latter acid with ethyl oxalate using potassium ethoxide. The use of such bases as triphenylmethylsodium (19) and mesitylmagnesium bromide (20) likewise failed to yield the expected condensation product. We therefore conclude that the inhibiting effect of alkyl substituents in vinylogous esters on the ester condensation is more pronounced than in saturated esters.

In the course of attempts to lactonize the oxalylcrotonic acids, simple pyrolysis was used. When 4-ethyl-2-hexene-5-one-1,6-dioic acid was heated to 170° a rapid evolution of carbon dioxide occurred and a brown oil was left. On distillation this gave a viscous oil which, in spite of failure to secure satisfactory analytical data, we consider to have the structure of γ-ethyl-γ-formyl crotonic acid and to arise by decarboxylation of the α-keto acid in the usual manner. As a γ-aldehydo acid this can exist in either the open aldehydo acid (X) or hydroxy lactone form (XI). When heated with acetic anhydride, the acetate of the hydroxy lactone was formed and the characteristic ferric chloride test of the formyl acid disappeared. This derivative is characteristic for γ-aldehydo acids (21). In addition to the aldehydo acid, a small amount of pyrone acid was found among the less volatile products of the pyrolysis reaction.

EXPERIMENTAL

All melting points and boiling points are corrected for stem exposure except as noted.

Diethyl 4-methyl-2-hexene-5-one-1,6-dioate. To a potassium ethoxide solution prepared from 7.8 g. of potassium and 34 cc. of absolute alcohol in 50 cc. of dry ether was added a solution of 29.2 g. of pure ethyl oxalate in 20 cc. of dry ether dropwise and with careful exclusion of moisture. The mixture was kept at 0°. After 15 minutes a solution of 26 g. of ethyl $\Delta^{\alpha,\beta}$-pentenoate (22) in 20 cc. of dry ether was added in the same way with shaking. The color of the solution immediately changed from a light orange to an intense yellow and the crystalline yellow potassium salt of the condensation product separated after about 15 minutes. Crystallization was complete after 15 hours in the refrigerator. The thick yellow mass was stirred up with its own volume of petroleum ether (Skellysolve B), the salt was removed by filtration and thoroughly washed with petroleum ether. After drying over paraffin the salt weighed 31 g. which corresponds to 65% yield. The potassium salt was dissolved in about 750 cc. of ice water and ice-cold dilute acetic acid was added until precipitation of the free ester was complete. The mixture was refrigerated for several hours and the white, voluminous precipitate was then filtered and washed with ice water. Since this ester and others of the same type decompose very readily at room temperature, they should be used immediately for the subsequent step without drying. However, the material may be stored in a vacuum desiccator in the refrigerator for several months. The crude product consists of at least two isomeric forms, probably

cis-trans isomers with respect to the 4,5-double bond of the enol form. The higher-melting isomer crystallized from petroleum ether in long needles and melted at 66–68°. The yield was 23.5 g. or 90%. The ester gave a dark brown color in alcoholic ferric chloride solution.

Anal. Calc'd for $C_{11}H_{16}O_5$: C, 57.9; H, 7.1.
Found: C, 58.1; H, 7.2.

The *2,4-dinitrophenylhydrazone* of the above ester crystallized as orange leaflets from dilute alcohol and melted at 116–117°.

Anal. Calc'd for $C_{17}H_{20}N_4O_8$: N, 13.7. Found: N, 13.9.

4-Methyl-2-hexene-5-one-1,6-dioic acid. Ten grams of diethyl 4-methyl-2-hexene-5-one-1,6-dioate was shaken with 50 cc. of conc'd hydrochloric acid at about 60–70° until completely dissolved. The slightly yellow solution was then refluxed for one hour and decolorized with charcoal (Norit). The solvent was removed under reduced pressure during which the acid started to crystallize. The acid may be recrystallized from conc'd hydrochloric acid or from a mixture of acetone and petroleum ether and melts at 161–162°. It is very soluble in water and acetone, sparingly soluble in chloroform and petroleum ether, and gives a strong violet color with aqueous ferric chloride solution. For subsequent steps the well-dried, crude acid was used.

Anal. Calc'd for $C_7H_8O_5$: C, 48.9; H, 4.7.
Found: C, 49.2; H, 4.8.

The p-*bromophenacyl ester* of the above acid was recrystallized from alcohol and melted at 157–159°. It gave no color test with ferric chloride.

Anal. Calc'd for $C_{23}H_{18}Br_2O_7$: C, 48.8; H, 3.2.
Fonud: C, 49.1; H, 3.3.

5-Methyl-6-carboxy-α-pyrone (II). Nine grams of crude 4-methyl-2-hexene-5-one-1,6-dioic acid was heated in a sealed tube with 30 cc. of glacial acetic acid, which had been previously saturated with dry hydrogen bromide at 0°, for two hours at 150°. The tube opened without pressure, and large prisms of the pyrone acid filled the dark brown solution. The solution and crystals were transferred to a flask and the solvent was removed under reduced pressure. The crystalline residue was taken up in water, decolorized with charcoal, and again concentrated to a small volume. The pyrone acid crystallized from a small volume of water as yellowish prisms and melted at 209–211°. After working the mother liquors, a total of 5.3 g. or 66% was obtained. The acid may also be recrystallized from glacial acetic acid or acetone. About 1 g. of starting material, which is more soluble in water, was recovered from the aqueous mother liquors. The pyrone acid gave no ferric chloride test.

Anal. Calc'd for $C_7H_6O_4$: C, 54.5; H, 3.9.
Found: C, 54.9; H, 4.1.

The *methyl ester* of the above acid was prepared with diazomethane. It formed large prisms from acetone and melted at 130–131°.

Anal. Calc'd for $C_8H_8O_4$: C, 57.2; H, 4.8.
Found: C, 57.2; H, 4.9.

5-Methyl-α-pyrone (V). Two hundred and fifty milligrams of 5-methyl-6-carboxy-α-pyrone was intimately mixed with 2.5 g. of freshly reduced copper powder and placed in a Pyrex tube 10 mm. in diameter and sealed at one end. The tube was bent at an angle of about 30° about 10 cm. from the sealed end. A layer of pure copper powder was placed above the mixture until the tube was filled up to the bend. The mixture was slowly heated with a free flame starting with the upper end and slowly moving the flame downward. A yellow distillate which amounted to 150 mg. or 84% collected in the open end of the tube. Distillation of this yielded a mobile, heavy, colorless oil of high dispersion, which solidified in a bath of cold water and

melted at 17–19°. The pyrone is soluble in most organic solvents and in water; it dissolves in alkali with a yellow color, and deposits silver from an ammoniacal silver solution after a short time. This and other α-pyrones of low molecular weight have a characteristic odor of fresh hay. n_D^{25} 1.5210.

Anal. Calc'd for $C_6H_6O_2$: C, 65.4; H, 5.5.
Found: C, 65.0; H, 5.6.

The *maleic anhydride addition compound* of the above α-pyrone was prepared from 100 mg. of the pyrone and 100 mg. of maleic anhydride in 2 cc. of dry toluene according to Diels and Alder (23). After recrystallization from acetone the substance melted at 194.5–195.5° with decomposition.

Anal. Calc'd for $C_{10}H_8O_5$: C, 57.7; H, 3.9.
Found: C, 57.6; H, 4.0.

3-Methyl-6-hydroxypicolinic acid (VIII). One gram of 5-methyl-6-carboxy-α-pyrone was refluxed with 1 cc. of glacial acetic acid, 1 cc. of acetic anhydride and 1 g. of dry ammonium acetate for 2.5 hours. The cooled melt was evaporated to dryness *in vacuo* and the residue was taken up in about 5 cc. of water. The pyridone acid was liberated from its ammonium salt by the addition of dilute hydrochloric acid and was recrystallized from very dilute alcohol with use of charcoal. The yield was 400 mg. The acid decomposes at about 290–300° and gives a yellow-to-red color with ferric chloride in water or acetone solution.

Anal. Calc'd for $C_7H_7N\ O_3$: C, 54.9; H, 4.6; N, 9.2.
Found: C, 54.9; H, 4.6; N, 9.4.

The position of the methyl group in the above acid was shown by conversion to β-picoline (IX) by zinc dust distillation. Thirty milligrams of the acid was heated with excess zinc dust in a bent tube sealed at one end. A drop of distillate of strong pyridine-like odor was obtained from which a picrate melting at 148–149°, and a gold salt melting at 185–188° (uncorrected) were prepared. Schwarz (24) reports these two derivatives of β-picoline as melting at 149–150° and 186° (uncorrected) respectively.

Diethyl 4-ethyl-2-hexene-5-one-1,6-dioate. This ester was prepared from ethyl oxalate and ethyl $\Delta^{\alpha,\beta}$-hexenoate (25) as described for the lower homolog. The yellow crystalline potassium salt formed along the walls of the flask when the reaction mixture was refrigerated for 18 hours. The average yield from several experiments was 30%. The free enol ester, obtained in 70–75% yield from the potassium salt, was recrystallized from petroleum ether and formed fine white needles which melted at 72–74°. Further recrystallization lowered the melting point to 58–59°. Both products gave identical analyses, indicating the presence of keto-enol tautomers or *cis-trans* isomers. The ferric chloride test in alcohol was dark brown.

Anal. Calc'd for $C_{12}H_{18}O_5$: C, 59.5; H, 7.5.
Found: For the substance melting at 58–59°: C, 59.4; H, 7.6.
For the substance melting at 72–74°: C, 59.6; H, 7.7.

The *2,4-dinitrophenylhydrazone* of the above ester crystallized as fine, yellow needles from dilute alcohol and melted at 102–105°.

Anal. Calc'd for $C_{18}H_{22}N_4O_8$: C, 51.2; H, 5.3.
Found: C, 51.3; H, 5.2.

4-Ethyl-2-hexene-5-one-1,6-dioic acid. This was prepared as described for the lower homolog and was recrystallized from conc'd hydrochloric acid. It formed colorless needles and melted at 116–119°. The acid gave a purple color with aqueous ferric chloride solution.

Anal. Calc'd for $C_8H_{10}O_5$: C, 51.6; H, 5.4.
Found: C, 51.4; H, 5.4.

The p-*bromophenacyl ester* of the above acid crystallized as colorless needles from dilute alcohol and melted at 115–116°.

Anal. Calc'd for $C_{24}H_{20}Br_2O_7$: C, 49.7; H, 3.5.
Found: C, 50.0; H, 3.6.

5-Ethyl-6-carboxy-α-pyrone (III). This was prepared as described for the lower homolog. It formed colorless needles melting at 158–159° from conc'd hydrochloric acid or petroleum ether and ether.

Anal. Calc'd for $C_8H_8O_4$: C, 57.2; H, 4.8.
Found: C, 57.6; H, 4.9.

The p-*bromophenacyl ester* of the above pyrone acid melted at 113–114° after crystallization from alcohol.

Anal. Calc'd for $C_{16}H_{13}BrO_5$: C, 52.7; H, 3.6.
Found: C, 52.5; H, 3.8.

5-Ethyl-α-pyrone (VI). This was prepared in the same manner as the corresponding methyl derivative. The yield of crude product was 80%. Distillation gave a colorless oil, slightly soluble in water and miscible with the usual organic solvents. n_D^{25} 1.5137.

Anal. Calc'd for $C_7H_8O_2$: C, 67.7; H, 6.5.
Found: C, 67.5; H, 6.7.

The *maleic anhydride addition compound* of 5-ethyl-α-pyrone formed thin plates from acetone-petroleum ether and melted at 161–162°.

Anal. Calc'd for $C_{11}H_{10}O_5$: C, 59.4; H, 4.5.
Found: C, 59.5; H, 4.6.

α-Pyrone (IV). α-Pyrone-6-carboxylic acid (13) was decarboxylated as described above. α-Pyrone was obtained in 80 to 85% yield as a colorless oil which solidified in an ice-bath. It was identical in every respect with von Pechmann's coumalin (7); n_D^{25} 1.5272.

Anal. Calc'd for $C_5H_4O_2$: C, 62.5; H, 4.2.
Found: C, 62.5; H, 4.5.

α-Pyridone-6-carboxylic acid (VII) was obtained in good yield when 700 mg. of α-pyrone-6-carboxylic acid was refluxed with 700 mg. of dry ammonium acetate and 1.4 cc. of glacial acetic acid for 2 hours. The reaction mixture was worked up as described for the methyl derivative. After purification with the aid of charcoal the acid crystallized from water in colorless needles which decomposed at about 280°. Fischer, Hess, and Stahlschmidt (26) give 284° as the decomposition point of α-pyridone-6-carboxylic acid.

Anal. Calc'd for $C_6H_5NO_3$: N, 10.1. Found: N, 10.3.

On distillation of the above acid with zinc dust a liquid of strong pyridine-like odor was obtained. The picrate prepared from the latter melted at 163° and gave no depression in melting point when mixed in varying proportions with known pyridine picrate.

γ-Formyl-γ-ethylcrotonic acid (X). Three and six-tenths grams of 4-ethyl-2-hexene-5-one-1,6-dioic acid was heated in an atmosphere of nitrogen to 170–180°. A rapid evolution of carbon dioxide occurred which practically ceased after about 2 hours. The reaction mixture was fractionally distilled under reduced pressure and gave a pale yellow oil which boiled at 97–98° at 0.5 mm. The oil was miscible with water, gave a strong purple color with ferric chloride solution and a positive Tollens test. On exposure to the air large prismatic crystals appeared in the oil. These melted at 100–104° and gave no test with ferric chloride. The crystalline material was exceedingly hygroscopic and had a relatively low carbon content (about 27%). The compound was not investigated further at this time. The formation of this

crystalline compound could not be prevented completely, which rendered the carbon figures for the yellow oil low. Neutralization equivalent for the oil: Calc'd: 142; Found: 142, 143, 143; n_D^{25} 1.4868.

Anal. Calc'd for $C_7H_{10}O_3$: C, 59.1; H, 7.1.
Found: C, 57.4, 57.9; H, 7.5, 7.1.

The acetate of the hydroxyl actone form of the above acid was prepared by refluxing 300 mg. of the acid with 5 cc. of acetic anhydride. The reaction product was distilled at 1 mm. pressure, yielding a colorless oil which solidified at 15° and gave no color with ferric chloride solution. Titration with 0.01 *N* alkali indicated the presence of a labile acetoxy lactone structure. Neutralization equivalent: Calc'd: 92; Found: 94, 92. After neutralization of the saponified material the Tollens test was positive and a purple color was given by ferric chloride.

Anal. Calc'd for $C_9H_{12}O_4$: C, 58.8; H, 6.6.
Found: C, 58.8; H, 6.6.

Diethylacetal of cyclohexylacetaldehyde. To the Grignard reagent prepared from 85 g. of cyclohexylmethyl bromide and 13 g. of magnesium in 170 cc. of dry ether was added 74 g. of ethyl orthoformate within 5 minutes with stirring. After refluxing the mixture for 2 to 3 hours, the reflux condenser was set downward for distillation and the ether was distilled off on the steam-bath. At this point the mixture in the flask had separated into an upper light, colorless liquid and a lower dark, viscous layer. While still hot the contents of the flask were poured into ice-cold dilute acetic acid. The viscous bottom layer of the reaction mixture usually solidified completely and was decomposed with fresh portions of cold dilute acetic acid. The organic material was separated and the aqueous solution was extracted with ether, the extracts being added to the material originally separated. The combined product was well washed with sodium bicarbonate solution, dried with anhydrous magnesium sulfate, and fractionally distilled under reduced pressure. The fraction boiling at 96–101° at 11 mm. was collected as the desired acetal. The yield was 56–60%; n_D^{25} 1.4390.

Anal. Calc'd for $C_{12}H_{24}O_2$: C, 72.0; H, 12.1.
Found: C, 72.5; H, 12.4.

Cyclohexylacetaldehyde. For the preparation of the aldehyde the crude acetal as obtained above may be used. The acetal was hydrolyzed by boiling with 5% hydrochloric acid in an atmosphere of nitrogen for 2 hours. The aldehyde layer was separated and the aqueous solution was extracted with ether, the extracts being added to the main portion of the aldehyde. After washing and drying with anhydrous magnesium sulfate, the aldehyde was distilled at reduced pressure, the portion boiling at 57–58° at 10 mm. being collected. This boiling point differs from the value of 79–80° reported by Skita (27). The yield was 47% based on the halide used for the preparation of the Grignard reagent; n_D^{25} 1.4509.

Cyclohexylacetaldehyde semicarbazone crystallized as leaflets from dilute alcohol and melted at 158–159°.

Anal. Calc'd for $C_9H_{17}N_3O$: C, 59.0; H, 9.4.
Found: C, 59.1; H, 9.0.

The *2,4-dinitrophenylhydrazone* melted at 124–125° after recrystallization from alcohol.

Anal. Calc'd for $C_{14}H_{18}N_4O_4$: C, 54.9; H, 5.9.
Found: C, 55.0; H, 5.9.

γ-Cyclohexylcrotonic acid. To a solution of 15 g. of dry malonic acid in 25 cc. of dry pyridine was added 13 g. of cyclohexylacetaldehyde. A boiling-stone was placed

in the solution and the flask was connected to a reflux condenser the top of which was protected by a calcium chloride tube. The mixture was allowed to stand at room temperature for about 3 days, or until evolution of carbon dioxide ceased. The condensation was completed by heating the mixture on the steam-bath for 5 hours. The dark red solution was cooled and poured into well-stirred, ice-cold 50% sulfuric acid. A rapidly crystallizing oil separated which was filtered off after standing for several hours in the refrigerator. The crude dried product amounted to 15.3 g. or 88%. The acid was recrystallized from petroleum ether and formed prisms which melted at 54-55°.

Anal. Calc'd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6.
Found: C, 71.7; H, 9.9.

The *amide* of the above acid crystallized from very dilute alcohol as leaflets and melted at 143-144°.

Anal. Calc'd for $C_{10}H_{17}NO$: C, 71.8; H, 10.3; N, 8.4.
Found: C, 72.1; H, 10.3; N, 8.6.

Ethyl γ-cyclohexylcrotonate was prepared from the crude acid with alcohol and sulfuric acid. The ester boiled at 95-97° at 0.8 mm. n_D^{25} 1.4687. The ester as thus prepared added a slight amount of bromine in acetic acid solution, which indicates the presence of contaminating $\Delta^{\beta,\gamma}$ isomer.

Anal. Calc'd for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3.
Found: C, 73.6; H, 10.4.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. The synthesis of α-pyrones by ring closure of γ-formylcrotonic acids is not practical because of the instability of the esters of such acids.

2. An improved simple synthesis of α-pyrone from γ-oxalylcrotonic acid has been described.

3. Ring closure of γ-oxalylcrotonic acids containing a primary alkyl substituent in the γ-position readily yields 5-substituted 6-carboxy-α-pyrones. These, in turn, can be easily decarboxylated by the copper method to yield 5-substituted α-pyrones.

4. Crotonic esters containing a secondary substituent in the γ-position do not condense readily with ethyl oxalate.

5. A satisfactory synthesis for cyclohexylacetaldehyde and for γ-cyclohexylcrotonic acid has been described.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. VI. THE ACTION OF DIAZOMETHANE ON CERTAIN DERIVATIVES OF α-PYRONE

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In the preceding paper (1) successful syntheses for 5-substituted α-pyrones carrying a primary alkyl substituent were described. The method failed when applied to the preparation of similar α-pyrones carrying a secondary substituent such as the cyclohexyl group. We have accordingly investigated certain reactions whereby it was hoped to utilize an available α-pyrone derivative already carrying a reactive substituent in the 5-position. The only such pyrone derivative at present available is the 5-carboxylic acid, or coumalic acid, which is readily available by von Pechmann's synthesis (2), and which offers attractive possibilities for the purpose in mind.

Von Pechmann (2) treated coumalic acid (I) with phosphorus pentachloride and obtained a crystalline solid which he considered to be impure coumalyl chloride, although it still contained phosphorus. Meyer (3) reported that the action of thionyl chloride on coumalic acid resulted in the formation of the chloride of formylglutaconic acid as a result of ring cleavage. In reinvestigating the action of thionyl chloride on coumalic acid we now find that, if scrupulously purified thionyl chloride is used, a single crystalline product is obtained. When this is heated with methyl alcohol, methyl coumalate is formed. The product of the reaction between thionyl chloride and coumalic acid is, therefore, the normal acid chloride (II), and not the acid chloride of the product of ring cleavage as reported by Meyer. Having thus obtained coumalyl chloride, it was hoped to proceed from it by means of the diazomethyl ketone which should result from treatment of the acid chloride with diazomethane. In this we have been partially unsuccessful because of the appearance of a remarkable reactivity of the carbon atom in the 6-position of certain α-pyrone derivatives.

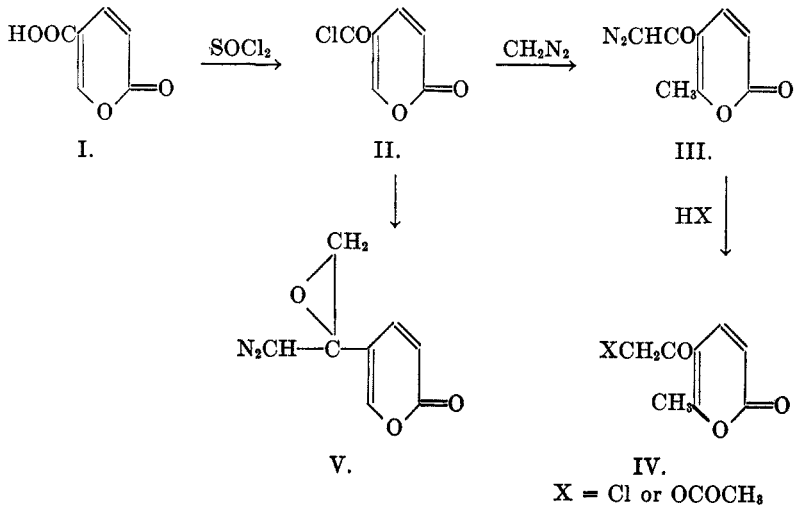
When coumalyl chloride is treated with an ethereal solution of diazomethane the desired diazomethyl ketone is formed. However, an additional methylene group is introduced into the molecule, and, as will be shown, this results from methylation in the 6-position. The product of the

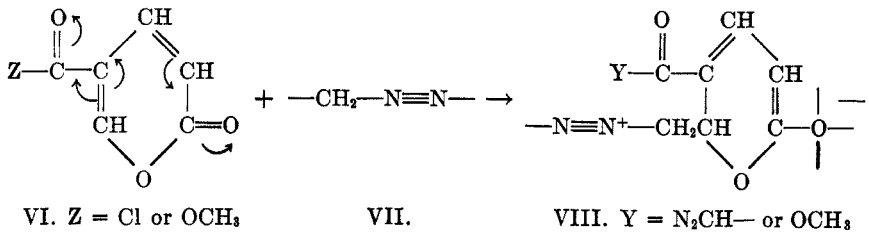
reaction thus has the structure represented by III. When the diazo methyl ketone is subjected to the action of hydrochloric or acetic acids, the normal chloromethyl and acetoxymethyl ketones are formed respectively (IV). The 6-methyl group is, of course, retained.

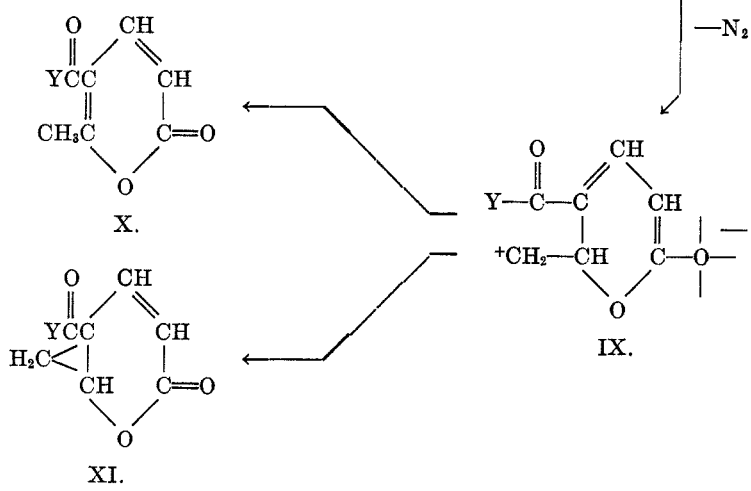
The point of methylation of coumalyl chloride could not be inferred from existing data on the substance, or on other α-pyrone derivatives. The action of diazomethane did not apparently involve rupture of the pyrone ring, since qualitative tests for α-pyrones, such as the yellow-to-blood-red color produced by alkali, which changes to purple on neutralization and treatment with ferric chloride, were still exhibited by the product. Admitting that the ring system is still intact after the diazomethane reaction, the remaining possibilities involve nuclear methylation of the pyrone ring in any one of the free positions, or attack of the carbonyl group of the diazomethyl ketone to yield an ethylene oxide (V). V should lead to a chlorohydrin on treatment with hydrochloric acid, and therefore may be eliminated from consideration by its failure to do so. Of the nuclear positions available for methylation, position 6 seemed the most likely point of attack by the following argument.

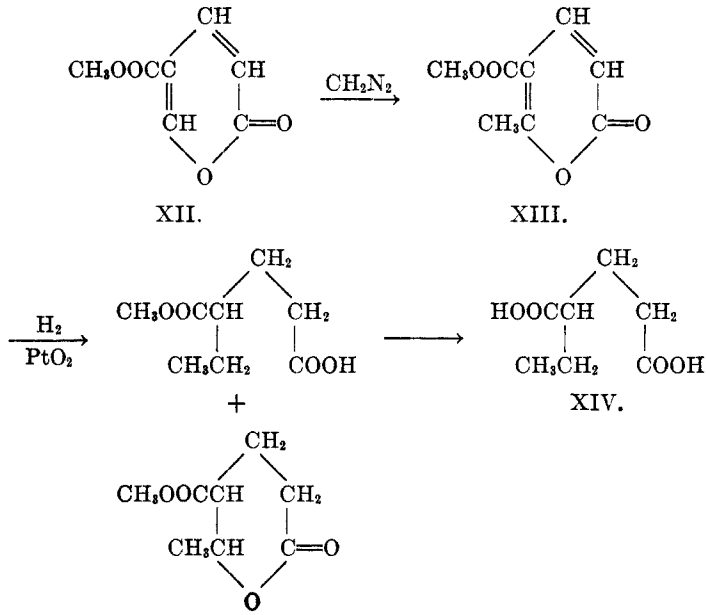
Coumalyl chloride may be represented by the resonance formula VI, from which it can be inferred that carbon atom 3 carries a residual negative charge, while carbon atoms 4 and 6 carry residual positive charges. In methylation reactions, diazomethane reacts in its resonance form, VII; its free electron pair would tend to attach itself to some electrophilic group such as carbon atom 4 or 6, but not to carbon atom 3. Of the likely possibilities, carbon atom 6 seems preferable since it is activated by both carbonyl groups. Therefore the reaction with diazomethane would yield VIII, which contains its nitrogen in the form of the nitrogen molecule. As such, nitrogen is easily lost to yield IX, which, in turn, can equalize its charge in two ways with the formation of either X or XI. Only the product corresponding to X was isolated from the reaction mixture but the uniform occurrence of some oily products of these reactions does not exclude the possibility that XI might also have been formed. This mechanism is similar to that suggested by Arndt and Eistert (4) for the Schlotterbeck reaction, to which the present case is analogous.

In order to substantiate the above conclusions, methyl coumalate (XII), the electron distribution of which is closely similar to that of coumalyl chloride, was treated with diazomethane. A vigorous reaction ensued and the reaction product which was isolated showed the presence of one additional methylene group. The structure of the substance (XIII) was demonstrated by catalytic reduction with platinum oxide. According to Stoll (5) and Wieland (6), α-pyrones on catalytic hydrogenation undergo


HOOC
SOCl2
ClCO
CH2N2
N2CHCO
CH3
O
I.
II.
III.
HX
CH2
N2CH
XCH2CO
V.
IV.
X = Cl or OCOCH3


Z
CH
CH2—N≡N—
Y
N≡N+—CH2CH
VI. Z = Cl or OCH3
VII.
VIII. Y = N2CH— or OCH3


—N2
YCC
CH3C
H2C
+CH2—CH
X.
IX.
XI.



ring cleavage to a greater or less extent to yield the saturated desoxy acid, as well as the saturated lactone, which behavior is characteristic of lactones of enolized aldehydo or keto acids (7). XIII reacted in the expected manner to give approximately seven parts of acid product and three parts of neutral material. The acid product, after hydrolysis, gave a dibasic acid which was identified as α-ethylglutaric acid (XIV). The neutral fraction, which can hardly be other than the saturated lactone, XV, was not further investigated. In view of the close analogy of the reaction of methyl coumalate with diazomethane with the similar reaction of coumalyl chloride with diazomethane, we believe that the latter reaction is correctly represented by II–IV.

The presence of an electronegative substituent in the 5-position of the pyrone is a necessary condition for the above reaction with diazomethane. This was demonstrated by the behavior of 5-methyl-α-pyrone under similar circumstances. No reaction was apparent and the original 5-methyl-α-pyrone was recovered. This was shown by catalytic hydrogenation of the material recovered from the reaction. The acid thus obtained was the six carbon atom acid, isocaproic acid, and was characterized by its piperazonium salt.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Coumalyl chloride (II). Thirty grams of finely powdered crude coumalic acid was refluxed with 60 cc. of pure thionyl chloride until all the solid had gone into solution.

The excess thionyl chloride was removed under reduced pressure leaving a dark red-brown residue which solidified on cooling. This was extracted with several 250-cc. portions of petroleum ether (Skellysolve B). The extracts were combined and, on cooling, the coumalyl chloride crystallized as stout, yellowish prisms. After 3 extractions with fresh solvent, the mother liquors were used again, so that not more than 750 cc. of petroleum ether was used in the whole operation. The yield was 23 g. of material which melted at 74–75° and which was sufficiently pure for subsequent reactions. An analytical sample was obtained by further recrystallization from petroleum ether. This melted at 77°. The substance turns dark purple on contact with moisture.

Anal. Calc'd for $C_6H_3ClO_3$: C, 45.5; H, 1.9.
Found: C, 46.0; H, 2.1.

6-Methyl-5-(ω-diazoaceto)-α-pyrone (III). To 200 cc. of a dry ethereal solution of diazomethane, prepared from 20 g. of nitrosomethylurea, was added dropwise a solution of 5 g. of coumalyl chloride in 100 cc. of dry ether with careful exclusion of moisture. During the addition of the coumalyl chloride the reaction mixture was kept at −10°. The addition of each drop resulted in the formation of a precipitate which decomposed with evolution of nitrogen. After addition of the acid chloride was complete, the mixture was kept at 0° for 2 hours and was then allowed to stand overnight at room temperature. The orange-yellow solution was filtered from a slight amount of a red precipitate and the filtrate was evaporated to dryness under reduced pressure. The yield of dark red crystalline material was 4.2 g. This was recrystallized in a Soxhlet extractor with petroleum ether. The diazo ketone crystallized in the flask as fine, lemon-yellow needles which melted at 76–77°. The substance dissolves in dilute alkali with an intense red color and gives a positive iodoform test.

Anal. Calc'd for $C_8H_6N_2O_3$: C, 54.0; H, 3.4.
Found: C, 54.0; H, 3.6.

6-Methyl-5-(ω-acetoxyaceto)-α-pyrone. Two hundred thirty milligrams of pure 6-methyl-5-(ω-diazoaceto)-α-pyrone was heated to 95° with 2 cc. of glacial acetic acid until evolution of nitrogen was complete. The yellow-brown solution was evaporated to dryness under reduced pressure, and the residual oil crystallized on cooling and rubbing under pentane. The substance was recrystallized from alcohol and formed colorless prisms, slightly soluble in ether, which melted at 97–98°. The yield was 160 mg. The substance gives an immediate strong Tollens test.

Anal. Calc'd for $C_{10}H_{10}O_5$: C, 57.1; H, 4.8.
Found: C, 57.2; H, 4.9.

6-Methyl-5-(ω-chloroaceto)-α-pyrone. Two hundred milligrams of the diazo ketone was dissolved in 1.5 cc. of pure anhydrous dioxane. After addition of 15 cc. of ether, a stream of dry hydrogen chloride was passed through the solution for 5–10 minutes during which the solution was chilled in ice. The solution was evaporated to dryness and the solid residue was recrystallized from dry acetone-ether or from alcohol. It melted at 65–66°.

Anal. Calc'd for $C_8H_7ClO_3$: C, 51.5; H, 3.8; Cl, 19.0.
Found: C, 51.7; H, 3.9; Cl, 18.8.

Methyl 6-methylcoumalate. One gram of methyl coumalate was suspended in 3 cc. of ice-cold methanol and an ethereal solution of diazomethane, prepared from 2 g. of nitrosomethylurea, was added in small portions. A vigorous evolution of gas ensued and the solution turned bright red, which, when the reaction was finished, changed to yellowish brown. After all the diazomethane had been added the mixture was kept at 0° for one hour and then at room temperature for several hours longer. After filtering from a small amount of insoluble material, the solution was evaporated

on the steam-bath and the residue was dried *in vacuo*. The partly crystalline residue was recrystallized from alcohol from which the new ester separated in rectangular plates which melted at 86–87°. An additional smaller crop was obtained from the mother liquors. The yield was 60–70%. The final mother liquors on evaporation always yielded a red oil which could not be crystallized and which was not further investigated.

Anal. Calc'd for $C_8H_8O_4$: C, 57.2; H, 4.8.
Found: C, 57.4; H, 4.9.

Catalytic reduction of methyl 6-methylcoumalate. Five hundred milligrams of the above ester was hydrogenated in methyl alcoholic solution with platinum oxide catalyst. Two hundred twenty-four cubic centimeters of wet hydrogen was taken up within 10 minutes. Calc'd for 3 moles at 25° and 760 mm.: 232 cc. The methyl alcohol was removed under reduced pressure and the residual oil was taken up in ether. The ethereal solution was thoroughly extracted with dilute sodium bicarbonate solution. The ethereal solution of neutral material was dried with anhydrous sodium sulfate and, on evaporation of the solvent, gave 100 mg. of a pleasant smelling oil which was not further investigated. The bicarbonate extract was acidified with hydrochloric acid and extracted with ether. The dried ether solution was concentrated and gave an oil which was boiled with 1 cc. of conc'd hydrochloric acid for one hour to hydrolyze the ester group. The hydrochloric acid was evaporated *in vacuo* leaving a heavy syrup which was crystallized from concentrated hydrochloric acid. As thus obtained the acid melted at 58–59°.

Anal. Calc'd for $C_7H_{12}O_4$: C, 52.5; H, 7.6.
Found: C, 52.5; H, 7.6.

Both melting point and analysis suggested that the above acid was α-ethylglutaric acid. The latter was synthesized from ethyl β-bromopropionate and diethyl ethylmalonate in ethereal solution followed by hydrolysis and simultaneous decarboxylation by means of conc'd hydrochloric acid. The two acids were identical in all respects.

For better identification the *dianilide* was prepared from the acid from both sources. One hundred milligrams of the acid was heated with 0.5 cc. of aniline at 180–190° for one hour. Three cubic centimeters of alcohol and 5 cc. of water were added and the solution was boiled for one minute. On cooling, the dianilide separated and was recrystallized from dilute alcohol after decolorizing with charcoal. The anilide formed fine needles which sintered slightly around 165° and melted at 188–190°. A mixture of the anilides prepared from the acids from the two sources showed no depression in melting point.

Anal. Calc'd for $C_{19}H_{22}N_2O_2$: C, 73.6; H, 7.1.
Found: C, 74.0; H, 7.2.

As a control for the hydrogenation reaction described above, 1 g. of methyl coumalate was hydrogenated exactly as in the preceding case. The hydrogen uptake was 463 cc. of wet hydrogen at 25° and 760 mm. in 5 minutes. Calc'd for 3 moles: 489 cc. The reaction mixture was worked up as before and the acidic fraction, after crystallization from conc'd hydrochloric acid, melted at 77°. Auwers (8) reports the melting point 77° for α-methylglutaric acid.

Anal. Calc'd for $C_6H_{10}O_4$: C, 49.4; H, 6.9.
Found: C, 49.6; H, 6.9.

The *dianilide* of α-methylglutaric acid crystallized as fine needles from dilute alcohol and melted at 179–180°.

Anal. Calc'd for $C_{18}H_{20}N_2O_2$: C, 72.9; H, 6.8.
Found: C, 72.7; H, 6.8.

The failure of a methyl substituent in the 5-position of the pyrone ring to induce the reaction with diazomethane was shown by the following experiment. Three hundred milligrams of 5-methyl-α-pyrone was dissolved in 1 cc. of methyl alcohol and an excess of an ethereal solution of diazomethane was added. Some nitrogen evolution occurred, but this ceased after about 20 minutes. After standing for 2 hours the solution was filtered and the solvent was removed under reduced pressure. The residue solidified in an ice-bath and weighed 270 mg. The material was then hydrogenated as before and took up 157 cc. of wet hydrogen at 25° and 760 mm. Calc'd for 3 moles: 193 cc. The reduction product was separated into an acidic and a neutral fraction as before. The oily acid fraction weighed 150 mg. and gave a well crystallizing piperazonium salt which melted at 115–116°. Analysis of this salt showed that a 6-carbon atom acid (isocaproic acid) had been formed by reduction of the pyrone, whereas, if methylation on carbon atom 6 had occurred, a 7-carbon atom acid (γ-methylcaproic acid) would have been formed. The piperazonium salt of the latter is reported as melting at 109° (9).

Anal. Calc'd for $C_{18}H_{38}N_2O_4$: C, 62.5; H, 11.4.
Calc'd for $C_{16}H_{34}N_2O_4$: C, 60.3; H, 10.8.
Found: C, 60.3; H, 10.7.

The microanalyses reported in this paper were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. Coumalyl chloride has been prepared.

2. α-Pyrone derivatives containing a negative substituent in the 5-position undergo nuclear methylation in the 6-position when treated with diazomethane.

3. A possible mechanism for this methylation reaction has been proposed.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE JOHNS HOPKINS UNIVERSITY]

TRIVALENT CARBON. I. THE DIPHENYLCARBETHOXYMETHYL RADICAL[1]

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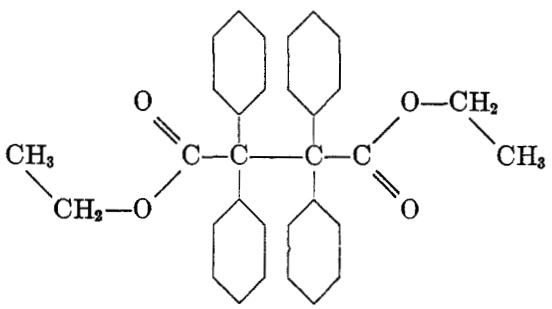
It is well known that hexaarylethanes in solution at room temperature undergo rapid dissociation into free triarylmethyl radicals. *Sym*-tetraarylethanes, on the other hand, do not dissociate into radicals even at relatively high temperatures. If the two remaining ethane hydrogen atoms are replaced by alkyl or acyl groups, however, the stability of the molecule is decreased to such an extent that the derivatives undergo most



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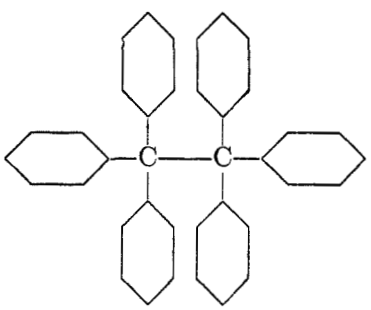

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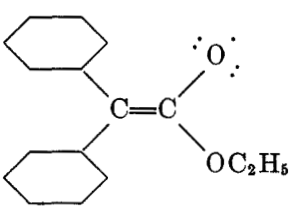


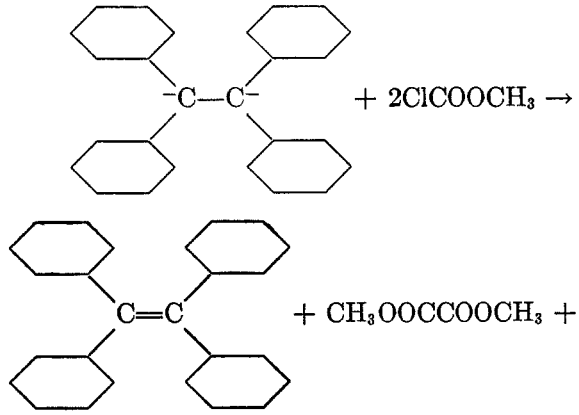
(III)

[1] From a dissertation submitted by Benjamin Witten in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Johns Hopkins University. We are indebted to the Hynson, Westcott, and Dunning Research Fund for a grant-in-aid covering a part of the cost of this research.

of the reactions characteristic of dissociating ethanes. As part of a general program to evaluate the relative importance of the factors promoting dissociation in molecules, we have started a study of the esters of tetraarylsuccinic acids. In this paper we report the preparation of diethyl tetraphenylsuccinate, (I), its acid catalyzed isomerization, and its rate of dissociation into diphenylcarbethoxymethyl radicals.

A comparison of the formulas for diethyl tetraphenylsuccinate (I), and hexaphenylethane (II), shows that the carbethoxy group corresponds roughly in size and shape to a phenyl group. Moreover, the carbethoxy group should contribute to the resonance stabilization of the free radical with respect to the dimer since it is possible to write a "Lewis structure" for the radical in which the odd electron is on one of the oxygen atoms (III). In so far as resonance and steric factors promote dissociation it is to be expected that tetraphenylsuccinic esters will prove to be intermediate in dissociating tendencies between *sym*-tetraphenylethane and hexaphenylethane.

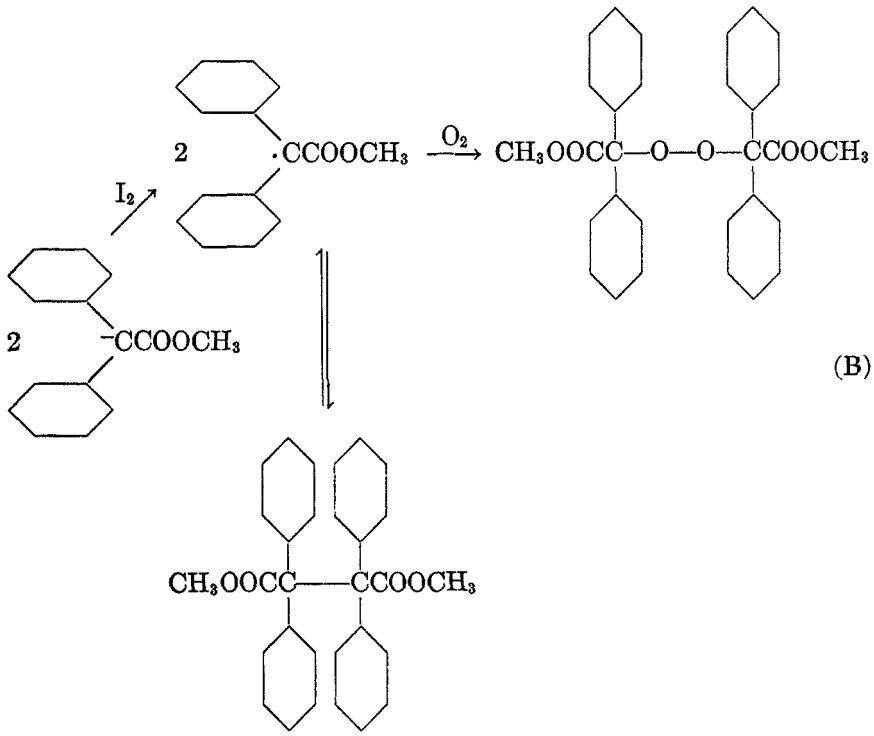
Preparation of Diethyl Tetraphenylsuccinate. There are recorded three previous attempts to synthesize esters of tetraphenylsuccinic acid, of which only one was described as successful. Schlenk and Bergmann (1) treated the anion of tetraphenylethane with methyl chloroformate; symmetrical coupling resulted, however, giving tetraphenylethylene and dimethyl oxalate (Equation A). Schlenk, Hillemann, and Rodloff (2)



(A)

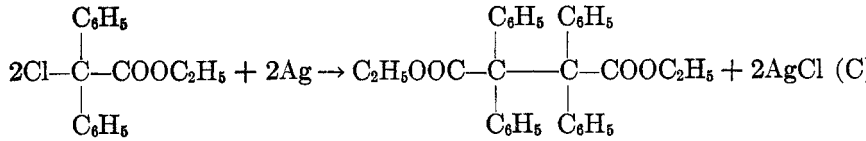
treated the anion of methyl diphenylacetate with iodine; the resulting solution on exposure to air gave diphenylcarbomethoxymethyl peroxide, which presumably resulted from the action of oxygen on the dissociating ester (Equation B). No intermediate products were isolated.

Bickel (3) heated a solution of ethyl diphenylchloroacetate with "molecular" silver at 120° and isolated a stable crystalline product melting at



(B)

88–89° which he believed to be diethyl tetraphenylsuccinate (Equation C). We shall present evidence to show that Bickel actually obtained a

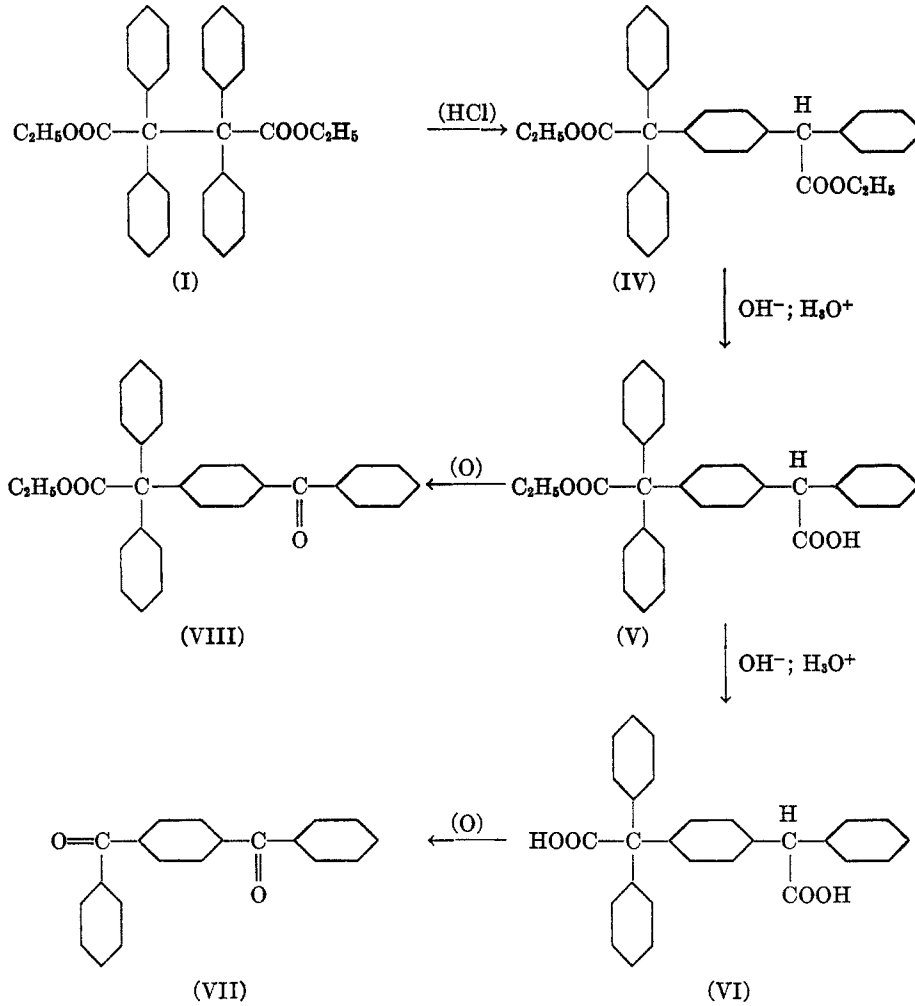


(C)

stable isomer of the succinic ester, a rearrangement product which can be prepared by the action of hydrogen chloride on diethyl tetraphenylsuccinate.

Neither Schlenk and his co-workers (2) nor we were able to isolate any crystalline product by following Bickel's procedure. Under less drastic conditions, *i.e.*, by shaking a solution of ethyl diphenylchloroacetate in benzene and ether with mercury, or by refluxing with "molecular" silver in an inert atmosphere, we obtained the desired ester as a colorless crystalline product melting to a yellow liquid at 90–94°. Solutions of diethyl tetraphenylsuccinate are pale yellow at room temperature. The intensity of absorption increases on warming; the color fades when the solutions are cooled. Solutions rapidly absorb oxygen at room temperature; the solid, however, is both stable and inert.

Rearrangement by Hydrogen Chloride. In the presence of hydrogen chloride diethyl tetraphenylsuccinate is converted to an isomer melting at 88–89° which does not absorb oxygen. The acid and base catalyzed isomerization of structurally similar compounds is known to give *para*-substitution products (4a), from which we deduced the structure of the



(I) (IV) (VIII) (V) (VII) (VI)

rearrangement product to be ethyl *p*-(phenylcarbethoxymethyl)triphenylacetate (IV). The structure was confirmed by degradation. Hydrolysis of the rearranged ester (IV), gave a monobasic acid, ethyl *p*-(phenylcarboxymethyl)triphenylacetate (V), and a dibasic acid, *p*-(phenylcarboxymethyl)triphenylacetic acid (VI), depending upon the conditions.

Oxidation of the dibasic acid gave terephthalophenone (VII), proving that the rearrangement involved the *para* position in one of the benzene rings. Oxidation of the monobasic acid (V) gave a crystalline product whose empirical formula is consistent with the structure, ethyl *p*-benzoyltriphenylacetate (VIII). It is evident that hydrolysis of the carbethoxy group on the secondary carbon atom is faster than the hydrolysis of the carbethoxy group on the tertiary carbon.

Since the melting points of diethyl tetraphenylsuccinate and its isomer are almost identical, this property does not characterize Bickel's ester adequately. It seems certain that Bickel obtained the rearrangement product, however, for the succinic ester would not have been isolated unless the reaction mixture had been protected from air. The melting point reported by Bickel for the dibasic acid obtained by the hydrolysis of his ester, 260–262°, with decomposition, is somewhat lower than that which we found for *p*-(phenylcarboxymethyl)triphenylacetic acid (VI), 287–291°, with decomposition. We do not regard this difference as significant, however, since the melting point is irreversible.

Absorption of Oxygen. Although tetraarylethane derivatives containing "negative", *e.g.* acyl, groups are described as generally reacting only slowly with oxygen (4b), we found that diethyl tetraphenylsuccinate in solution absorbs oxygen rapidly even at room temperature. The absorption was quantitative (98.6 mole per cent) and diphenylcarbethoxymethyl peroxide was isolated from the reaction mixture (*v.* Equation B for an analogous reaction with the methyl ester). The peroxide was cleaved and hydrolyzed by refluxing with alkali, to give benzilic acid. The surprisingly rapid oxygen absorption indicated to us that diethyl tetraphenylsuccinate was undergoing dissociation into free radicals at room temperature and suggested the utilization of this reaction to measure the rate of dissociation.

Ziegler and co-workers (5) have demonstrated that the rate of oxygen absorption by solutions of hexaphenylethane at 0° is a measure of the rate of dissociation of the ethane into free radicals if an oxidation inhibitor, suitably pyrogallol, is present in excess during the reaction. Under these conditions the amount of oxygen absorbed is increased to two moles for each mole of hexaphenylethane; no triphenylmethyl peroxide is formed; the rate of oxygen absorption is proportional to the hexalphenylethane concentration and independent of the oxygen pressure or pyrogallol concentration. The identity of the rate of oxygen absorption with the rate of absorption of nitric oxide and with the rate of reaction with iodine is ample proof that the rate controlling step in each case is the rate of formation of triphenylmethyl radicals. Bachmann and Wiselogle (6) extended this study by measuring the rate of oxygen absorption by pentaphenylethane

at 100° and established the validity of this method for determining the rates of dissociation of polyarylethanes.

We have now applied this reaction to determine the rate of dissociation of diethyl tetraphenylsuccinate. In the presence of pyrogallol the amount of oxygen absorbed corresponded to two moles for each mole of the succinic ester. The rate of oxygen absorption was proportional to the ester concentration but independent of the oxygen pressure or pyrogallol concentration. For such a first-order reaction the equation expressing the rate at a given temperature is conveniently written in the form: $-\log(1 - Z) = kt/2.3$, where Z is the fraction of succinic ester reacted (or the fraction of oxygen absorbed) in time, t, and k is the specific reaction

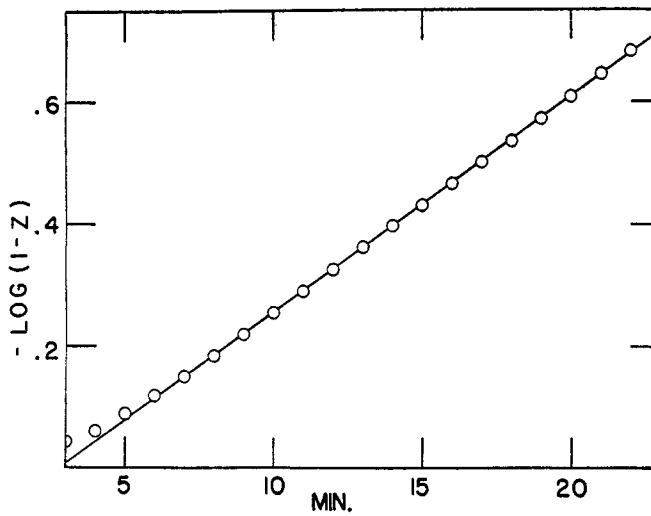


FIG. 1. RATE OF OXYGEN ABSORPTION BY DIETHYL TETRAPHENYLSUCCINATE (Plotted from Data in Table III)

rate constant. The rate constant may be evaluated by plotting $-\log(1 - Z)$ against t; the slope of the curve thus obtained multiplied by 2.3 gives the value of k.

Data obtained in a representative experiment at 0° using *o*-dichlorobenzene as solvent have been plotted in Fig. 1. It is clear that, except for the first five minutes during which time the sample was dissolving, the curve through the points is a straight line. The slope of the line is constant throughout the reaction, and the rate is therefore proportional to the succinic ester concentration. Experiments performed with various oxygen pressures and pyrogallol concentrations gave equally straight lines with identical slopes. These data are collected in Table I.

The reaction is first-order, therefore, and the rate controlling step is

undoubtedly the dissociation of diethyl tetraphenylsuccinate, a unimolecular process. The subsequent reaction steps are probably analogous to those proposed by Ziegler for the oxygen absorption by hexaphenylethane (5). The radicals resulting from the dissociation process react quanti-

TABLE I

RATE OF OXYGEN ABSORPTION BY DIETHYL TETRAPHENYLSUCCINATE IN *o*-DICHLOROBENZENE AT 0°

CONC. OF ESTER (MOLES/LITER)	CONC. PYROGALLOL (MOLES/LITER)	OXYGEN PRESSURE (ATMOS.)	VELOCITY CONSTANT, k (MIN.$^{-1}$)
0.0026	0.021	1.0	0.0802
.0017	.010	1.0	.0814
.0014	.010	1.0	.0815
.0017	.010	0.2	.0834
.0014	.020	0.2	.0822
Average			.0817 ±0.005
Half-life			8.47 min.

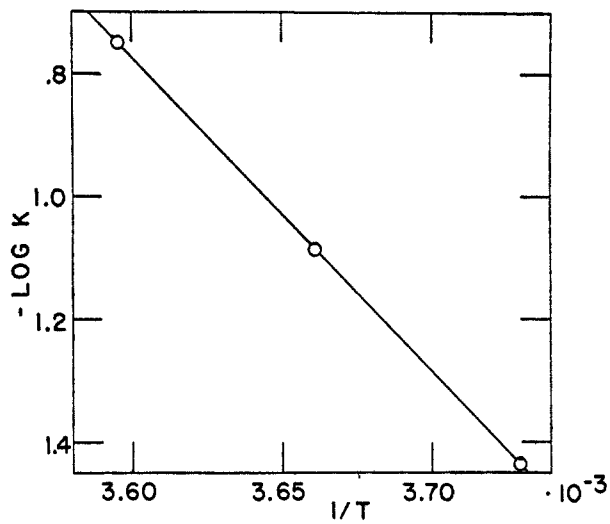


FIG. 2. RATE OF DISSOCIATION OF DIETHYL TETRAPHENYLSUCCINATE IN *o*-DICHLOROBENZENE AT −5.02, 0.00 AND 4.98°

tatively and rapidly with oxygen to give peroxy radicals of the form R—O—O—, which in turn are quantitatively destroyed by the pyrogallol. We have not identified the ultimate reaction products.

We have verified the dissociation process as the rate controlling step at +4.98° and at −5.02°. The values of the rate constants obtained are

listed in Table II. From the average values of the rate constants at the three temperatures we have calculated the activation energy for the dissociation process, E. Using the Arrhenius equation, $\log k = E/2.3RT + C$, where R is the gas constant and T the absolute temperature, we plotted $\log k$ against $1/T$. The slope of the straight line so obtained (Fig. 2) multiplied by $2.3R$ gave 23.3 kcal. for the energy of activation.

Discussion. We shall postpone a quantitative comparison of the dissociating tendencies of the various diacyltetraphenylethanes. It shall suffice to indicate that diethyl tetraphenylsuccinate has a greater rate of dissociation than any other diacyltetraphenylethane yet studied, a dissociation rate at 0° practically identical with that of hexaphenylethane. Since the activation energy for the dissociation of diethyl tetraphenylsuccinate (23.3 kcal. in *o*-dichlorobenzene) is considerably higher than for hexaphenylethane (19.6 kcal. in toluene) the large value for the rate

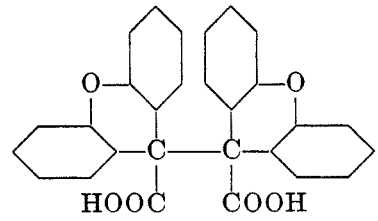
TABLE II

RATE OF OXYGEN ABSORPTION BY DIETHYL TETRAPHENYLSUCCINATE AT DIFFERENT TEMPERATURES

OXYGEN PRESSURE (ATMOS.)	VELOCITY CONSTANT, k	
	4.98°	−5.02°
1.0	0.1791	0.0371
1.0	.1782	.0361
0.2	.1768	.0361
0.2	.1759	.0365
Average	.1778	.0365
Half-life (min.)	3.91	19.0

constant of the succinic ester dissociation must be attributed to a relatively high entropy of activation.

It is particularly surprising that diethyl tetraphenylsuccinate has a much greater rate of dissociation than the structurally similar bixanthyl-9,9′-dicarboxylic acid (IX) or its dimethyl ester. The bixanthyldicarboxylic acid absorbed only ten mole per cent of oxygen in fifty-two



(IX)

hours at 25°, and the dimethyl ester absorbed no detectable quantity of oxygen (7). Although the xanthyl group is much more effective than two phenyl groups in promoting dissociation in hexaarylethanes, the reverse holds for the succinic esters. It appears, therefore, that the effectiveness of a group in promoting dissociation must depend upon the other groups present in the molecule. Any table listing groups in relative order of effectiveness in promoting dissociation must have limited application.

EXPERIMENTAL

Diethyl tetraphenylsuccinate (I). Ethyl diphenylchloroacetate was prepared from diphenylchloroacetyl chloride (8) and ethyl alcohol following the method outlined by Bickel (3). Into a 200 cc. balloon flask provided with ground glass connections were placed 8.4 g. of "molecular" silver, 2.0 g. of ethyl diphenylchloroacetate, and 25 cc. each of anhydrous ether and benzene. The flask was provided with a reflux condenser through which a stirrer extended; a mercury seal prevented access of air. Before the reagents were introduced, the air in the system was displaced by nitrogen and the system was maintained under a small positive nitrogen pressure. The mixture was refluxed and stirred for three hours over a water-bath at 60–80°. The solution was then forced through a sintered glass funnel into a "free radical" bulb and the remaining silver and precipitated silver chloride were twice washed with 20-cc. portions of benzene. Concentration of the filtrate left a light yellow oil to which was added 15 cc. of low-boiling petroleum ether. After standing for five days at 0° colorless crystals began to form. When crystallization appeared to be complete, several days later, the product was filtered in an atmosphere of carbon dioxide. There was obtained 1.45 g. (84%) of diethyl tetraphenylsuccinate, melting to a yellow liquid at 90–94° with previous softening at 80°.

The ester was also obtained by shaking for forty-eight hours a mixture of 12.1 g. of ethyl diphenylchloroacetate, 10 cc. of mercury, 25 cc. of benzene, and 25 cc. of ether in a "free radical" bulb of 200 cc. capacity. The yield was 6.45 g. (61%).

Diethyl tetraphenylsuccinate crystallized in the form of hexagonal plates. The crystallization process was always slow. In some early runs we obtained the stable isomer; in later experiments, therefore, scrupulous care was used to exclude all traces of water or alcohols which could liberate hydrogen chloride from ethyl diphenylchloroacetate.

Diphenylcarbethoxymethyl peroxide. A solution of diethyl tetraphenylsuccinate prepared from 2.05 g. of ethyl diphenylchloroacetate by means of mercury was filtered and the solvent was allowed to evaporate in the presence of air. The residual oil crystallized when stirred with alcohol. Recrystallization from benzene and alcohol gave 1.03 g. (54%) of colorless peroxide melting with decomposition at 116–118°.

Anal. Calc'd for $C_{32}H_{30}O_6$: C, 75.3; H, 5.9.
Found: C, 75.3; H, 5.7.

Hydrolysis of the peroxide. A solution of 0.28 g. of diphenylcarbethoxymethyl peroxide and 0.3 g. of potassium hydroxide in 10 cc. of methanol was refluxed for one hour. Acidification of the aqueous layer remaining after dilution with water and extraction with ether precipitated 0.19 g. (76%) of benzilic acid, which on recrystallization melted at 147–149°; the melting point of a mixture with benzilic acid showed no depression.

Rearrangement of diethyl tetraphenylsuccinate. To 1.52 g. of the ester (I) in a "free radical" bulb was added 25 cc. of benzene which had been saturated with hydrogen

chloride. The solution was allowed to stand at room temperature in an inert atmosphere for several hours. Removal of the solvent left an oil from which 1.32 g. (87%) of colorless ethyl *p*-(phenylcarbethoxymethyl)triphenylacetate (IV) crystallized when stirred with alcohol and benzene. The product melted at 88–89°.

Anal. Calc'd for $C_{32}H_{30}O_4$: C, 80.3; H, 6.3.
Found: C, 80.3; H, 6.5.

Hydrolysis of the rearranged ester. A solution of 4.52 g. of ethyl *p*-(phenylcarbethoxymethyl)triphenylacetate (IV), 25 cc. of methanol, and 1.0 g. of potassium hydroxide was refluxed for one hour. The solution was diluted with 100 cc. of water, acidified and extracted with ether. Removal of the ether left an oil which crystallized from benzene and alcohol, giving 2.24 g. (55%) of colorless ethyl *p*-(phenylcarboxymethyl)triphenylacetate (V), melting at 206–207°.

Anal. Calc'd for $C_{30}H_{26}O_4$: C, 80.0; H, 5.8; neutralization equivalent: 450.
Found: C, 79.7; H, 5.8; neut. equiv., 439.

A mixture of 0.52 g. of the rearranged ester (IV), 10 g. of potassium hydroxide, and 10 cc. of methanol was heated to 100° for fifteen minutes. The dibasic acid (VI) precipitated when the solution was diluted with water and acidified. The product was recrystallized from a mixture of acetone, in which the acid is very soluble, and benzene in which the acid is practically insoluble. The recrystallized product melted with gas evolution to a red oil at 287–291°. The same product was obtained by hydrolysis of the monobasic acid, (V).

Anal. Calc'd for $C_{28}H_{22}O_4$: neut. equiv., 211.
Found: neut. equiv., 221.

Oxidations. A mixture of 0.3 g. of ethyl *p*-(phenylcarboxymethyl)triphenylacetate (V), 0.3 g. of chromic anhydride, and 25 cc. of glacial acetic acid was refluxed for thirty minutes. The solution was diluted with 50 cc. of water and extracted with ether. The oil remaining after removal of the ether crystallized from acetic acid and water and melted at 126–127°. The analysis is in agreement with that predicted for the structure (VIII); we have not yet synthesized the compound by an independent method.

Anal. Calc'd for $C_{29}H_{24}O_3$: C, 82.8; H, 5.8.
Found: C, 82.6; H, 5.6.

A mixture of 0.271 g. of the dibasic acid (VI), 0.72 g. of chromic anhydride, and 10 cc. of glacial acetic acid was refluxed for ten minutes. Terephthalophenone precipitated when the mixture was diluted with water. Crystallization from a mixture of acetic acid and water gave 0.066 g. (36%) melting at 158–160°. The melting point of a mixture with authentic terephthalophenone showed no depression.

Anal. Calc'd for $C_{20}H_{14}O_2$: C, 83.9; H, 4.9.
Found: C, 84.2; H, 4.9.

Oxygen absorption by diethyl tetraphenylsuccinate. The apparatus for the rate determinations was similar to that recently described by Rowley and Anderson (9). A 200 cc. round-bottom flask was provided with a standard taper 24/40 female joint. Into this neck was fitted a vertical tube 36 cm. long and 2 cm. in diameter provided with a capillary side tube which connected with a 10 cc. gas burette. A glass plunger extending nearly to the bottom of the flask was suspended from the top of the vertical tube by a short rubber band. The top of the plunger, which was sealed, contained an insert of 10 cm. lengths of iron wire. A coil of wire was wound around the outside of the vertical tube such that the iron core was approximately one-half within the coil. For stirring, an intermittent current corresponding to the natural period of the rubber band (260 oscillations per minute) was passed through the coil. The flask

and coil were totally immersed in a water thermostat the temperature of which was maintained manually to ±0.05° by use of ice or ice and salt.

Since neither pyrogallol nor the ester dissolved rapidly in the solvent at low temperatures, we were forced to use dilute solutions. About 60 mg. of sample was weighed out into a micro-boat which was placed in a hollow in the glass plunger.

TABLE III

RATE OF OXYGEN ABSORPTION BY DIETHYL TETRAPHENYLSUCCINATE. TYPICAL DATA OBTAINED IN REPRESENTATIVE EXPERIMENT

Wt. ester: 0.0729 g.; wt. pyrogallol: 0.13 g.; vol. *o*-dichlorobenzene: 100 cc.; oxygen pressure: 1.0 atmos.; thermostat temp.: 0.00°; calc'd absorption: 7.56 cc.; observed absorption: 6.98 cc. (92.2%); rate constant, from curve (Fig. 1): 0.0814 min^{-1}; time correction, used in calculating column 4: −2.80 min.

TIME INTERVAL (MIN.)	VOLUME OF GAS YET TO BE ABSORBED (CC.)	$-\log(1-Z)$ =	$kt/2.3$
0.00	6.98	0.0000	0.0000
1.00	6.87	.0069	
2.00	6.70	.0178	
3.00	6.44	.0350	.0071
4.00	6.09	.0592	.0424
5.00	5.71	.0872	.0778
6.00	5.32	.1180	.1131
7.00	4.94	.1502	.1485
8.00	4.57	.1839	.1838
9.00	4.22	.2186	.2196
10.00	3.88	.2551	.2544
11.00	3.58	.2900	.2898
12.00	3.30	.3254	.3252
13.00	3.04	.3610	.3605
14.00	2.80	.3967	.3959
15.00	2.59	.4306	.4312
16.00	2.39	.4655	.4666
17.00	2.20	.5015	.5019
18.00	2.03	.5364	.5372
19.00	1.87	.5721	.5726
20.00	1.72	.6084	.6079
21.00	1.58	.6452	.6433
22.00	1.45	.6825	.6786
23.00	1.33	.7200	.7140
24.00	1.12	.7946	.7493
inf.	0.00		

The hollow was so constructed that before the run started the sample remained above the liquid surface and, accordingly, did not absorb oxygen. About 100 cc. of *o*-dichlorobenzene and 130 mg. of pyrogallol were placed in the flask and the assembled apparatus was lowered into the thermostat. The system was repeatedly evacuated and filled with oxygen for runs where the partial pressure was 1 atmosphere. The burette was filled with oxygen. As soon as the system acquired the temperature of

the thermostat, as determined by the constancy of volume, the intermittent current was started through the coil; the oscillations of the plunger caused the boat to fall into the liquid. The sample slowly dissolved and began to absorb oxygen; periodic readings of the volume were made. Data obtained in a typical run are reproduced in Table III. The extent of reaction was always based on the amount of oxygen absorbed, which varied from 90–100% of that calculated from the weight of the ester.

SUMMARY

Diethyl tetraphenylsuccinate has been synthesized from ethyl diphenylchloroacetate by the action of mercury or "molecular" silver. Solutions of diethyl tetraphenylsuccinate are yellow at room temperature and rapidly absorb oxygen giving a peroxide. Hydrogen chloride effects a rearrangement of the succinic ester giving a stable isomer, ethyl *p*-(phenylcarbethoxymethyl)triphenylacetate.

The rate of oxygen absorption by diethyl tetraphenylsuccinate at 0° in the presence of pyrogallol is a measure of the rate of dissociation into free radicals. The half-life of the ester in *o*-dichlorobenzene at 0° is 8.47 min.; the energy of activation for the dissociation is 23.3 kcal.

BALTIMORE, MD.

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[COMMUNICATION NO. 791 FROM THE KODAK RESEARCH LABORATORIES]

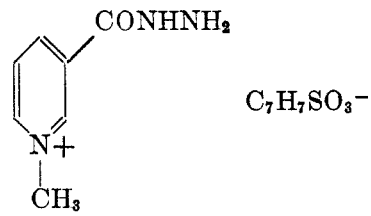
THE IDENTIFICATION OF CARBONYL COMPOUNDS BY THE USE OF N-METHYL-β-CARBOHYDRAZIDOPYRIDINIUM *p*-TOLUENESULFONATE

C. F. H. ALLEN AND J. W. GATES, JR.

Received February 28, 1941

The identification of carbonyl compounds by the formation of solid derivatives has been greatly facilitated during the past decade by the introduction of useful reagents for this purpose (1). While any such reagents are useful with aromatic compounds, but a limited number serve with members of the aliphatic series. The two most useful are semicarbazide and 2,4-dinitrophenylhydrazine. Even with these, in some circumstances the melting points of the derivatives are rather low. For example, the semicarbazones of the normal aliphatic aldehydes from C_6 to C_{14} melt between 100° and 106°, and the range of the 2,4-dinitrophenylhydrazones is between 96° and 107°, while ω-undecylenic aldehyde forms a semicarbazone, m.p. 26°, and a 2,4-dinitrophenylhydrazone, m.p. 91° (2).

By the use of the methyl *p*-toluenesulfonate addition product of nicotinic acid hydrazide (I), it is possible to secure solid derivatives of aliphatic



I

aldehydes, which have melting points about 40° higher than those of both the corresponding 2,4-dinitrophenylhydrazones (Fig. 1) and the semicarbazones. The derivatives are relatively easy to secure in good yield and are readily purified. Their melting points are not as far apart as might be desired; in this respect they resemble the semicarbazones. The derivatives obtained through the use of reagent (I) are all soluble in water. Aqueous solutions where the radical contains more than seven carbon atoms show a tendency to foam.

Nicotinic hydrazide itself might be used as a reagent, but the aliphatic

derivatives are oily or low-melting solids. Quarternarizing nicotinic hydrazide with methyl *p*-toluenesulfonate results in raising the melting point of the derivative by 50°; *e.g.*, benzaldehyde nicotinic hydrazide is reported to melt at 149–152° (3), whereas the quaternarized derivative described in this paper has the melting point 208°. Ethyl *p*-toluenesulfonate is not suitable for making a salt, since the latter is a liquid.

A further advantage of the use of the new reagent is that the carbonyl compound can be recovered by a short acid hydrolysis. In this respect it resembles the Girard reagent (4), which, however, is unsuited for making

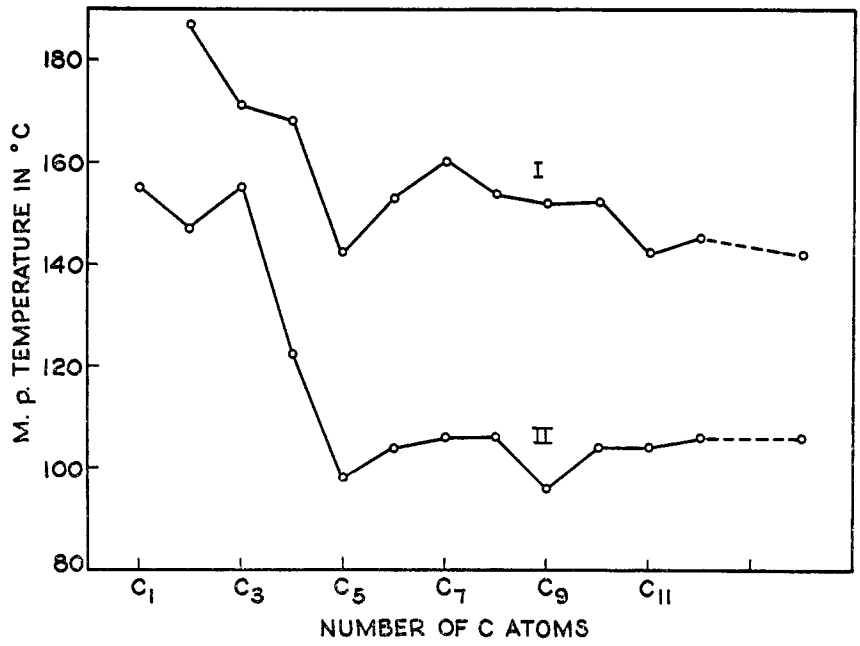


FIGURE 1

solid aliphatic derivatives in general. A novel application makes it possible to prepare a derivative by the use of the new reagent for characterization, determine its physical constants, and then use the same specimen to prepare a second derivative. The process is illustrated in the experimental part of this paper, a 2,4-dinitrophenylhydrazone being selected because of its slight solubility.

The new reagent can be successfully used with halogen-containing ketones, a further point in its favor. Since it usually gives oily products, it is not generally applicable to α,β-unsaturated ketones; a list of those that were tried is given in the experimental section.

EXPERIMENTAL

*Preparation of the reagent; nicotinic acid hydrazide metho-*p*-toluenesulfonate* (I). A mixture of 15 g. of ethyl nicotinate, 18.6 g. of methyl *p*-toluenesulfonate, and 50 cc. of absolute alcohol was refluxed for four hours and, after cooling, 6 g. of 85% hydrazine hydrate in 10 cc. of absolute alcohol was added and the whole refluxed for fifteen minutes. On cooling and scratching, the product which slowly separated was filtered. The yield was 20 g., and the melting point 155–157°. This material is satisfactory for the preparation of derivatives. A larger sized run, using 121 g. of ethyl nicotinate, 149 g. of methyl *p*-toluenesulfonate, 48 g. of 85% hydrazine hydrate, and 200 cc. of absolute alcohol, gave 226 g. (87%) of the reagent, having a pale pink color. The product is readily purified by recrystallization from absolute alcohol, from which it separates in very pale yellow plates, m.p. 160°.

A metastable form, m.p. 130–131°, may be obtained in the absence of the stable variety. Both forms crystallize in flat plates; those from the 131° form have six sides, while the others are parallelograms. Both forms give derivatives having the same melting point.

Anal. Calc'd for $C_{14}H_{17}N_3O_4S$: C, 52.0; H, 5.3; N, 13.0.
Found: (131°) C, 52.0; H, 5.1; N, 12.8;
(160°) C, 52.3; H, 5.4; N, 12.8.

Preparation of derivatives. The general procedure is as follows. A mixture of 3.2 g. (0.01 mole) of the reagent, 0.011 mole of the carbonyl compound, and 15 cc. of absolute alcohol is refluxed for fifteen minutes. On cooling, the derivative that crystallizes is filtered and its melting point determined. It is purified by recrystallizing to constant melting point. Usually absolute alcohol is a suitable solvent; in a few instances 1:1 alcohol-ether is preferable. In favorable instances, *i.e.*, where the product is not too soluble, as little as 0.5 g. of the carbonyl compound may be identified.

The properties of the derivatives secured by the use of the new reagent are shown in Table I. It may be mentioned that some of the derivatives show a reluctance to crystallize in the absence of seed; three days in the ice-box was the longest time that elapsed before a solid was secured in the least favorable case.

Regeneration of the carbonyl compound by acid hydrolysis. This is conveniently illustrated by the heptyl derivative, 21 g. of which was dissolved in 100 cc. of water containing 5 cc. of conc'd sulfuric acid, warmed to 60° for fifteen minutes, and cooled. The cold mixture was extracted with three 100-cc. portions of ether, the extract was dried over anhydrous magnesium sulfate, and the aldehyde distilled. The recovery of heptaldehyde was 4.8 g. (84%). Its identity was confirmed by preparation of the known 2,4-dinitrophenylhydrazone.

Conversion of derivative into the corresponding 2,4-dinitrophenylhydrazone. This may be illustrated by the use of the derivative from acetophenone. To a solution of 2.1 g. of this derivative in 25 cc. of warm (50–60°) water is added 1 cc. of mineral acid, with stirring. After five minutes, this warm solution is poured into 100 cc. of warm alcohol containing 1 g. of 2,4-dinitrophenylhydrazine and a drop of sulfuric acid. The acetophenone 2,4-dinitrophenylhydrazone precipitates quantitatively immediately. The conversion is equally satisfactory for small amounts, such as are usually encountered in routine qualitative organic analysis. In this case, the solution is added to 5 cc. of the prepared reagent (hydrochloric acid solution) (5). An immediate separation of the dinitrophenylhydrazone usually occurs.

The substance (I) failed to react, or gave non-crystallizing products with the following carbonyl compounds: formaldehyde, phenacyl bromide, α-ionone, commer-

TABLE I

PROPERTIES OF DERIVATIVES

CARBONYL COMPOUND	CORR. M.P., °C*	ANALYSES	
		Calc'd: N, %	Found: N, %
Acetaldehyde	187	12.0	11.9
Propionaldehyde	171	11.6	11.4
n-Butyraldehyde	168	11.1	11.1
i-Butyraldehyde	173	11.1	10.8
n-Valeraldehyde	142	10.7	10.8
i-Valeraldehyde	159	10.7	10.7
n-Caproaldehyde[a]	153	10.4	10.4
n-Heptaldehyde	160	10.0	10.0
n-Octaldehyde	154	9.7	9.7
n-Nonylaldehyde	152	9.4	9.4
n-Decylaldehyde	152	9.1	9.0
n-Undecylaldehyde	142	8.8	8.8
n-Duodecylaldehyde	145	8.6	8.3
n-Tetradecylaldehyde	142	8.1	8.2
α-Methyl-*n*-nonylacetaldehyde	132	8.6	8.4
α-Ethyl-*n*-butyraldehyde	137	10.4	10.3
α-Ethyl-*n*-hexaldehyde	131	9.7	9.6
Crotonaldehyde	193	11.2	11.0
α-Methyl-β-ethylacrolein	182	10.4	10.1
α-Ethyl-β-*n*-propylacrolein	197	9.5	9.5
Citronellal[b]	142	9.2	9.1
n-ω-Undecylenic aldehyde	145[c]	8.9	8.8
Furfural	164	10.5	10.3
Benzaldehyde	211	10.2	10.2
Cuminic aldehyde	259	9.3	9.4
Phenylacetaldehyde	165	9.9	9.9
Hydratropic aldehyde[b]	125	9.6	9.5
Hydrocinnamic aldehyde	160	9.6	9.5
Cinnamic aldehyde	235	9.6	9.6
4-*i*-Propylcinnamic aldehyde	241	8.8	8.8
α-*n*-Propylcinnamic aldehyde	187	8.8	8.8
α-*n*-Butylcinnamic aldehyde	163	8.5	8.3
α-*n*-Amylcinnamic aldehyde	126	8.3	8.0
α-*n*-Hexylcinnamic aldehyde	113	8.1	7.7
Cyclopentanone[b]	181	10.8	10.7
Cyclohexanone[b]	146	10.4	10.4
Cyclopentadecanone[b]	144	7.9	8.0
2-Heptylcyclopentanone	136	8.6	8.5
Isophorone[b]	156	9.5	9.5
Acetone	166	11.6	11.8
Methyl octyl ketone[b, d]	109	9.1	9.1
Methyl nonyl ketone[b]	110	8.8	8.9
Methyl decyl ketone[b]	111	8.6	9.1
β-Ionone[b, d]	147	8.5	8.5

TABLE I—*Concluded*

CARBONYL COMPOUND	CORR. M.P., °C*	ANALYSES	
		Calc'd: N, %	Found: N, %
Diacetyl	264	12.1	12.3
Acetonylacetone[e]	212	10.5	10.4
Acetophenone	191	9.7	9.8
p-sec.-Amylacetophenone[b]	143	8.9	8.5
Phenacyl chloride[b, f, g]	120	9.1	9.1
2,4-Dimethylphenacyl chloride[b, f]	196	8.6	8.7
Chloroacetone[b, f]	135	10.6	10.6
Dichloroacetone[b, f]	115	9.7	9.8
Chloromethyl ethyl ketone[b, f]	137	10.2	10.2
Ethyl levulinate[b, h]	136	9.4	9.7
Methyl levulinate[b, i, j]	160	9.7	9.6
β-Chloropropiophenone[f]	171	8.9	8.7

* In each instance, the melting point was over a 1° range: the value given is the upper limit.

[a] The commercial aldehyde is a mixture; the crude product melts at 138–142°. A specimen prepared from synthetic hexaldehyde was identical with the pure derivative.

[b] Recrystallized from 1:1 alcohol-ether.

[c] Mixed melting point with *n*-undecylic aldehyde, 138–141°.

[d] Recrystallized from dioxane.

[e] This is apparently a cyclic compound formed by loss of water. Anal. Calc'd for $C_{20}H_{23}N_3O_4S$: C, 59.9; H, 5.7; Mol. wt., 401. Found: C, 60.4; H, 5.8; Mol. wt., 390, 392 (in alcohol).

[f] The derivatives from haloketones are unstable to heat.

[g] Calc'd: Cl, 7.5%. Found: Cl, 7.4%.

[h] Calc'd for $C_{21}H_{27}N_3O_6S$: C, 56.1; H, 6.0. Found: C, 55.9; H, 6.2.

[i] Recrystallized from methanol.

[j] Calc'd for $C_{20}H_{25}N_3O_6S$: C, 55.2; H, 5.8. Found: C, 55.5; H, 6.0.

cial ionone, methyl vinyl ketone, phenyl vinyl ketone, heptylidene acetone, 2-heptylidene cyclopentadecanone, mesityl oxide, diacetone alcohol, hydroxycitronellal, glucose, benzalacetone, levulinic acid, phorone, fenchone, di-*n*-butyl ketone, di-*i*-butyl ketone, chloral, and 2,5-dimethylfuran. With di-*n*-butyl and di-*i*-butyl ketones and with fenchone, there was no reaction even after three days' refluxing. The furan did not react; this was examined because acidic reagents used to detect a carbonyl group open the ring so easily, to give acetonylacetone, which at once forms a derivative.

SUMMARY

A new reagent, the hydrazide of 3-carboxy-1-methylpyridinium *p*-toluenesulfonate, which is well suited for the characterization of most carbonyl compounds, has been described. Procedures are given for its preparation and uses.

Since the carbonyl compounds can be readily regenerated, the reagent can be used to separate them from mixtures of other substances. It is also possible to make two derivatives for characterization with the same sample of aldehyde or ketone.

ROCHESTER, N. Y.

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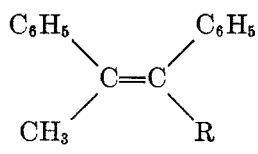
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE PREPARATION OF SOME CHLOROMETHYLINDENES AND THE DETERMINATION OF THEIR REACTIVITIES TOWARDS SODIUM IODIDE[1]

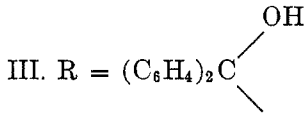
C. F. KOELSCH AND R. V. WHITE

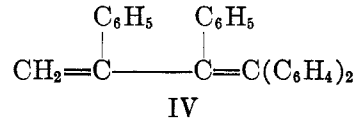
Received March 17, 1941

The bimolecular rate constants for the reactions between sodium iodide and organic chlorides (1) depend in a largely unpredictable way on the structures of the latter substances. But even though a quantitative explanation for the rate constants is not available, still their values are qualitatively in agreement with our ideas of the reactivities of many types of organic chlorides (2). It was hoped that such rate constants could be used to determine if the indene nucleus substituted into methyl chloride has as great an influence on the reactivity of the halogen as does an aromatic ring similarly placed, and for this reason a study of the rates of reaction of some chloromethylindenes with sodium iodide was carried out.

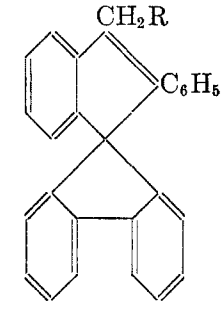


I. R = Br
II. R = COOH





IV



V. R = H
VI. R = $OCOCH_3$
VII. R = Cl

The results obtained are listed in Table I. They indicate, as expected, that the reactivity of a substituted 2- or 3-chloromethylindene is greater than that of an alkyl chloride and lies in the range of reactivities of the substituted benzyl chlorides. But since the rate constants are so highly

[1] Abstracted from a thesis submitted by R. V. White to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Ph.D. degree, October, 1939.

dependent on apparently insignificant structural features of the chloromethylindenes, it is not possible to make a precise summarizing statement.

Of more general interest than the reactivities are the syntheses of the compounds involved. To obtain 3-chloromethyl-2-phenyl-1-diphenyleneindene (VII), α-methylstilbene was brominated, giving α-bromo-α,β-diphenylpropylene (I). The bromo compound was converted into a Grignard reagent, from which α,β-diphenylcrotonic acid (II) could be obtained in a yield of 30%, and this Grignard reagent with fluorenone yielded α-diphenylene-β,γ-diphenylcrotyl alcohol (III). Under mild dehydrating conditions, the alcohol gave α-diphenylene-β,γ-diphenylbutadiene-α,γ (IV), while under somewhat more vigorous conditions either

TABLE I

REACTIVITIES OF CHLOROMETHYL COMPOUNDS

COMPOUND	$k(t_1)$	$k(t_2)$	A[a]	$k(50°)$	R[b]
3-Chloromethyl 2-phenyl-1-diphenyleneindene (VII)	7.0 (0°)	13.02 (5°)	4091	(1461)[c]	36,400
2-Chloromethyl-3-phenyl-1-diphenyleneindene (XII)	0.525 (20°)	0.868 (25°)	3817	(8.51)[c]	212
2-Chloromethyl-1,1,3-triphenylindene (XVII)	0.874 (45°)	1.262 (50°)	3277	1.262	31
Chloroacetamide	0.355 (25°)				
Benzyl chloride[d]	0.786 (25°)	1.31 (30°)	4000	7.89	197
o-Bromobenzyl chloride[d]	4.31 (−10°)	16.5 (0°)	4200	(3092)[c]	77,300
Chloroacetamide[d]	0.360 (25)	0.603 (30°)	4000	3.95	99

[a] $\log \frac{k(t_1)}{k(t_2)} = A\left(\frac{1}{T_2} - \frac{1}{T_1}\right)$.

[b] R(butyl chloride, 50°) = 1.

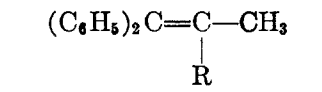
[c] Calculated.

[d] From Conant, Kirner, and Hussey, Ref. 2.

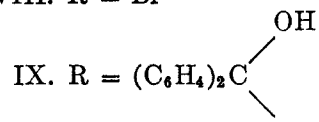
the alcohol or the diene was converted into 3-methyl-2-phenyl-1-diphenyleneindene (V). This hydrocarbon, whose structure was substantiated by oxidation to benzoic acid and diphenylenephthalide, was brominated, and the bromo compound was converted *via* the acetate (VI) to 3-chloromethyl-2-phenyl-1-diphenyleneindene (VII).

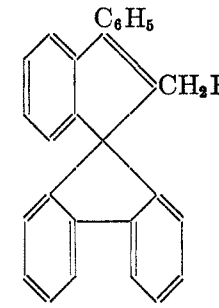
The preparation of 3-chloromethyl-1,1,2-triphenylindene by an analogous series of reactions was abandoned after all attempts to crystallize α,α,β,γ-tetraphenylcrotyl alcohol (similar to III but prepared using benzophenone) or to obtain crystalline dehydration products from it had failed. A second attempt which might have led to 3-methyl-1,1,2-triphenylindene through the reaction between triphenylvinylmagnesium bromide and acetophenone, and a third through the reaction between methylmagnesium

iodide and 2,3,3-triphenylhydrindone were both unsuccessful. In each case the Grignard reagent enolized the ketone, and the latter was recovered after hydrolysis of the reaction mixture.



VIII. R = Br



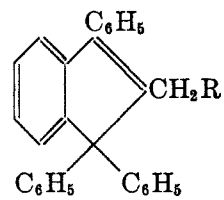


X. R = H
XI. R = $OCOCH_3$
XII. R = Cl

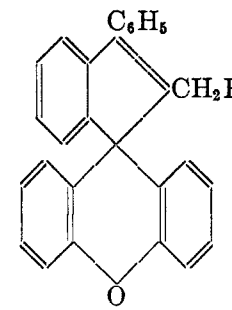
To obtain 2-chloromethyl-3-phenyl-1-diphenyleneindene (XII), α,α-diphenylpropylene was brominated, giving β-bromo-α,α-diphenylpropylene (VIII). The bromide was converted into a Grignard reagent, and this with fluorenone yielded an oily carbinol (IX). Dehydration of this carbinol gave 2-methyl-3-phenyl-1-diphenyleneindene (X)[2] which was

$(C_6H_5)_2C{=}C(CH_3)C(C_6H_5)_2OH$

XIII



XIV. R = H
XV. R = Br
XVI. R = $OCOCH_3$
XVII. R = Cl



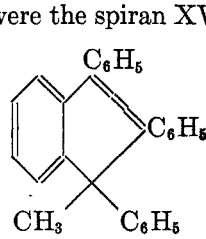
XVIII. R = H
XIX. R = $OCOCH_3$
XX. R = Cl

[2] If it is considered that dehydration of IX proceeds through a positive organic ion, then the elimination of a proton from this ion resulting in cyclization can give 1,1-diphenyl-2-methyl-3,4-phenyleneindene. But such a structure is strained and will not be formed if a relatively unstrained product (X) is possible (3). This effect must likewise direct the ring closure of III to V, a case where the structure of the product was proved.

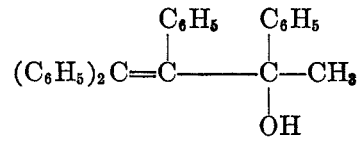
converted through its bromination product and the acetate (XI) into 2-chloromethyl-3-phenyl-1-diphenyleneindene (XII).

To obtain 2-chloromethyl-1,1,3-triphenylindene (XVII), the Grignard reagent from VIII was treated with benzophenone, yielding β-methyl-$\alpha,\alpha,\gamma,\gamma$-tetraphenylallyl alcohol (XIII). This alcohol gave 2-methyl-1,1,3-triphenylindene (XIV) on dehydration, and the usual subsequent reactions through the bromo compound (XV) and the acetate (XVI) led to the desired chloromethyl compound (XVII). The structure assigned to XIV was confirmed by oxidation; with chromic acid, the indene gave *o*-benzoyltriphenylacetic acid and *o*-benzoyl-α,α,α-triphenylacetone.

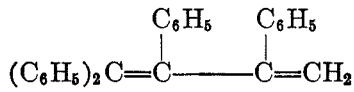
Although no study of the reactivity of the product was made, *spiro*-2-chloromethyl-3-phenylindene-1,9-xanthene (XX) was prepared by a series of reactions analogous to those just described. The starting materials were the Grignard reagent from VIII and xanthone, and the intermediates isolated were the spiran XVIII,[3] and the acetate XIX.



XXI



XXII



XXIII

An attempt was made to obtain 1-bromomethyl-1,2,3-triphenylindene by brominating 1-methyl-1,2,3-triphenylindene (XXI). But since the product was found to contain an unreactive bromine atom, it is probable that substitution of an aromatic hydrogen took place. The 1-methyl-1,2,3-triphenylindene used was prepared by treating 1-bromo-1,2,3-triphenylindene with methylmagnesium iodide. It melted at 96–98° and was obviously different from a compound melting at 118° described as 1-methyl-1,2,3-triphenylindene by Kohler and Nygaard (5). The synthesis used by these investigators, involving the dehydration of $\alpha,\alpha,\beta,\gamma$-tetraphenylbutenol-$\gamma$ (XXII) with acetic anhydride, was repeated, and their 118° product was obtained. It was found that this substance was

[3] This structure is preferred to the one which would result by ring closure on the 4-position of the xanthene nucleus, since it is quite generally true that ring closures in a position meta to an ether oxygen are difficult (4).

converted into the 96–98° indene when it was treated with sulfuric acid in acetic acid. Furthermore, although oxidation of the 118° compound with chromic acid in acetic acid yielded *o*-(α-methyldesyl)benzophenone and *o*-dibenzoylbenzene as reported by Kohler and Nygaard, when the oxidation was carried out in the absence of acids with potassium permanganate in acetone there was obtained triphenylacrylophenone. These results indicate that the 118° compound is the diene (XXIII), and that the 96–98° substance is the indene XXI.

EXPERIMENTAL

α-Bromo-α,β-diphenylpropylene (I). α,β-Diphenylpropanol was obtained in a yield of 88% by treating acetophenone with benzylmagnesium chloride. It boiled at 122–124°/2 mm. and melted at 49–51° (literature (6), m.p. 50–51°). The carbinol (182 g.) was boiled in acetic acid (250 ml.) containing sulfuric acid (0.8 ml.) for five hours; the resulting α-methylstilbene (154 g.) melted at 79–81.5° (literature (7) 82–83°).

Bromine (126 g.) in acetic acid was added slowly and with stirring to a solution of α-methylstilbene (147 g.) in acetic acid (400 ml.) at 60°. The mixture was then heated to boiling, and most of the acetic acid was distilled under reduced pressure. The product was washed, dried, and distilled through a Hickman still head, giving 159 g. (74%) of α-bromo-α,β-diphenylpropylene which boiled at 153–156° at 0.001 mm. The refractive index (n_D) was 1.6536 (15°), 1.6510 (20°), 1.6484 (25°), 1.6457 (30°).

Anal. Calc'd for $C_{15}H_{13}Br$: C, 65.9; H, 4.8.
Found: C, 65.8; H, 5.4.

A Grignard reagent from α-bromo-α,β-diphenylpropylene (10 g.), magnesium (1 g.), and ether (100 ml.) was carbonated by pouring onto solid carbon dioxide. The resulting α,β-diphenylcrotonic acid (II), purified by solution in sodium carbonate, was obtained in yields of 30–35%. Recrystallized from ligroin it melted at 124–126°.

Anal. Calc'd for $C_{16}H_{14}O_2$: C, 80.6; H, 5.9.
Found: C, 80.7; H, 6.0.

An attempt to cyclize α,β-diphenylcrotonic acid (4.3 g.) to 2-phenyl-3-methylindone by heating it with phosphorus oxychloride (10 g.) in benzene gave α-methylstilbene as the only crystalline product.

α-Diphenylene-β,γ-diphenylbutadiene (IV). An ether solution of fluorenone (10.5 g.) was added to a Grignard reagent from α-bromo-α,β-diphenylpropylene (30 g.). The mixture, in which a yellow precipitate formed, was boiled for one hour and then decomposed with iced hydrochloric acid. The ether was removed and the oily residue was dissolved in acetic acid (50 ml.) containing three drops of sulfuric acid. The solution was heated to boiling and then cooled, giving α-diphenylene-β,γ-diphenylbutadiene which melted at 185–190°; yield, 21–28%. Recrystallized from acetic acid, the diene formed yellow platelets that melted at 197–198°.

Anal. Calc'd for $C_{28}H_{20}$: C, 94.3; H, 5.7.
Found: C, 93.5; H, 6.2.

3-Methyl-2-phenyl-1-diphenyleneindene (V). The indene was obtained when the boiling with acetic acid-sulfuric acid described in the preceding paragraph was prolonged to thirty minutes. But since the indene was more soluble than the diene, it could be isolated in better over-all yield if the diene was isolated first. One gram

of the diene boiled for one hour with 30 ml. of acetic acid containing a few drops of sulfuric acid gave 0.75 g. of pure 3-methyl-2-phenyl-1-diphenyleneindene. This substance formed white plates that melted at 152.5–153.5°.

Anal. Calc'd for $C_{28}H_{20}$: C, 94.3; H, 5.7.
Found: C, 94.3; H, 5.5.

The indene (1 g.) in acetic acid (40 ml.) containing chromic anhydride (1.3 g.) was allowed to stand at room temperature for twenty-four hours. The mixture was then worked up in the usual way giving benzoic acid and diphenylenephthalide. The latter melted at 220–222° (literature (8), 219–220°).

Anal. Calc'd for $C_{20}H_{12}O_2$: C, 84.5; H, 4.2.
Found: C, 84.7; H, 4.2.

3-Chloromethyl-2-phenyl-1-diphenyleneindene (VII). A solution of bromine (2.12 g.) in chloroform (10 ml.) was added to 3-methyl-2-phenyl-1-diphenyleneindene (4.3 g.) in 20 ml. of the same solvent. The mixture was exposed to direct sunlight, causing the bromine to disappear rapidly, and the chloroform was evaporated. The resulting bromo compound, crystallized from ligroin but not analyzed, was boiled for ten minutes with potassium acetate (4 g.) in acetic acid (60 ml.). The potassium bromide was filtered and the filtrate was concentrated and cooled, giving the acetate VI (4.8 g.). Recrystallized from acetic acid, 3-acetoxymethyl-2-phenyl-1-diphenyleneindene formed colorless prisms that melted at 172–173°.

Anal. Calc'd for $C_{30}H_{22}O_2$: C, 86.9; H, 5.4.
Found: C, 86.9; H, 5.8.

The acetoxy compound was recovered unchanged after treatment in boiling acetic acid with hydrogen chloride, but the desired chloro derivative was obtained when the acetoxy compound (3.85 g.) was heated at 150° for four and one-half hours in a sealed tube with 20 ml. of a mixture of equal volumes of acetic acid and conc'd hydrochloric acid. Recrystallized from acetic acid, 3-chloromethyl-2-phenyl-1-diphenyleneindene (VII) formed colorless prisms (2.7 g.) that melted at 145.5–146.5°.

Anal. Calc'd for $C_{28}H_{19}Cl$: C, 86.0; H, 4.9.
Found: C, 85.9; H, 5.2.

β-Bromo-α,α-diphenylpropylene (VIII). α,α-Diphenylpropylene (7) was obtained in a yield of 74% by treating ethyl propionate with phenylmagnesium bromide and dehydrating the resulting carbinol by heating it at 215°. The propylene (143 g.) in acetic acid (200 ml.) was treated with bromine (38 ml.) and the dibromide was decomposed by heating the mixture on a steam-bath. The solution was poured into water and the oil was distilled, giving 166 g. (82%) of β-bromo-α,α-diphenylpropylene which boiled at 169–173° at 13 mm. (literature (9), 169–170°/12).

2-Methyl-3-phenyl-1-diphenyleneindene (X). β-Bromo-α,α-diphenylpropylene (40 g.), magnesium (3.7 g.), and a crystal of iodine in ether (500 ml.) usually started to react after five to ten minutes; in some cases it was necessary to add a drop of ethyl bromide. The reaction proceeded briskly for twenty minutes, and the mixture was then boiled for two hours. To such a Grignard reagent was added an ether solution of fluorenone (26.4 g.); the mixture was boiled for thirty minutes and then decomposed with iced hydrochloric acid. The carbinol formed could not be crystallized; it was accordingly dissolved in acetic acid containing a little sulfuric acid; the solution was boiled for ten minutes and then cooled. The 2-methyl-3-phenyl-1-diphenyleneindene so obtained crystallized from acetic acid in the form of fine white plates (23.5 g., 45%) that melted at 173–174.5°.

Anal. Calc'd for $C_{28}H_{20}$: C, 94.3; H, 5.7.
Found: C, 94.1; H, 5.7.

2-Chloromethyl-3-phenyl-1-diphenyleneindene (XII). 2-Methyl-3-phenyl-1-diphenyleneindene (16 g.) was brominated and the bromo compound was treated with potassium acetate in the same way as described for the 3-methyl-2-phenyl isomer. There was obtained 14.5 g. of 2-acetoxymethyl-3-phenyl-1-diphenyleneindene (XI) which melted at 148.5–150° after crystallization from acetic acid.

Anal. Calc'd for $C_{30}H_{22}O_2$: C, 86.9; H, 5.4.
Found: C, 86.7; H, 5.5.

A solution of the acetoxy compound (12 g.) in hot acetic acid (60 ml.) was saturated with hydrogen chloride; 2-chloromethyl-3-phenyl-1-diphenyleneindene precipitated before the solution cooled. Recrystallized from acetic acid containing hydrogen chloride, it formed white needles (9.5 g.) that melted at 134–136°.

Anal. Calc'd for $C_{28}H_{19}Cl$: C, 86.0; H, 4.9.
Found: C, 85.6; H, 4.9.

2-Methyl-1,1,3-triphenylindene (XIV). Benzophenone (26.7 g.) in ether was added to a Grignard reagent prepared from 40 g. of β-bromo-α,α-diphenylpropylene. The oily carbinol obtained by working up the reaction mixture in the usual way was boiled with acetic acid-sulfuric acid, and the product was recrystallized from acetic acid. There was obtained 21.5 g. of 2-methyl-1,1,3-triphenylindene which formed white prisms that melted at 157–159.5°.

Anal. Calc'd for $C_{28}H_{22}$: C, 93.8; H, 6.2.
Found: C, 93.6; H, 6.2.

2-Methyl-1,1,3-triphenylindene (4 g.) in 200 ml. of hot acetic acid was treated with 5 g. of chromic anhydride. After five minutes the reaction was complete. The solution was poured into water, the products were filtered, washed, and taken up in ether. This solution was shaken with 10% sodium carbonate, and the insoluble sodium *o*-benzoyltriphenylacetate formed was filtered and crystallized from methanol-ether. It melted and decomposed at 129° (literature (10), 130°). The neutral compound left in the ether by the sodium carbonate treatment was *o*-benzoyl-α,α,α-triphenylacetone; from acetic acid it formed colorless prisms (0.7 g.) that melted at 172–173.5°.

Anal. Calc'd for $C_{28}H_{22}O_2$: C, 86.1; H, 5.7.
Found: C, 85.8; H, 5.9.

2-Chloromethyl-1,1,3-triphenylindene (XVII). Bromine (3.7 g.) in 30 ml. of chloroform was added slowly to a stirred boiling solution of 2-methyl-1,1,3-triphenylindene (24 g.) in 100 ml. of chloroform. The reaction proceeded smoothly in direct sunlight, and when the bromine had disappeared the chloroform was distilled. The product was crystallized from ethyl acetate, giving 20 g. of 2-bromomethyl-1,1,3-triphenylindene which formed large white prisms that melted at 154–156°.

Anal. Calc'd for $C_{28}H_{21}Br$: C, 76.9; H, 4.8.
Found: C, 76.8; H, 4.9.

The bromo compound (20 g.), boiled for ten minutes in acetic acid with potassium acetate (6 g.), yielded 2-acetoxymethyl-1,1,3-triphenylindene (XVI). The product, recrystallized from acetic acid, formed colorless prisms (13 g.) that melted at 178.5–180°.

Anal. Calc'd for $C_{30}H_{24}O_2$: C, 86.5; H, 5.8.
Found: C, 86.3; H, 5.8.

To a concentrated solution of 2-acetoxymethyl-1,1,3-triphenylindene (13 g.) in hot acetic acid was added 10 ml. of acetic acid which had been saturated with hydrogen chloride. After the mixture had been allowed to cool it deposited 2-chloromethyl-1,1,3-triphenylindene; recrystallized from ethyl acetate the compound formed colorless prisms (10.5 g.) that melted at 154–155.5°.

Anal. Calc'd for $C_{28}H_{21}Cl$: C, 85.6; H, 5.4.
Found: C, 85.3; H, 5.4.

Spiro-*2-methyl-3-phenylindene-1,9-xanthene* (XVIII) was obtained in a yield of 18% using xanthone and the Grignard reagent from β-bromo-α,α-diphenylpropylene. From acetic acid it formed colorless prisms that melted at 153.5–155°.

Anal. Calc'd for $C_{28}H_{20}O$: C, 90.3; H, 5.4.
Found: C, 90.4; H, 5.6.

Spiro-*2-acetoxymethyl-3-phenylindene-1,9-xanthene* (XIX) was obtained from the above spiran (2.5 g.) by bromination and then treatment with potassium acetate. From acetic acid it formed small white prisms (1.4 g.) that melted at 203.5–205°.

Anal. Calc'd for $C_{30}H_{22}O_3$: C, 83.7; H, 5.1.
Found: C, 83.6; H, 5.4.

Spiro-*2-chloromethyl-3-phenylindene-1,9-xanthene* (XX) was obtained by warming the acetoxy spiran (1 g.) with acetic acid which had been saturated with hydrogen chloride. It formed colorless prisms (0.4 g.) that melted at 144–145°.

Anal. Calc'd for $C_{28}H_{19}ClO$: C, 82.6; H, 4.7.
Found: C, 82.5; H, 4.9.

1-Methyl-1,2,3-triphenylindene. 2,3-Diphenylindone was obtained in a yield of 52% from 2-phenylindandione-1,3 and phenylmagnesium bromide. It was converted into 1,2,3-triphenylindenol-1 by treatment with phenylmagnesium bromide. This difficultly crystallizable carbinol was isolated in the form of its methyl ether, prepared by dissolving the carbinol in methanol containing a few drops of sulfuric acid (yield 80%). The resulting 1-methoxy-1,2,3-triphenylindene (30 g.) was warmed with 20 ml. of acetic acid which had been saturated with hydrogen bromide. On cooling, the solution deposited 1-bromo-1,2,3-triphenylindene (30 g.) which melted at 125–127° (literature (10), 129°).

To a solution of methylmagnesium iodide containing 5 g. of magnesium was added 30 g. of 1-bromo-1,2,3-triphenylindene in benzene (150 ml.). The mixture was boiled for three hours and then worked up in the usual way giving 1-methyl-1,2,3-triphenylindene, which formed small white prisms (13 g.) that melted at 96–98° after crystallization from acetic acid.

Anal. Calc'd for $C_{28}H_{22}$: C, 93.8; H, 6.2.
Found: C, 94.1; H, 5.9.

Several brominations of 1-methyl-1,2,3-triphenylindene under varied conditions gave products melting unsharply in the range 140–165°. Bromination with one equivalent of bromine in acetic acid gave a product which sintered at 162° and melted at 170–171°. None of the products reacted with boiling alcoholic silver nitrate; the 170–171° compound was analyzed.

Anal. Calc'd for $C_{28}H_{21}Br$: C, 76.9; H, 4.8.
Found: C, 76.9; H, 5.1.

α,α,β,γ-Tetraphenylbutadiene-α,γ (XXIII). Triphenylacrylophenone was prepared in yields of 30–40% by the action of benzoyl chloride on triphenylvinylmagnesium bromide (11). Treated with methylmagnesium iodide according to the procedure of Kohler and Nygaard, triphenylacrylophenone (22 g.) yielded α,α,β,γ-tetraphenylbutenol-γ (11 g.) which melted at 96–98° (literature (5), 96–97°).

Tetraphenylbutenol (3 g.), boiled for five hours with sodium acetate (1 g.) in acetic anhydride (15 ml.), gave 2.2 g. of α,α,β,γ-tetraphenylbutadiene which melted at 118.5–120°. A solution of the diene (1.62 g.) in acetone (80 ml.) was boiled while powdered potassium permanganate was added in portions as long as its color was discharged; a total of 6.16 g. of the oxidizing agent was consumed. The solution was

filtered and evaporated, and the residue was crystallized from ethanol. There was obtained 0.95 g. of triphenylacrylophenone, which melted at 146–147° alone and at 147.5–148.5° when mixed with an authentic sample. For further identification, the triphenylacrylophenone was reduced with zinc dust in acetic acid to α,β,β-triphenylpropiophenone, which melted at 180–181° (literature (12), 181°) alone or mixed with an authentic sample.

Boiled for five minutes in acetic acid containing a drop of sulfuric acid, $\alpha,\alpha,\beta,\gamma$-tetraphenylbutadiene-$\alpha,\gamma$ was converted into 1-methyl-1,2,3-triphenylindene, and similar treatment of $\alpha,\alpha,\beta,\gamma$-tetraphenylbutenol-$\gamma$ gave the same product. In each case the reaction proceeded quantitatively and the identity of the product was confirmed by direct comparison with 1-methyl-1,2,3-triphenylindene obtained from 1-bromo-1,2,3-triphenylindene.

Rate studies. The procedures of Conant (2) were followed closely. The concentration of sodium iodide was 0.04 *N* and that of organic chloride 0.2 molar. As a check on technique, the reaction constant for chloroacetamide at 25° was determined and found to be 0.348 (1 hour) and 0.362 (2 hours); Conant reports the value 0.360 for this halide under the same conditions.

3-CHLOROMETHYL-2-PHENYL-1-DIPHENYLENEINDENE

AT 0°			AT 5°		
Time, hours	Percentage reacted	*k*	Time, hours	Percentage reacted	*k*
0.167	22.89	6.97	0.167	38.25	13.19
.25	31.93	6.95	.25	50.30	12.95
.333	39.16	6.80	.333	59.04	12.91
.417	48.19	7.51			
.5	51.81	6.77			
Av.		7.00			13.02

2-CHLOROMETHYL-3-PHENYL-1-DIPHENYLENEINDENE

AT 20°			AT 25°		
0.5	5.52	0.491	0.5	9.64	0.876
1.0	12.10	.561	1.0	18.39	.878
1.5	15.97	.507	1.5	25.44	.874
2.0	19.77	.539	2.0	31.95	.855
Av.		0.525			0.868

2-CHLOROMETHYL-1,1,3-TRIPHENYLINDENE

AT 45°			AT 50°		
0.5	9.68	0.873	0.5	14.37	1.337
1.0	18.47	.884	1.0	25.51	1.285
1.5	26.09	.881	1.5	34.31	1.236
2.0	31.97	.847	2.0	41.41	1.189
Av.		0.874			1.262

SUMMARY

The preparations of three indenes chloromethylated in the five-membered ring are described, and measurements of the reactivities of these substances towards sodium iodide in acetone are reported.

It is shown that a compound previously formulated as 1-methyl-1,2,3-triphenylindene is in reality $\alpha,\alpha,\beta,\gamma$-tetraphenylbutadiene-$\alpha,\gamma$.

MINNEAPOLIS, MINN.

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[CONTRIBUTION NO. 67 FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

OIL OF *ARTEMISIA TRIDENTATA* (AMERICAN SAGE BRUSH)

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One of the most common of the desert plants growing in at least ten of the western states in their more arid portions is the native sage brush (*Artemisia tridentata*). Some thirty varieties of *Artemisia* have been distinguished in these districts, but *tridentata* is by far the most common. Preliminary investigations (1, 2) have shown that the leaves and green twigs contain about one per cent of a steam-volatile oil which contains α-pinene, cineole or eucalyptole, l-camphor, and other substances which were unidentified. In view of the importation of large quantities of eucalyptus oil and camphor, as well as the incomplete identification of the components of the oil, it appeared desirable to investigate the oil further.

Adams and Billinghurst (1) have found that the maximum yield of oil was obtained in the late summer or fall. The oil, also, is much more easily obtained by air-drying the plant material before steam distillation. This was established by comparing the yields of oil from the fresh and dried plant material. Eighty pounds of sage flower shoots were collected and divided into two 40-pound lots. The first was distilled fresh as soon as transported to the laboratory, while the second was distilled seven days later when it weighed 22 pounds. A comparison of the yields of oil will be found in Table I.

From the data in Table I, it is apparent that the oil is removed more readily and rapidly by allowing the sage to dry before distillation.

The composition of the Utah oil (see Table II) appeared to be essentially the same as the Nevada oil reported by Adams and Oakberg (2) with the exception that the optical rotation was *dextro* and not *levo*. This indicated a differentiation of the species of the plant, but nothing appears to be known of this.

The data in Table II show that about 30% of the oil falls into the cineole fraction. This could be increased to about 42% by the inclusion of the pinene fraction, which is present in eucalyptus oil. The camphor was separated readily by refractionation and chilling the high-boiling fractions, but experiments with steam distillation indicate that the separation would be accomplished more effectively by this means. The camphor from the

Utah oil was *dextro*rotatory and this accounts for the *dextro*rotation of the oil to a considerable extent. The amount of crude crystalline camphor isolated was less than that estimated for the Nevada oil by Adams and Oakberg and probably does not exceed 30% in the Utah oil. In the event of a shortage of either eucalyptus oil or camphor, these substances could be manufactured from sage brush oil which could be produced from large areas in western United States.

TABLE I

DISTILLATION OF FRESH AND DRY SAGE BRUSH FLOWER SHOOTS

TIME OF DIST.	YIELD IN GRAMS	
	Fresh	Dry
minutes		
0–10	23.5	52.3
10–20	18.3	27.4
20–50	28.0	34.1
50–80	13.5	11.7
Total	83.3	125.5
Yield, fresh basis	0.45%	0.69%
Yield, dry basis	—	1.26%

TABLE II

RELATIVE COMPONENTS OF UTAH AND NEVADA SAGE OIL

MAIN CONSTITUENT	UTAH OIL			NEVADA OIL	
	Temp., °C., 645 mm.	% by Weight		Temp., °C. 650 mm.	% by Weight
Methacrolein	40–140	3.7	2.3		
α-Pinene	140–160	13.0	12.9	130–165	20.7
Cineole	160–193	29.9	28.8	165–198	28.8
Camphor	Cryst. camphor	25.9	26.3	105 (14 mm.)	25.3
Artemisol	90–175 (20 mm.)	20.2	20.6	105–150 (13 mm.)	14.4
	residue and loss	7.3	9.1	residue and loss	11.3
		100.0	100.0		100.0

Adams and Oakberg estimated that about 5% of the oil distilled from the plant material was an unidentified aldehyde. The odor of the plant was ascribed to this aldehyde which they named artemisal. On distillation of the Utah sage oil it was found that the initial boiling point was about 40°. The boiling point rose rapidly until the pinene fraction was reached where a leveling off of the distillation curve appeared. From three to four per cent of the oil fell into the first fraction, together with some water. The

fraction gave various tests for aldehydes and for unsaturation. The odor and action on mucous membranes was similar to that of acrolein, and, in our opinion, is hardly characteristic of the plant, which is quite camphoraceous. The main constituent of this fraction was found to be methacrolein. It was identified as the 2,4-dinitrophenylhydrazone[1] (3). Undoubtedly, this is the substance described by Adams and Oakberg in their work and named by them artemisal. The identification of methacrolein in plant material adds a new substance to those found in nature. Its branched structure suggests a relationship with the isoprene derivatives and may be an intermediate in their formation.

The water which separated from the low-boiling oil was found to contain acetic acid. Probably the water and acetic acid were produced in the original fractionation by the thermal decomposition of high-boiling fractions, because this process has been observed to take place. However, several of the fractions on standing for some days absorbed oxygen and, when redistilled, liberated water.

The fraction boiling from 120° to 140°, while giving positive Tollens' and Schiff's tests, did not contain sufficient aldehyde to permit isolation of a derivative. It appeared that most of this fraction was the hydrocarbon concentrated in the 140–144° fraction.

The 140–144° fraction yielded a small amount of a 2,4-dinitrophenylhydrazone melting at 219–221°. This substance was different from the hydrazone of methacrolein. No known 2,4-dinitrophenylhydrazone has a melting point in the neighborhood of 220° and consequently the identity of the substance was not ascertained. By refluxing with sodium, the 140–144° fraction was freed from a considerable proportion of the aldehyde present. The resulting material gave analytical and molecular weight values of a simple terpene $C_{10}H_{16}$. The low boiling point, density, index of refraction, optical rotation, and positive color test with acetic anhydride and sulfuric acid all indicated α-thujene. No solid derivative of α-thujene suitable for identification purposes is known, but α-thujene has been hydrogenated to thujane and the physical properties of this substance determined. The sage terpene reacted readily with hydrogen in the presence of Adams' catalyst and absorbed one mole per mole of terpene. The hydrogenated sage oil had the boiling point and index of refraction of thujane, but the density and optical rotation were too low. On repeating this work with another sample of the terpene, similar results were obtained, indicating that the hydrocarbon was probably not α-thujene. It is possible that the density of thujane has been incorrectly determined, but this

[1] Through the kindness of Prof. R. L. Shriner of the University of Illinois, a sample of this derivative was obtained.

does not seem likely since the value in the literature has been checked by two investigators (4, 5).

The low density of the hydrogenated sage terpene indicated that it was monocyclic rather than bicyclic like thujane and pinane. On the other hand, the boiling point of the original terpene was not raised as much as would be expected by the opening of a ring by the addition of hydrogen. In view of these conflicting data, it appears possible that the hydrocarbon belongs to the nine carbon series as does santene. The hydrocarbon was present in the oil to less than one-half of one per cent and, consequently, was not investigated further.

The presence of α-pinene was confirmed in the Utah oil by means of the nitrosochloride. A slightly higher-boiling fraction was isolated (152–153°) which did not form a nitrosochloride and must, consequently, be some other substance, such as β-pinene. This fraction, also, was small and was not investigated further.

Cineole was identified by Adams and Oakberg in the Nevada oil and, likewise, was verified in the Utah oil by means of the phosphoric acid and resorcinol addition products. However, the density and refractive index of this fraction indicated the presence of other components. This was further borne out by the yield of the cineole addition product, which was 63.5%. Negative tests on the decineolated oil were obtained for limonene, dipentene, terpinolene, sylvestrene, and phellandrene. On the other hand, the nitrosite of α-terpinene was isolated and identified by mixed melting point.

Terpinene may be removed from certain other hydrocarbons by means of cold Beckmann's chromic acid mixture. When the decineolated oil was so treated, about 37% was unattacked, indicating the presence of a third component, resistant to cold chromic acid. *p*-Cymene would be such a compound and should yield terephthalic acid with boiling chromic acid. The residue from the cineole fraction failed to yield terephthalic acid, and, consequently, the residue must contain some other substance. The fraction boiling from 164–169°, then, appeared to be about 63.5% cineole, 23% α-terpinene and 13.5% unidentified.

The next fraction of consequence boiled above 193°, which is the temperature at which camphor appeared in the condenser. No other substance crystallized from the high-boiling oil on cooling, even after careful vacuum fractionation into cuts of short boiling range. Neither were solid derivatives obtained from the high-boiling oil, other than those of camphor. The camphor remaining in the oil was removed by making the phenylhydrazone and vacuum distilling the oil, leaving the phenylhydrazone in the residue. The purified compound had the molecular formula of an oxygenated terpene, $C_{10}H_{18}O$. The odor was very characteristic and

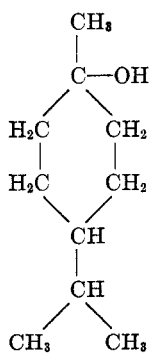
probably this is the substance which is peculiar to sage oil. Since the compound was found to be an alcohol it was named artemisol.

Artemisol, when heated with methylmagnesium iodide, yielded two moles of methane. Since the molecule contained only one oxygen atom, the two moles of methane must have been the result of a reaction with a molecule of water split from an alcohol structure. This loss of water was also observed when the substance was treated with phenylisocyanate at room temperature. Under these conditions diphenylurea was formed in high yield. Probably, then, the substance is an alcohol which is easily dehydrated. Artemisol is unsaturated. When hydrogenated in the presence of Adams' catalyst, one mole of hydrogen was absorbed per mole of alcohol, indicating the presence of one double bond. When heated with phosphorus pentasulfide, followed by sodium, *p*-cymene was obtained. These data suggest that artemisol is a *p*-menthenol, isomeric with terpineol.

Since α-terpinene was found in the cineole fraction, and since artemisol is very easily dehydrated and yields a product boiling in the α-terpinene range, it appeared possible that the terpinene present in the sage oil was produced by the dehydration of the artemisol during the process of fractionation. However, the dehydration product of the alcohol did not form a nitrosite with nitrous acid as terpinene should; and neither did it react with hydrogen chloride to form terpinene dihydrochloride. These facts indicate that the terpinene was not produced from the artemisol. There remains, however, the possibility that the unidentified, third component of the cineole fraction is related to artemisol.

If artemisol is one of the *p*-menthenols, it should yield on hydrogenation one of the seven *p*-menthanols, following. All are known except *p*-menthanol-7 and -9, structures V and VII respectively.

The hydrogenated artemisol readily lost a molecule of water to phenylisocyanate, behaving like the unhydrogenated alcohol. Three of the



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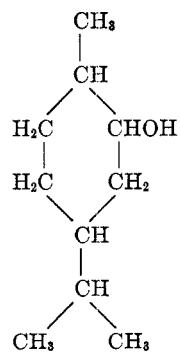

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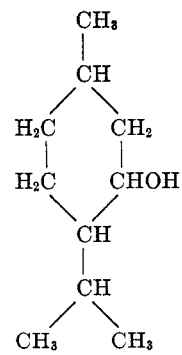
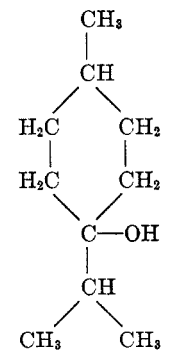


III



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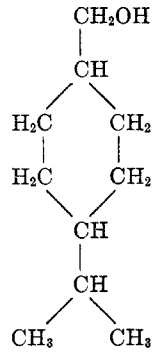
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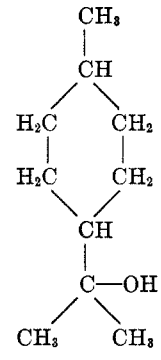
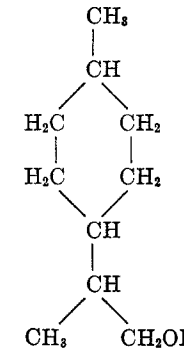
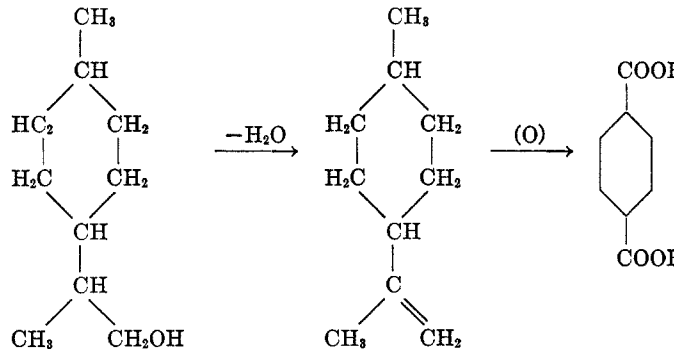

VI


VII

p-menthanols above, *p*-menthanol-1, -3, and -8, form phenylurethanes and, therefore, may be excluded as possibilities at once. The hydrogenated alcohol was dehydrated by heating with fused sodium bisulfate, followed by heating with metallic sodium. The resulting hydrocarbon was then oxidized by refluxing with an acidified, aqueous solution of chromic acid for thirty-five hours, and yielded terephthalic acid. The formation of terephthalic acid proved that the hydrogenated sage alcohol has the *p*-menthanol-9 structure, VII, since none of the other *p*-menthanols would yield this acid, because the dehydration of all of the structures from I to V inclusive would yield olefins which on oxidation would lead to cleavage of the ring. Structure VI, terpineol, was excluded on the chemical grounds described previously.


VII

The determination of the position of the double bond in the sage alcohol and the synthesis yet remain to be done.

The appearance of acetic acid in the low-boiling fraction and the presence of an easily dehydrated alcohol in the higher-boiling fractions suggested the

possibility that the acetic acid ester of artemisol was present in the high-boiling oil. On hydrolyzing one of the high-boiling fractions, acetic acid was identified as the *p*-bromophenacyl derivative. The acetic ester appeared to be concentrated in the fraction distilling below the alcohol and probably is the ester of artemisol, although the identity of the alcohol has not been verified.

EXPERIMENTAL PART

The fractionation of Utah oil of Artemisia tridentata. The oil was produced by the steam distillation of sage brush flower shoots collected near the mouth of Little Cottonwood Canyon, Salt Lake County, Utah. The oil was fractionated best by the following method. It was topped at 150° at atmospheric pressure (645 mm.) and then vacuum distilled, cuts being made at 90° and 145°. The topped oil and the first vacuum fraction were then refractionated separately through a 54-cm. column packed with glass helices and externally heated. A reflux ratio of about 20 to 1 was used. The initial boiling point was about 40°, but the temperature rose rapidly. Water began to collect in the stopcock in the head of the column and was removed as it collected. Cuts were made at 120°, 140°, and then at 4° intervals until 193° was reached, when camphor began to crystallize from the distillate. Like fractions were combined and all were refractionated. Considerable resin was formed and it is possible that some of the constituents cannot withstand the prolonged refluxing.

The water removed from the first fraction was distinctly acidic. It was neutralized and distilled to remove water-soluble neutral compounds. The distillate, on treatment with 2,4-dinitrophenylhydrazine, yielded the same hydrazone as that obtained from the 40–80° fraction below. Other hydrazones appeared to be formed, but the amount was too small to isolate them in a pure state. The water solution was evaporated and the salt of the acid recovered. The *p*-bromophenacyl ester of the acid was made, and melted at 83–84°. A mixed melting point identified the ester as that of acetic acid.

The oil boiling from 40° to 120° was distinctly yellow in color, which was noticeable even in the fractionating column. This suggested the possibility of the presence of a compound of the type of diacetyl, but no evidence for this was obtained. The density of the fraction was 0.8614 and the index of refraction was 1.4325, both at 20°. This fraction was cut into smaller fractions and tested as follows.

The 40–80° fraction. The 40–80° fraction was treated with 2,4-dinitrophenylhydrazine using the method of Brady (6). The hydrazone formed at once and was purified by recrystallization from ethyl acetate. After three recrystallizations the melting point rose to 206–207° with decomposition, if the rate of heating was fairly rapid. If heated very slowly, the melting point was 200–201° with decomposition. The substance was also recrystallized from benzene and from chloroform, but no change in the melting point was observed. It was identified by mixed melting point as the 2,4-dinitrophenylhydrazone of methacrolein (3).

The mother liquors from the purification of the methacrolein derivative were evaporated and extracted with 95% alcohol, in which the methacrolein derivative was only slightly soluble. On concentration, a product melting at 115–118° was obtained. Upon recrystallization from alcohol, reddish-orange needles and yellow leaflets formed. These crystals were separated by mechanical means. The orange needles, upon recrystallization from alcohol, melted at 119–120°. This product was dissolved in ethyl acetate, but when the substance failed to crystallize the solvent was evapo-

rated on a water-bath. The residue was in the form of red granules which *failed* to dissolve in alcohol and had the indefinite melting point 120–130°. Because of the small quantity of material nothing more was done with it.

The yellow leaflets were not obtained in sufficient amount for further purification. Their melting point was 108°.

Vapors condensed at −77°. Adams and Oakberg found that an appreciable quantity of the low-boiling material passed through a water-cooled condenser. In order to recover this material they passed the dried vapors through a trap cooled with solid carbon dioxide. They were unable, however, to identify the liquid aldehyde so obtained. We have repeated this and have identified the aldehyde as methacrolein, through the 2,4-dinitrophenylhydrazone. In addition, a small amount of a 2,4-dinitrophenylhydrazone was isolated in orange needles, melting at 163–164°. A mixture with the hydrazone of acrolein melted at 151–154°.

The 80–100° fraction. The 80–100° fraction was treated with 2,4-dinitrophenylhydrazine using Brady's method (6). The product which formed had the melting point 100–105°. After several recrystallizations from methyl alcohol the melting point was 140–142° and the color orange yellow. The yield was small. A mixture with the 2,4-dinitrophenylhydrazone of acetaldehyde melted at 122–126°.

The 100–120° fraction. The 100–120° fraction yielded a compound with 2,4-dinitrophenylhydrazine which crystallized from methyl alcohol in brown plates melting at 123°. The compound, probably, is not a 2,4-dinitrophenylhydrazone, because its molecular weight values, determined in camphor and in benzene, were found to be 131 and 108 respectively, which are much too low.

The 120–140° fraction. The 120–140° fraction gave qualitative tests for aldehydes with Schiff's and Tollens' reagents, but attempts to prepare 2,4-dinitrophenylhydrazones, semicarbazones, or *m*-nitrobenzhydrazones were unsuccessful. Probably the fraction was largely composed of the hydrocarbon found in the next higher fraction. The density of the 120–140° fraction was 0.8558 and the index of refraction 1.4520, both at 20°.

The 140–144° fraction. The 140–144° fraction had the density 0.8367 and the index of refraction 1.4562, both at 20°. The fraction gave a positive test with Schiff's and Tollens' reagents. When treated with 2,4-dinitrophenylhydrazine, a reddish colored product was obtained, melting at 196–197°. A mixed melting point with the 207–208° hydrazone was lowered to 181°. After several recrystallizations from alcohol, and from chloroform plus alcohol, the melting point rose to 219–221°. A mixed melting point with the 207–208° compound was lowered to 186–188°.

The alcoholic solution of the 140–144° fraction remaining after the treatment described above distilled completely below 95°. This azeotropic mixture was broken up by adding water which caused the sage oil to separate. The oil was redistilled, and the 140–144° fraction was refluxed with sodium to remove as far as possible oxygenated derivatives. The material was then fractionated from the sodium. Two different samples gave the following physical data.

TABLE III

PROPERTY	SAMPLE 1	SAMPLE 2
Boiling point	140–143°	140–144°
d_4^{20}	0.8216	0.8290
n^{20}	1.4574	1.4531
$[\alpha]_D^{20}$		+27.54°

Anal. Calc'd for $C_{10}H_{16}$: C, 88.9; H, 11.1; Mol. wt., 136.
Found: C, 86.6; H, 10.9; Mol. wt., 139.
C, 86.4; H, 11.2; Mol. wt., 141.
C, 86.5; H, 11.1.

The low percentage of carbon found may be accounted for by the incomplete removal of oxygenated derivatives.

The hydrocarbon was oxidized readily by cold, neutral potassium permanganate. A 5% solution of bromine in carbon tetrachloride was rapidly decolorized without the evolution of hydrogen bromide. The terpene was soluble in cold concentrated sulfuric acid with the formation of a red color and appeared to be thrown out of solution unchanged by dilution. A 50% solution in acetic anhydride gave an intense red coloration with a drop of concentrated sulfuric acid.

The terpene reacted readily with hydrogen in the presence of Adams' catalyst. A 4.1 g. sample dissolved in 25 ml. of ethyl acetate combined with 1100 ml. of moist hydrogen, measured over water at 645 mm. pressure and at 26°, instead of the calculated volume of 907 ml. The ethyl acetate was removed by hydrolysis with sodium hydroxide. The product was refluxed with metallic sodium and then fractionated from the sodium. The boiling point of the product was 144–150° at 645 mm.; the density, 0.7795 at 20°; the index of refraction, 1.4374 at 20°; and $[\alpha]_D^{20} + 27.48°$. The hydrocarbon reduced alkaline permanganate only very slowly. When treated with a 5% solution of bromine in carbon tetrachloride, bromine appeared to react without the evolution of hydrogen bromide. The compound was soluble in cold concentrated sulfuric acid. A 50% solution in acetic anhydride did not give a red coloration with a drop of sulfuric acid. A second sample of the sage terpene was hydrogenated and similar results were obtained, particularly the low density.

The 148–152° fraction. α-Pinene was identified in the 151–152° fraction of the Nevada oil. The density of the 148–152° fraction of the Utah oil was 0.8619 and the index of refraction 1.4661, both at 20°. These data indicated α-pinene. When treated with amyl nitrite, acetic acid, and concentrated hydrochloric acid, the material formed a nitrosochloride derivative melting at 100°. The nitrosochloride was identified as that of α-pinene by a mixed melting point determination.[2]

The 152–156° fraction. The 152–156° fraction had the density 0.8719 and an index of refraction 1.4664, both at 20°. On refractionation a distinct concentration occurred at 152–153°. This fraction failed to yield a nitrosochloride under the same conditions as those which produced the nitrosochloride of α-pinene from the 149–150° fraction[2] and, without doubt, the fraction was not α-pinene. On standing, the fraction deposited a brown resin. This property was shown to a more marked degree by the fraction boiling from 153–160°, which became quite viscous after standing two years.

The 164–168° fraction. The next concentration of distillate occurred in the neighborhood of 167–168°. The density of this fraction was 0.9040 and the index of refraction 1.4615, both at 20°. The Nevada oil contained cineole or eucalyptole in a similar fraction, and this substance was readily identified in the 167–168° fraction by its reaction with phosphoric acid and with resorcinol. However, the low density of the fraction indicated that some other substance or substances were present.

The presence of other substances was demonstrated by treating the oil boiling at

[2] This work was done by Randall M. Barker in partial fulfillment of the requirements for the degree of Bachelor of Science in Chemical Engineering, May, 1938.

164–168° with phosphoric acid to remove the cineole. The cineole-phosphoric acid compound was hydrolyzed and the cineole distilled. The density was then 0.9192 at 20°, which was close to that of pure cineole. The yield of cineole using the resorcinol method was 63.5%. The residual oil which did not react with phosphoric acid had a boiling range of 160–172°, the density 0.8498 at 20° and the index of refraction 1.4772, also at 20°. On refractionation the data shown in Table IV were obtained.

These data, particularly the long boiling range, indicated that probably more than one substance was present.

The presence of α-terpinene in the decineolated residue was shown by the preparation of the nitrosite melting at 154°. The identity was verified by a mixed melting point. Terpinene may be removed from substances more resistant to oxidation by oxidation with cold Beckmann's chromic acid mixture, and when 10 ml. of the oil freed from cineole was treated with the chromic acid mixture, 3.7 ml. was recovered unchanged. On this basis the cineole fraction was 63.5% cineole, 23% α-terpinene, and the residue unidentified.

The residue was oxidized with boiling chromic acid, but no terephthalic acid or hexahydroterephthalic acid was produced showing the absence of *p*-cymene or substances which might be oxidized to these acids.

The high-boiling fraction. When the temperature of distillation reached 193°, camphor crystallized from the distillate and the distillation was stopped. Large

TABLE IV

Fraction	$d^{20°}$	$n^{20°}$
160–167°	0.8433	1.4780
167–172°	0.8507	1.4820

amounts of camphor crystallized from the residue in the distillation flask on cooling. Still more was obtained by cooling the residue in a freezing mixture. The filtered oil was further fractionated *in vacuo* and additional amounts of camphor obtained. The yield of camphor has been given in the introduction.

The sage alcohol, artemisol. In addition to camphor, a liquid fraction boiling from 90° to 165° in a vacuum of about 20 mm. was obtained. This material was decomposed slowly by distillation at atmospheric pressure, and consequently, should be vacuum distilled. When this is done, less than one per cent of residue remains at 165°.

The largest fraction of high-boiling oil distilled at 100–120° at about 20 mm. The camphor remaining in the oil was removed by heating with phenylhydrazine in alcoholic solution with a trace of acetic acid. After distilling off the alcohol on a water-bath, the material was dissolved in benzene and extracted five times with dilute sulfuric acid to remove the excess phenylhydrazine. The benzene was removed on a water-bath and the residue vacuum distilled. This procedure did not remove the camphor completely, and was repeated. The purified oil was fractionated through the 54 cm. column *in vacuo*, and the data in Table V were obtained. The vacuum, unfortunately, was not constant, due to a change in the water pressure, and fractions 6 and 9 appear to contain two substances of different boiling point. These fractions were found to have similar physical and chemical properties, however, and probably were composed largely of the sage alcohol, artemisol.

The following analytical data have been obtained on fractions 5, 6, and 9.

Anal. Calc'd for $C_{10}H_{18}O$: C, 77.9; H, 11.7; Mol. wt., 154.
Found, Fraction 5a: C, 76.2; H, 10.5; Mol. wt., 198.
b: C, 75.7; H, 10.4; Mol. wt., 193.
c: C, 75.9; H, 10.4; Mol. wt., 194.
Fraction 6a: C, 77.2; H, 10.5; Mol. wt., 172.
b: C, 77.0; H, 10.4; Mol. wt., 165.
c: C, 77.3; H, 10.3;
Fraction 9a: C, 78.7; H, 10.4; Mol. wt., 173.
b: C, 78.6; H, 10.4; Mol. wt., 165.

The slightly low analyses of Fraction 6 may be accounted for by the presence of some of the lower-boiling material in Fraction 5 which obviously contained another compound with a smaller percentage of carbon, probably the ester (see the section on the hydrolysis of these fractions). In the same way Fraction 9 probably contained some higher-boiling material which is richer in carbon.

TABLE V

FRACTION NO.	WEIGHT, GRAMS	B.P. °C.	PRESSURE, MM.	n_D^{20}	d_4^{20}
1	3	–88	15.5	1.4848	
2	6	88–100	15.5	1.4797	0.9630
3	5	100–105	15.5	1.4786	0.9497
4	3	105–106	15.5	1.4787	
5	12	106–110	15.5	1.4760	0.9397
6	16	110–112	15.5	1.4760	0.9447
7	5	112–115	18	1.4773	0.9463
8	5	115–117	16.5	1.4790	0.9445
9	20	117–120	16.5	1.4794	0.9474
10	5	120–123	16.5	1.4808	0.9375
11	8	123–130	16.5	1.4865	0.9360
12	12	Residue			

1. Active hydrogen. Active hydrogen was determined by heating the substance with methylmagnesium iodide in butyl ether solution. The results are in Table VI. Since only one oxygen atom is present in the molecule the two moles of methane must be formed from a water molecule which was removed from an alcohol structure.

2. Reaction with phenylisocyanate. A 0.5 g. sample of the substance was mixed with an equal quantity of phenylisocyanate and allowed to stand 24 hours at room temperature. Crystals formed which melted at 240° and were identified by a mixed melting point to be carbanilide. On heating the filtrate on a steam-bath for 30 minutes, followed by standing 12 hours, another crop of carbanilide was obtained. On standing three weeks, the filtrate failed to deposit more crystals and was discarded.

3. Hydrogenation of artemisol. Attempts were made to reduce the alcohol with sodium and alcohol; but because of the uncertainty of the results, this method was abandoned in favor of catalytic hydrogenation. In the presence of Adams' catalyst and in ethyl acetate solution, the compound rapidly absorbed hydrogen. A ten gram sample reacted with 2000 ml. of moist hydrogen at 647 mm. and 33–34°. The calculated amount was 2035 ml. The catalyst was removed and the solvent was distilled off. The product was vacuum distilled and the major portion was collected between

125° and 135° at 38 mm. The index of refraction was 1.4618 and the density 0.9153, both at 20°.

Half a gram of the hydrogenated alcohol was mixed with phenylisocyanate and allowed to stand 24 hours at room temperature. Crystals of carbanilide formed and were identified by mixed melting point.

4. Conversion of artemisol into p-*cymene.* Ten grams of artemisol was added to two grams of phosphorus pentasulfide. When the mixture was warmed, a reaction set in, liberating hydrogen sulfide. After the reaction had subsided, the mixture was refluxed for thirty minutes, then distilled and refluxed another thirty minutes with fresh phosphorus pentasulfide. Finally the product was refluxed for a total of 24 hours with metallic sodium. The yield of *p*-cymene was about two grams; the boiling point, 170–180°; the index of refraction, 1.4915 at 20°; and the density, 0.8663 at 20°.

One gram of the hydrocarbon was refluxed eight hours with 40 ml. of 1:3 nitric acid. On cooling, colorless crystals were obtained. On recrystallization from hot water their melting point was 180–182°. The original mixture was refluxed several hours longer and another crop of crystals was obtained. This material was added to that obtained before, and the mixture recrystallized from hot water. The first crop of crystals melted at 182–185°, and the second crop did not melt when heated

TABLE VI

SAMPLE	GRAMS	ML. OF CH_4 AT STANDARD CONDITIONS		
		Obs'd	Calc'd for 1 OH	Calc'd for HOH
Fraction 6a	0.1139	42.7	15.1	30.2
b	0.1380	39.5	18.3	36.6
Fraction 9a	0.1488	40.8	19.7	39.4
b	0.1590	42.6	21.1	42.2

as high as 260°. The first crop was converted into the *p*-bromophenacyl derivative, which melted at 154–155°. The same ester made from *p*-toluic acid melted at 155–156°. The mixed melting point was 155°. The higher-melting product from the oxidation was undoubtedly terephthalic acid which sublimes above 300°.

5. The dehydration and oxidation of hydrogenated artemisol. Eight grams of hydrogenated artemisol was refluxed with two grams of freshly fused sodium bisulfate. After heating one hour, two grams more of the bisulfate was added and the refluxing continued for two hours. Water appeared in the condenser. The product was distilled and refluxed with metallic sodium for several hours. A reddish-yellow sodium compound formed. The oil was distilled and again refluxed with fresh sodium. The hydrocarbon on distillation weighed three grams. The boiling range was 170–175°; the index of refraction, 1.4723, and the density, 0.8520, both at 20°.

Two grams of the hydrocarbon was refluxed five hours with five grams of chromic anhydride, 30 ml. of water, and 4 ml. of concentrated sulfuric acid. Another lot of the oxidizing reagent was added and the refluxing continued for a total of thirty hours. A water-insoluble, colorless product was filtered out. This was dissolved in a slight excess of hot sodium carbonate solution. The solution was filtered and the acid precipitated with dilute hydrochloric acid. Upon recrystallization from hot water the acid sublimed above 300°.

The methyl ester was prepared through the acid chloride, which was made by heating the acid with phosphorus pentachloride. The ester crystallized in long needles melting at 135–136°. Recrystallization from dilute ethyl alcohol failed to raise the melting point. A mixture with the methyl ester of terephthalic acid melted at 137–138°.[3]

6. Derivatives attempted. The sage alcohol was saturated with gaseous hydrogen chloride. The oil darkened and appeared to be attacked by the reagent, but no crystalline product was formed.

A sample of the alcohol was dehydrated by heating it with fused sodium bisulfate for one and one half hours. The hydrocarbon was distilled, and refluxed with metallic sodium for another hour and one half. The product distilled at 170–175° and had the index of refraction 1.4840, and the density 0.8557, both at 20°.

The product of dehydration was cooled with acetic acid in a freezing mixture. To the cold mixture, a cooled solution of sodium nitrite was added dropwise. A green oil formed, which was separated from the water solution and allowed to stand; no nitrosite crystallized. The process was repeated on a fresh sample; but, again, no crystalline product was obtained.

Hydrolysis of the higher-boiling fractions. Each of the high-boiling fractions, 90–100°, 100–120°, and 120–170° at about 20 mm., was refluxed for ten hours with alcoholic potassium hydroxide to which some water had been added. Each mixture was further diluted to separate the water-insoluble oil and the water solution distilled to remove the alcohol. The water solutions were then acidified and the volatile acids distilled. The distillates were neutralized with sodium hydroxide and evaporated to dryness. Each of the three fractions yielded, under these conditions, a salt which was rather impure. However, 0.5 g. of each was treated with *p*-bromophenacyl bromide. From the first fraction a crystalline product was obtained, which upon recrystallization melted at 82–83°. A mixed melting point with the ester of acetic acid melted at 83–84°, proving the presence of an acetic ester in this fraction of the oil. The remaining samples deposited an oily product, in addition to crystals of the unchanged reagent.

SUMMARY

The production of oil of sage brush, *Artemisia tridentata*, native to Utah, has been investigated. On fractionation of the oil four main divisions were obtained.

The first was characterized by the presence of the aldehyde, methacrolein.

The second contained essentially α-pinene. In addition, a lower- and a higher-boiling terpene were isolated.

The third was the cineole fraction. α-Terpinene, also, was identified, and evidence obtained for the presence of a third substance, in smaller quantity.

The fourth fraction contained large amounts of *d*-camphor. In addition,

[3] This work was done by Gordon S. Christianson in partial fulfillment of the requirements for the degree of Bachelor of Science in Chemical Engineering, May, 1941.

a liquid alcohol, isomeric with terpineol, was obtained and named artemisol. The acetate of artemisol appeared to be present in this fraction, also.

SALT LAKE CITY, UTAH.

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(2) ADAMS AND OAKBERG, *J. Am. Chem. Soc.*, **56**, 457 (1934).
(3) SHRINER AND SHARP, *J. Am. Chem. Soc.*, **62**, 2245 (1940).
(4) TSCHUGAEFF AND FOMIN, *Compt. rend.*, **151**, 1058 (1910).
(5) KISHNER, *J. Russ. Phys.-Chem. Soc.*, **42**, 1198 (1910).
(6) BRADY, *J. Chem. Soc.*, **133**, 756 (1931).

[CONTRIBUTION FROM THE GEORGE S. COX MEDICAL RESEARCH INSTITUTE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. V. ACETOLYSIS OF THE STEREOISOMERIC 5,6-OXIDES AND PREPARATION OF THE ACETATES OF 4-ANDROSTENE-3,17-DIONE-6(α)-OL AND 6(α)-HYDROXY-11-DESOXYCORTICOSTERONE.[1]

MAXIMILIAN EHRENSTEIN

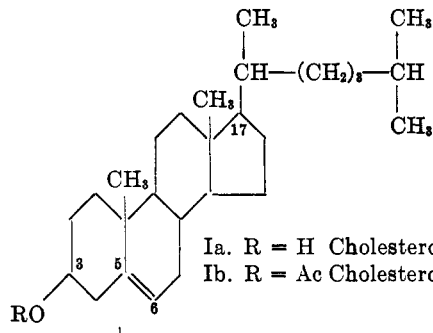
Received May 31, 1941

From cholesterol (Ia) two stereoisomeric oxides can be derived which may be expressed by formulas IIa and IIIa. They are called α-cholesterol oxide and β-cholesterol oxide respectively. The assigning of formulas IIa and IIIa is arbitrary.

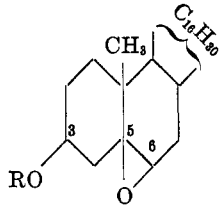
Hattori (1) recently studied the different behavior of the oxide rings of the two stereoisomeric forms towards various chemical reagents. He examined, for instance, the action of glacial acetic acid on the acetates of α-cholesterol oxide (IIb) and β-cholesterol oxide (IIIb) respectively. Special care was taken to ensure the purity of the two isomeric forms (IIb and IIIb) which served as starting material. He showed that in the α-isomer (IIb) the oxide ring is ruptured with the formation of a 6-acetoxy compound (IV) whereas the β-isomer (IIIb) furnishes a 5-acetoxy compound (V). The latter two reaction products (IV, V) were not characterized but were immediately subjected to mild acetylation (boiling with acetic anhydride). Since the α-isomer (IIb) eventually furnished the 3,6-diacetate (IV) one must assume that this diacetate was already the immediate result of the acetolysis of the oxide ring. The β-isomer eventually yielded the 3,5,6-triacetate (VI) which can only have arisen from the acetolysis product V.

In a recent publication Ehrenstein and Decker (2) studied the oxidation with permanganate of dehydroisoandrosterone acetate (VII). It was observed, unexpectedly, that two isomeric oxides could be isolated from the reaction mixture (VIII and IX). The lower-melting compound (m.p. 188–190°) was arbitrarily called α-oxide and the higher-melting one (m.p. 221–222.5°) β-oxide. We decided to investigate the behavior of these two oxides towards glacial acetic acid according to the procedure described by Hattori (1).

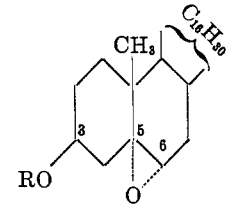
[1] Aided by a grant from the Smith, Kline, and French Laboratories in Philadelphia. Read before the Division of Organic Chemistry at the St. Louis meeting of the American Chemical Society, April 8, 1941 and in part before the Physiological Society of Philadelphia, May 20, 1941.



Ia. R = H Cholesterol.
Ib. R = Ac Cholesterol acetate.

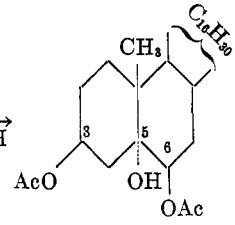


IIa. R = H α-Cholesterol oxide.
IIb. R = Ac Acetate of α-Cholesterol oxide.

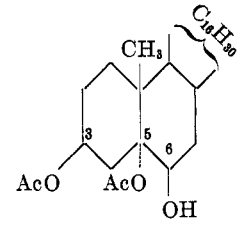


IIIa. R = H β-Cholesterol oxide.
IIIb. R = Ac Acetate of β-Cholesterol oxide.

IIb $\xrightarrow[CH_3COOH]{\text{glacial}}$



IV. Cholestane-3(β),5,6(*trans*)-triol 3,6-diacetate.[2]



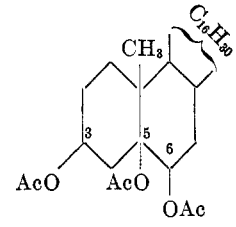
$\xleftarrow[CH_3COOH]{\text{glacial}}$ IIIb

V. Cholestane-3(β),5,6(*trans*)-triol 3,5-diacetate.[2]

Ac_2O ↓

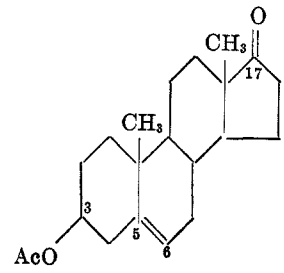
No Change.

Ac_2O ↓

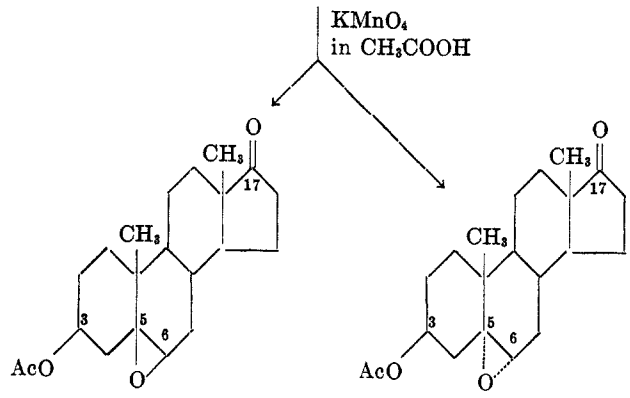


VI. Cholestane-3(β),5,6(*trans*)-triol triacetate.[2]

[2] The marking of the configurations at carbon atoms 5 and 6 is in conformity with findings of Ellis and Petrow, *J. Chem. Soc.*, **1939**, 1078.

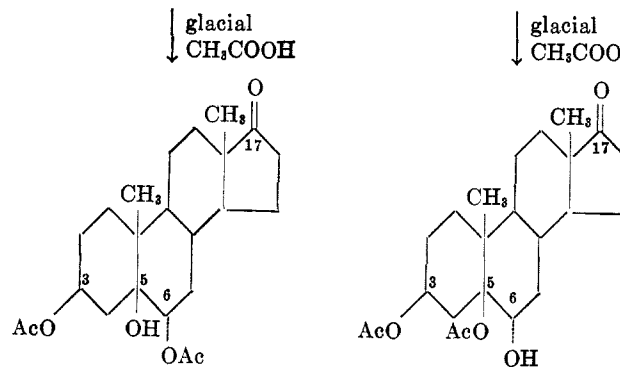


VII. Dehydroisoandrosterone acetate.



VIII. Androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate.[3] (Oxide of m.p. 221–222.5°)

IX. Androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate.[3] (Oxide of m.p. 188–190°)

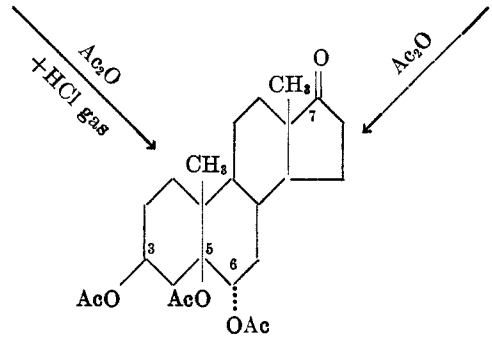


X. Androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate.[4]

XI. Androstane-17-one-3(β),5,6(*trans*)-triol 3,5-diacetate.[4]

[3] Note the change of nomenclature.

[4] The marking of the configurations at carbon atoms 5 and 6 is in conformity with conclusions drawn by Ehrenstein, *J. Org. Chem.*, **4**, 506 (1939). See also Ehrenstein and Decker (2).



XII. Androstane-17-one-3(β),5,6(*trans*)-triol triacetate.[4]

The higher-melting isomer (VIII) furnished, by treatment with glacial acetic acid, an almost quantitative yield of androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (X), a compound which had been previously prepared in this laboratory (2). This proves that the acetolytic rupture of the oxide ring had resulted in an acetoxyl group at carbon atom 6 and a hydroxyl group at carbon atom 5.

The lower-melting oxide (IX), treated with glacial acetic acid, yielded a hitherto unknown substance which could only be interpreted as androstane-17-one-3(β),5,6(*trans*)-triol 3,5-diacetate (XI). Hence the acetolytic rupture of the oxide ring gave in this instance an acetoxyl group at carbon atom 5 and a hydroxyl group at carbon atom 6. In agreement with this conclusion, mild acetylation (boiling with acetic anhydride) of the acetolysis product (XI) furnished androstane-17-one-3(β),5,6(*trans*)-triol triacetate (XII). The same triacetate (XII) could also be obtained by more vigorous acetylation of androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (X) with acetic anhydride and hydrogen chloride gas.

It follows that the higher-melting oxide (VIII), which Ehrenstein and Decker (2) arbitrarily called β-oxide, behaves towards glacial acetic acid as does the acetate of α-cholesterol oxide in that it furnishes a 6-acetoxy compound. In turn, the lower-melting oxide (IX), which Ehrenstein and Decker (2) described as α-oxide, yields with glacial acetic acid a 5-acetoxy compound, and hence behaves in this respect as does the acetate of β-cholesterol oxide. One is entitled to assume that oxides with analogous configurations of the oxide rings will furnish analogous acetolytic products.

Change of Nomenclature. We therefore propose that contrary to the nomenclature used in our earlier publication (2) the higher-melting isomer (m.p. 221–222.5°; $[\alpha]_D^{26}$ −10.0°)[5] be called androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate (VIII) and the lower-melting isomer (m.p. 188–190°; $[\alpha]_D^{26}$ − 58.4°)[5] be called androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate

[5] In the previous paper (2) the rotation was erroneously recorded with a plus sign. See also: Ruzicka, Grob, and Raschka (6).

(IX). In this way the configurational relationship of these substances to the corresponding oxides of cholesterol is properly expressed.

As is known (3), treatment of cholesterol with perbenzoic acid furnishes mainly α-cholesterol oxide, whereas with cholesterol acetate, the main product appears to be β-cholesterol oxide acetate. Treatment of dehydroisoandrosterone with perbenzoic acid yields (4,5) mainly an α-oxide (new nomenclature). The acetate of dehydroisoandrosterone furnishes with perbenzoic acid likewise mainly an α-oxide. This observation is in agreement with a recent finding of Ruzicka, Grob, and Raschka (6).

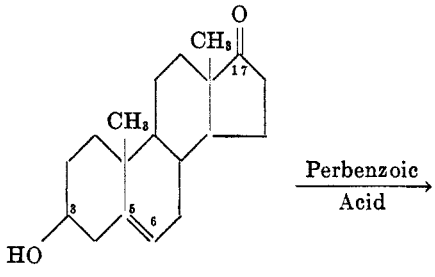
About one year ago Ehrenstein and Stevens (7) described the synthesis of 6-acetoxyprogesterone. In this substance, carbon atom 3 forms a keto group, there is a double bond between carbon atoms 4 and 5, and an acetoxyl group is attached to carbon atom 6. The method of preparation used in the case of 6-acetoxyprogesterone is a limited one. As will be shown later, a more general procedure has been developed for the preparation of this type of compounds.

As mentioned before, dehydroisoandrosterone (XIII) furnishes (4,5) with perbenzoic acid mainly an α-oxide [androstane-(5,6) (α)-oxide-17-one-3(β)-ol] (XIV). When this substance was refluxed with glacial acetic acid, rupture of the oxide ring occurred and androstane-17-one-3(β),5,6(*trans*)-triol 6-monoacetate (XV) resulted. Under these experimental conditions there occurred to a certain extent also acetylation at carbon atom 3 with formation of androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (X). This side reaction can be largely suppressed by refluxing with glacial acetic acid for a shorter period of time. The 3,6-diacetate (X) was also obtained by acetylating the 6-monoacetate (XV) with acetic anhydride. When the 6-monoacetate (XV) was subjected to oxidation with chromic acid, the corresponding 3-keto compound, namely androstane-3,17-dione-5,6(*trans*)-diol 6-monoacetate (XVI) resulted. Dehydration of the latter substance with dry hydrogen chloride in a solution of chloroform yielded 4-androstene-3,17-dione-6(α)-ol acetate [6(α)-acetoxy-4-androstene-3,17-dione] (XVII). The configuration of this compound at carbon atom 6 is probably analogous to that of 6(α)-acetoxyprogesterone (7). The ultraviolet absorption spectrum[6] (Figure 1) is in agreement with the proposed structure. The maximum absorption was found to be at 235mμ; the molecular extinction coefficient is 16020.

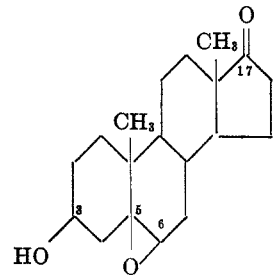
The 6(α)-acetoxy-4-androstene-3,17-dione (XVII) was examined by means of the comb growth method through the courtesy of Dr. F. C. Koch at the University of Chicago. It was found to be one-fifth as active as

[6] We are indebted to Professor George R. Harrison of the Department of Physics of the Massachusetts Institute of Technology for the determination of the ultraviolet absorption spectrum.

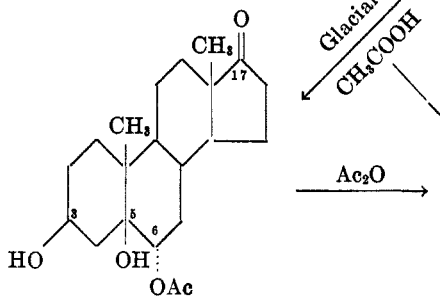
androsterone by the comb growth test (local application). Assays on 4-androstene-3,17-dione by the same method gave the same order of



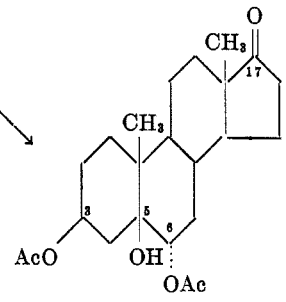
XIII. Dehydroisoandrosterone.



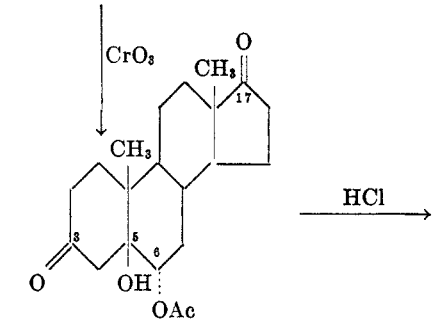
XIV. Androstane-(5,6)(α)-oxide-17-one-3(β)-ol.



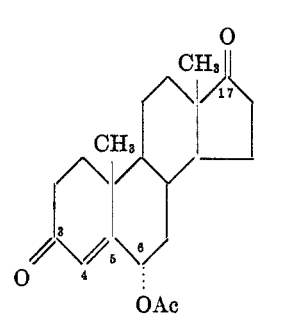
XV. Androstane-17-one-3(β), 5,6(*trans*)-triol 6-monoacetate.[4]



X. Androstane-17-one-3(β),5, 6(*trans*)-triol 3,6-diacetate.[4]



XVI. Androstane-3,17-dione-5,6(*trans*)-diol 6-monoacetate.[4]



XVII. 4-Androstene-3,17-dione-6(α)-ol acetate. [6(α)-Acetoxy-4-androstene-3,17-dione]

activity as androsterone. The same relative activities were also found by the intramuscular injection capon method for androsterone and 4-an-

drostene-3,17-dione. The new androgenic substance (XVII) still has to be examined for its effect on the genital tract (seminal vesicles, etc.).

The remaining experiments of this paper are based on considerations

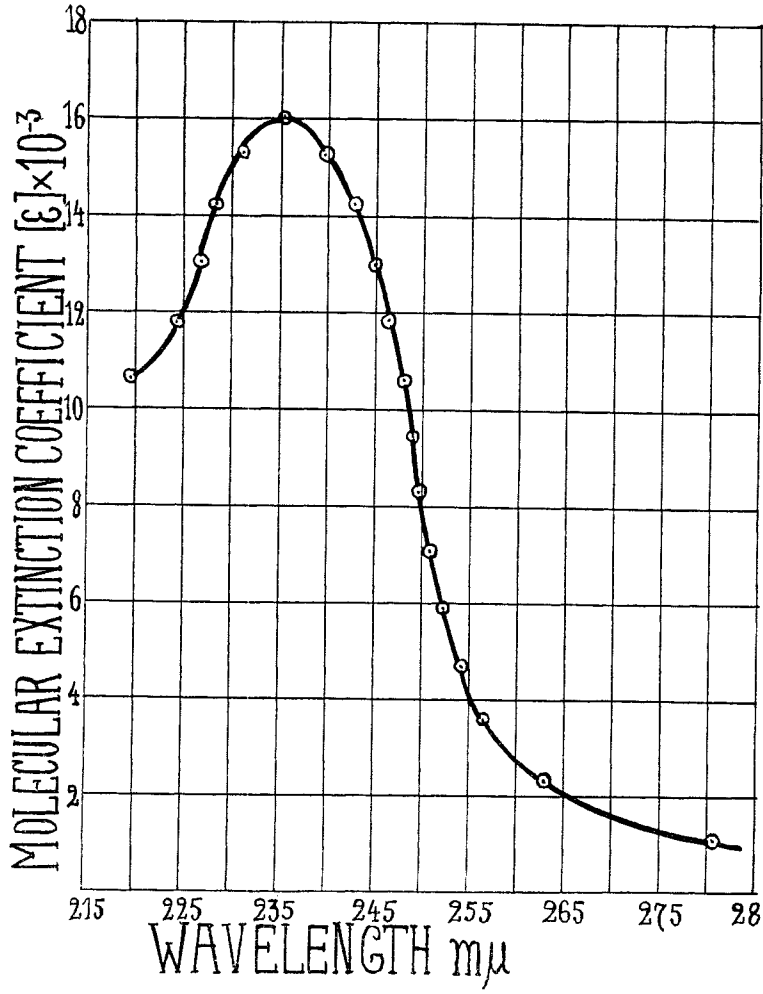
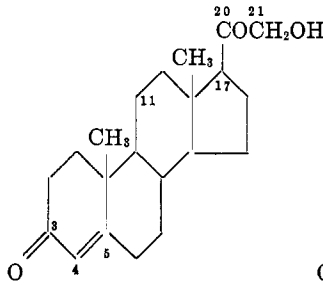


FIG. 1. ABSORPTION CURVE OF 6(α)-ACETOXY-4-ANDROSTENE-3,17-DIONE (IN ABSOLUTE ALCOHOL)

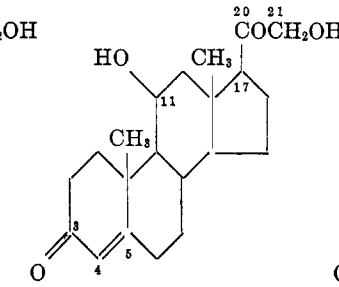
which arise in connection with the physiological activities of the various adrenal cortical hormones. From a chemical point of view 11-desoxy-corticosterone (A) represents the simplest compound with adrenal cortical action. The other hormones of the adrenal cortex are derived from this

substance in that they are oxygenated at carbon atom 11 (B and C), at carbon atom 17 (D) or at both carbon atoms 11 and 17 (E and F). It is known that 11-desoxycorticosterone (A) maintains the life of adrenalectomized animals, and that it prevents loss of sodium chloride and water. It has no significant influence upon carbohydrate metabolism or muscular activity. The hormones which have oxygen attached to carbon atom 11 (B, C, E, and F) are not very effective as so-called life-maintenance hormones. They possess, however, a pronounced influence on carbohydrate

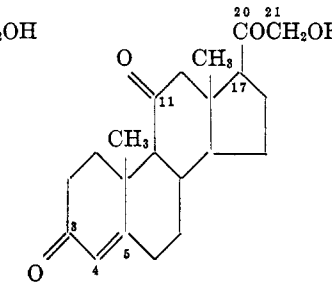
Adrenal Cortical Hormones



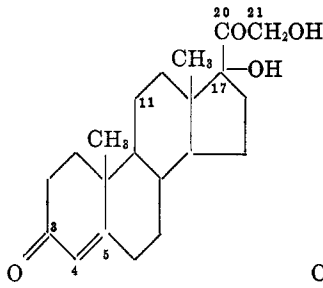
A. 11-Desoxycorticosterone. [21-Hydroxyprogesterone]



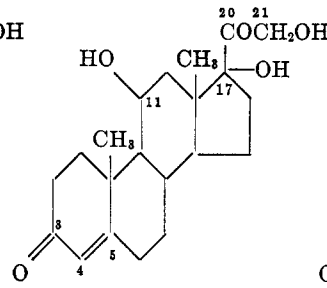
B. Corticosterone.



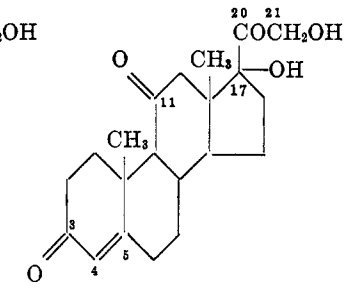
C. 11-Dehydrocorticosterone.



D. 17-Hydroxy-11-desoxycorticosterone.



E. 17-Hydroxy-corticosterone.



F. Hydroxy-11-dehydrocorticosterone.

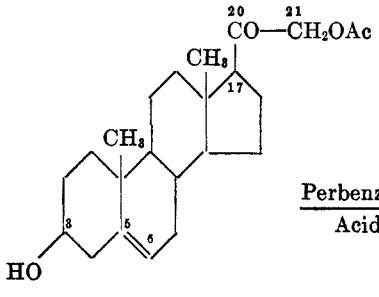
metabolism in that they produce a diabetogenic action. At the same time they enhance the work performance of adrenalectomized animals. Ingle (8) found recently that 17-hydroxy-11-desoxycorticosterone (D), Reichstein's (9) substance "S", manifests no diabetogenic effect and is not effective in his work performance test. It appears, therefore, that a hydroxyl group attached to carbon atom 17 has no influence upon these two physiological manifestations. At the present time no data are available which would indicate that the adrenal cortical hormones E and F are

physiologically more active than hormones B and C respectively. Hence the conclusion may be drawn that only the oxygen attached to carbon atom 11 is essential for diabetogenic action and muscle work and that the hydroxyl group at carbon atom 17 in hormones E and F is not significant as far as these manifestations are concerned.

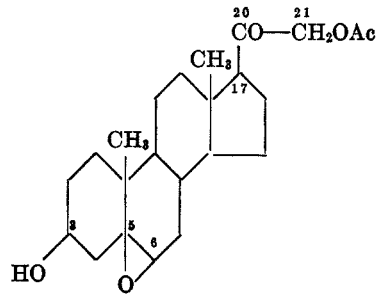
At present only 11-desoxycorticosterone (A) (10) and 17-hydroxy-11-desoxycorticosterone (D) (11) are available synthetically. The former of these two substances is comparatively easily accessible. It occurs in adrenal glands only to a small extent and, as explained above, exerts only part of the physiological manifestations of whole adrenal cortical extract. It is therefore suggested to the chemist to synthesize some of the adrenal cortical hormones which have oxygen attached to carbon atom 11. The synthesis of such compounds appears very difficult for reasons which will not be discussed here. However, the question arises whether the introduction of oxygen at a carbon atom other than 11 of the 11-desoxycorticosterone molecule (A) can be successfully carried out and whether this will modify the physiological activity in a useful manner. As pointed out, no carbohydrate or work effect followed the introduction of oxygen at carbon atom 17.

It has been possible to prepare the diacetate of a substance which is derived from 11-desoxycorticosterone (A) in that this substance carries a hydroxyl group at carbon atom 6. Such a compound is an isomer of corticosterone. The method of preparing this substance is analogous to the experiment in the androstane series described above.

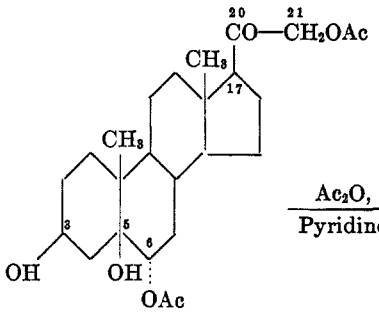
Starting material for this sequence of reactions was 21-acetoxy-4-pregnene-20-one-3(β)-ol (XVIII), a substance which represents an intermediary in the synthesis of 11-desoxycorticosterone (A) (10). Treatment of this substance with perbenzoic acid happened to yield mainly the (5,6)(α)-oxide (XIX) as shown by the subsequent reactions. When pregnane-(5,6)(α)-oxide-20-one-3(β),21-diol 21-monoacetate (XIX) was treated with glacial acetic acid a certain quantity of pregnane-20-one-3(β),5,6(*trans*),21-tetraol 3,6,21-triacetate (XXI) was obtained. The amount of this substance could be kept small by the selection of proper experimental conditions. The main product of the reaction was pregnane-20-one-3(β),5,6(*trans*),21-tetraol 6,21-diacetate (XX). Acetylation of this compound with acetic anhydride and pyridine furnished the above mentioned 3,6,21-triacetate (XXI). Oxidation of the 6,21-diacetate (XX) with chromic acid yielded pregnane-3,20-dione-5,6(*trans*),21-triol 6,21-diacetate (XXII). Dehydration of the latter substance with dry hydrogen chloride resulted in the formation of 4-pregnene-3,20-dione-6(α),21-diol diacetate [6(α)-hydroxy-11-desoxycorticosterone diacetate] (XXIII). The relative configuration at carbon atoms 5 and 6 in compounds XX, XXI, and XXII is given as "*trans*" in analogy with condi-



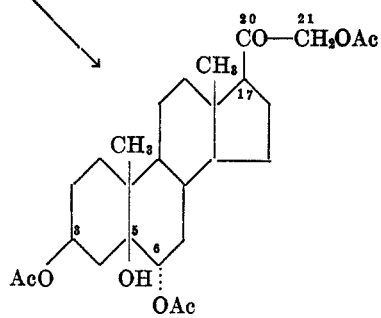
XVIII. 5-Pregnene-20-one-3(β),21-diol 21-monoacetate. (21-Acetoxy-4-pregnene-20-one-3(β)-ol)



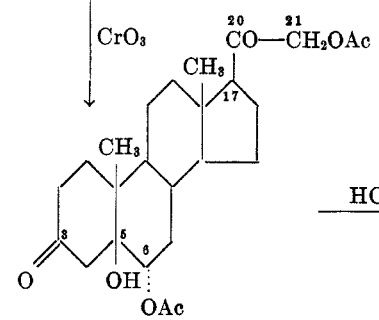
XIX. Pregnane-(5,6)(α)-oxide-20-one-3(β),21-diol 21-monoacetate.



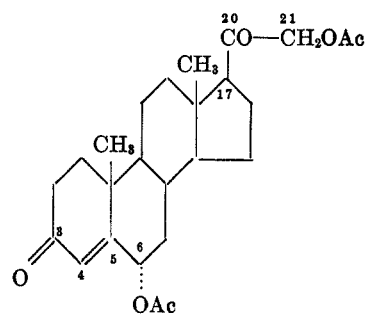
XX. Pregnane-20-one-3(β),5,6(*trans*),21-tetraol 6,21-diacetate.



XXI. Pregnane-20-one-3(β),5,6(*trans*),21-tetraol 3,6,21-triacetate.



XXII. Pregnane-3,20-dione-5,6(*trans*),21-triol 6,21-diacetate.



XXIII. 4-Pregnene-3,20-dione-6(α),21-diol diacetate. [6(α)-Hydroxy-11-desoxycorticosterone diacetate.]

tions in the cholestane and androstane series. The actual configuration at carbon atom 5 is not known. The designation "α" applied to the configuration of the acetoxyl group at carbon atom 6 of the last compound

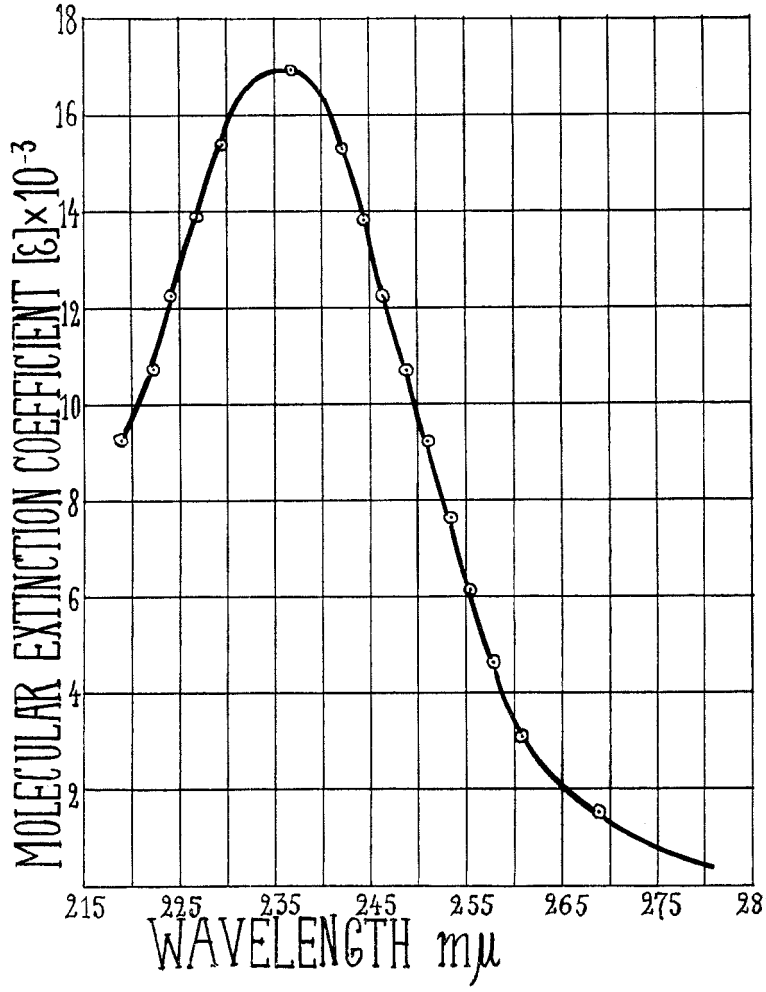


FIG. 2. ABSORPTION CURVE OF 6(α)-HYDROXY-11-DESOXYCORTICOSTERONE DIACETATE (IN ABSOLUTE ALCOHOL)

of this series (XXIII) is arbitrary. The ultraviolet absorption spectrum[6] of the diacetate of 6(α)-hydroxy-11-desoxycorticosterone (XXIII) (Figure 2) has its maximum at a wave length of about 236 mμ; the molecular extinction coefficient in 16900.

The new substance (XXIII) underwent a preliminary physiological examination by D. J. Ingle in this laboratory who found that it produced no diabetogenic action in partially depancreatized rats given up to one milligram per day and that it had no influence upon the work performance of adrenalectomized rats (up to two milligrams per day). The activity of this compound in respect to its ability to maintain life and growth of adrenalectomized rats is definitely less than that of 11-desoxycorticosterone acetate. A daily dose of 0.05 milligrams of 11-desoxycorticosterone acetate uniformly maintains life and permits weight gains in adrenalectomized rats. The effective dose of the new substance (XXIII) is not less than 0.5 milligrams daily and appears to lie between 0.5 and 1.0 milligrams. The compound still has to be examined for its effect upon salt metabolism and for possible other manifestations.

We believe that the sequence of reactions which was utilized for the preparation of 6(α)-acetoxy-4-androstene-3,17-dione (XVII) and of the diacetate of 6(α)-hydroxy-11-desoxycorticosterone (XXIII) can be generally applied for the preparation of 4,5-unsaturated steroids in which carbon 3 forms a keto group and in which an acetoxyl group is attached to carbon atom 6. Hence the 6(α)-acetoxyprogesterone previously prepared by Ehrenstein and Stevens (7) according to another procedure should also be accessible by means of the new scheme. Experiments on this line will be published separately.

EXPERIMENTAL

All melting points were determined with the Fisher-Johns melting point apparatus of the Fisher Scientific Company (Pittsburgh, Pa.). The readings are sufficiently near the true melting points so that no corrections have been made. All microanalyses, unless otherwise stated, were carried out by Mr. William Saschek, Columbia University, New York. The dehydroisoandrosterone and 21-acetoxypregnenonol were kindly furnished by Dr. Erwin Schwenk of the Schering Corporation in Bloomfield, N. J.

Androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate (VIII). (Note the change of nomenclature.) To a solution of 840 mg. of dehydroisoandrosterone acetate (m.p. 168–169°) in 17 cc. of chloroform was added in the cold-room 7.7 cc. of a chloroform solution containing about 20% excess of perbenzoic acid (422 mg.). This mixture was allowed to stand in the cold-room for 27 hours and at room temperature for 3.5 days. It was then treated with a solution of *N* sodium carbonate, washed with water, and finally dried with sodium sulfate. On removing the solvent, 898 mg. of a white crystalline residue was obtained. Recrystallization from ether yielded a first crop of m.p. 217–220°; weight 350 mg. The subsequent fractions obtained from the mother liquor had considerably lower melting points. Renewed crystallization of the first crop from ether raised the melting point to 223–224°. No attempt was made to separate from the lower-melting fractions the acetates of the (5,6)(α)-oxide and (5,6)(β)-oxide respectively.

Acetolysis of androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate (VIII); *preparation*

of androstane-3(β),5,6(trans)*-triol 3,6-diacetate* (X). A solution of 203 mg. of pure androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate (VIII) (note the change of nomenclature) in 6 cc. of glacial acetic acid was refluxed for a period of two hours and then brought to dryness *in vacuo*. After the addition of water and some subsequent standing, the reaction product was filtered and then dried in a vacuum desiccator. Yield: 230 mg. This material was recrystallized from ether, in which it was comparatively easily soluble. The following crystalline fractions were obtained: First crop: wt. 95.7 mg.; m.p. 216.5–217°. Second crop: wt. 71.9 mg.; m.p. 216.5–217°. Third crop: wt. 36.5 mg.; m.p. 212–215°. Fourth crop: wt. 3.2 mg.; m.p. 207–211°. Total of crystalline fractions: 207.3 mg. When the mother liquor was brought to dryness a resinous residue resulted. There was no depression of the melting point when the crystalline fractions were mixed with an authentic sample of androstane-3(β),5,6(*trans*)-triol 3,6-diacetate (12).

Acetolysis of androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate (IX); *preparation of androstane-17-one-3(β),5,6*(trans)*-triol 3,5-diacetate* (XI). Seventy-five milligrams of androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate (IX) (preparation of m.p. 187.5–188.5° (13) (note the change of nomenclature) was dissolved in 3.2 cc. of glacial acetic acid. This solution was refluxed for two hours and then brought to dryness *in vacuo*. Water was added to the resinous residue. The sticky mass gradually solidified when it was subjected to some kneading. After subsequent standing overnight, the solidification was complete. The precipitate was then filtered, washed, and dried in a vacuum desiccator; weight: 65.1 mg. (trace lost by accident). This material was purified by means of chromatographic fractionation, for which purpose it was dissolved in a mixture of 10 cc. of benzene and 10 cc. of petroleum ether. This solution was filtered through a suitably prepared column of 2.2 g. of aluminum oxide (aluminum oxide anhydrous, standardized for chromatographic adsorption according to Brockmann, E. Merck, Darmstadt).

Chromatographic Fractionation

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE (MG.)	APPEARANCE OF RESIDUE
1	10 cc. benzene + 10 cc. petroleum ether	1.2	Resin and crystals
2	13 cc. benzene + 7 cc. petroleum ether	3.1	Colorless glass
3	30 cc. benzene	17.1	Colorless glass
4	10 cc. benzene + 10 cc. ether	22.5	Mainly crystalline
5	5 cc. benzene + 15 cc. ether	5.6	Resin with some crystalline centers
6	20 cc. ether	4.9	Resin with some crystalline centers
7	20 cc. ether	2.8	Resin
8	15 cc. ether + 5 cc. chloroform	2.2	Resin, trace of crystals
9	10 cc. ether + 10 cc. chloroform	2.4	Mainly crystalline
10	5 cc. ether + 15 cc. chloroform	1.2	Resin
11	30 cc. chloroform	2.5	Resin
12	30 cc. chloroform + 10 cc. methanol	1.4	Resin
Total		66.9	

The residues of fractions 3 and 4 were treated with a little ether which caused crystals to separate from fraction 3 also. The crystalline separations were filtered after some standing. Yields: From fraction 3: 7.3 mg., m.p. 203.5–205°. From fraction 4: 21.1 mg.; m.p. 203.5–205.5°. These two crystalline crops were combined and dissolved in the necessary amount of ether. When this solution was brought to a smaller volume and a little petroleum ether was added, crystallization of rosettes of large prisms took place. Yield: 22.4 mg.; m.p. 202.5–204°. A second crop (3.0 mg.) melted slightly higher. It may be mentioned that the crystalline separations obtained from fractions 5 and 6 also had a slightly higher melting point. When a sample of the main crop (m.p. 202.5–204°) was mixed with an authentic sample of androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (m.p. 216.5–217°) (12) there was complete melting at 188–190°; $[\alpha]_D^{26.1}$ + 22.7° (6.6 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{23}H_{34}O_6$: C, 67.94; H, 8.43.
Found: C, 67.67; H, 8.31.

Androstane-17-one-3(β),5,6(trans)-*triol 3,5,6-triacetate* (XII): *A. From androstane-17-one-3(β),5,6*(trans)-*triol 3,5-diacetate* (XI). A solution of 10.0 mg. of androstane-17-one-3(β),5,6(*trans*)-triol 3,5-diacetate (XI) in 0.2 cc. of acetic anhydride was refluxed for 85 minutes. After cooling to room temperature, water was added. The sticky precipitate gradually solidified when it was subjected to some kneading; it was eventually filtered and dried; yield: 9.1 mg. This material was recrystallized from methanol to which some water was added. On standing stout crystals separated slowly. First crop: wt. 3.3 mg.; m.p. 184–185°. Second crop: wt. 3.0 mg.; m.p. 184–185°.

Anal. Calc'd for $C_{25}H_{36}O_7$: C, 66.92; H, 8.09.
Found: C, 66.86; H, 8.12.

B. From androstane-17-one-3(β),5,6(trans)-*triol 3,6-diacetate* (X). One hundred milligrams of androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (X) was dissolved in 10.0 cc. of acetic anhydride. This solution was refluxed for a period of 75 minutes during which time a stream of dry hydrogen chloride was passed through it. The reaction mixture was then poured into ice-water, which caused a white precipitate to appear. Dry weight: 88 mg.; m.p. about 175–180°. This substance was recrystallized from methanol to which some water was added. First crop: wt. 46.7 mg.; m.p. 185–186°. Second crop: wt. 22.6 mg.; m.p. 184–185.5°. There was no depression of the melting point when this pure material was mixed with a sample of the substance (m.p. 184–185°) described above under the heading "A"; $[\alpha]_D^{26.1}$ − 8.2° (23.3 mg. in 2.0 cc. of acetone).

Acetolysis of androstane-(5,6)(α)-oxide-17-one-3(β)-ol (XIV);[7] *preparation of androstane-17-one-3(β),5,6*(trans)-*triol 3,6-diacetate* (X) *and of androstane-17-one-3(β),5,6*(trans)-*triol 6-monoacetate* (XV). A solution of 81 mg. of androstane-(5,6)(α)-oxide-17-one-3(β)-ol (XIV) (note change of the nomenclature) in 2.5 cc. of glacial acetic acid was refluxed (metal-bath) for two hours and then brought to dryness *in vacuo*. On adding water to the residue, the latter turned to a white powder. It was filtered after brief standing; dry weight 93.7 mg. This material was subjected to chromatographic adsorption, for which purpose it was dissolved in 55 cc. of benzene; this solution was filtered through a suitably prepared column of 3 g. of aluminum oxide (Brockmann).

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[7] Prepared by Thelma O. Stevens and Marguerite Twaddell Decker according to the procedure of Miescher and Fischer (5).

Chromatographic Fractionation

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE (MG.)	APPEARANCE OF RESIDUE
1	55 cc. benzene (original solution)	2.3	Resinous
2	30 cc. benzene	14.2	Resinous
3	7.5 cc. benzene + 7.5 cc. ether		Lost by accident
4	5 cc. benzene + 10 cc. ether	6.9	Partly crystalline?
5	20 cc. ether	5.8	Resinous
6	20 cc. ether	5.4	Resinous, some crystal centers
7	10 cc. ether + 5 cc. chloroform	5.0	Many crystal centers
8	5 cc. ether + 10 cc. chloroform	8.0	Many crystal centers
9	30 cc. chloroform	11.0	Resinous
10	10 cc. chloroform + 5 cc. methanol	26.0	Crystalline
11	15 cc. methanol	4.8	White mass
Total		89.4	

Androstane-17-one-3(β),5,6(trans)*-triol 3,6-diacetate* (X). When the residues of fractions 2, 4, 5, 6, 7, and 8 of the chromatographic treatment were separately recrystallized from ether to which some petroleum ether was added, fair amounts of material melting between 213° and 218° could be secured. There was no depression of the melting point when the various crystalline fractions were mixed with an authentic sample of androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (12).

Androstane-17-one-3(β),5,6(trans)*-triol 6-monoacetate* (XV). The residues of fractions 9 and 10 of the chromatographic treatment proved to be very difficultly soluble in ether. Various crystalline crops, totalling 34.5 mg. and melting between 270° and 275° could be secured by recrystallizing from acetone. These crops were combined and once more recrystallized from acetone; stout prisms crystallized slowly. The substance melted with decomposition to a light brown liquid at 276–277°; $[\alpha]_D^{23.9}$ + 23.6° (21.9 mg. in 2.0 cc. of methanol).

Anal. Calc'd for $C_{21}H_{32}O_5$: C, 69.18; H, 8.85.
Found: C, 69.18; H, 8.76.

On the basis of the observations made in connection with the above described experiment, the following simplified procedure for the preparation of androstane-17-one-3(β),5,6(*trans*)-triol 6-monoacetate (XV) was developed:

A solution of 855 mg. of androstone-(5,6)(α)-oxide-17-one-3(β)-ol (XIV) in 26 cc. of glacial acetic acid was refluxed (metal-bath, temperature about 125°) for a period of 45 minutes. Immediately thereafter it was brought to dryness *in vacuo*. The residue was a white crystalline mass which was suspended in some water and filtered after some standing. Dry weight: 954 mg. This material was treated with ether with the intention of removing the androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (X). For this purpose it was boiled for several minutes with 150 cc. of ether. After subsequent standing at room temperature, the suspension was filtered. A white powder (690 mg.) was obtained which melted and decomposed at 274–275°. When the ethereal filtrate was concentrated to a smaller volume a second crop (48 mg.) was secured; m.p. about 245–250°; this material obviously represented a mixture. Recrystallization of the first crop from acetone yielded a number of crystalline fractions, all of which melted at 275–276° (decomp.).

Androstane-17-one-3(β),5,6(trans)*-triol 3,6-diacetate* (X) *by acetylating androstane-17-one-3(β),5,6*(trans)*-triol 6-monoacetate* (XV). A solution of 10 mg. of androstane-17-one-3(β),5,6(*trans*)-triol 6-monoacetate (XV) (m.p. 275–277°) in 0.2 cc. of acetic anhydride was refluxed for thirty minutes. Thereafter some water was added; crystallization began after rubbing with a glass rod. The crystalline precipitate was filtered after some standing. Dry weight 9.4 mg.; m.p. between 208° and 214°. When this substance was recrystallized from a mixture of ether and petroleum ether, a rosette arrangement of prisms was obtained; wt. 6.0 mg.; m.p. 216.5–217.5°. A second crop (2.1 mg.) melted at 212–214°. This material did not show a depression of the melting point when it was mixed with an authentic sample of androstane 17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (12).

Anal. Calc'd for $C_{23}H_{34}O_6$: C, 67.94; H, 8.43.
Found: C, 67.76; H, 8.21.

Androstane-3,17-dione-5,6(trans)*-diol 6-monoacetate* (XVI). Two hundred and fifty-five milligrams (0.7 millimole) of androstane-17-one-3(β),5,6(*trans*)-triol 6-monoacetate (XV) was dissolved in 10.5 cc. of glacial acetic acid by warming on the water-bath for a few minutes only and then cooling with water to room temperature. To this solution was added 16.1 cc. (the equivalent of 1.15 atoms of O) of a solution of 333 mg. of chromium trioxide in 100 cc. of 90% acetic acid. The mixture was allowed to stand at room temperature for 22 hours. After subsequent addition of 12 cc. of alcohol it was brought almost to dryness *in vacuo*. On adding water to the residue, a white precipitate appeared which was taken up in a rather large volume of ether. The ether phase was washed with a solution of *N* sodium carbonate and thereafter three times with water. After the removal of the solvent 227 mg. of a white crystalline residue was obtained. It was dissolved in a large volume of ether. By gradually concentrating the latter to a smaller volume, several crops of rather stout needle-shaped crystals, totalling 182 mg., were obtained; the melting points were between 217° and 219°. Considerably lower-melting crops were secured on further concentrating the ethereal solution. The high-melting material was once more recrystallized from ether; m.p. 219–220.5°; $[\alpha]_D^{25.1}$ + 44.6° (5.6 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{21}H_{30}O_5$: C, 69.57; H, 8.35.
Found: C, 68.94; H, 8.26.

4-Androstene-3,17-dione-6(α)-ol acetate. [*6(α)-hydroxy-4-androstene-3,17-dione acetate, 6(α)-acetoxy-4-androstene-3,17-dione*] (XVII). One hundred milligrams of androstane-3,17-dione-5,6(*trans*)-diol 6-monoacetate (XV) was dissolved in 17 cc. of alcohol-free redistilled chloroform. A moderate stream of dry hydrogen chloride was passed through for a period of three hours while the solution was cooled with ice and the temperature kept below +2°. After this the reaction mixture was poured into an ice-cold solution of *N* sodium carbonate and shaken in a separatory funnel. The chloroform phase was washed three times with water and thereafter dried with sodium sulfate overnight. After removal of the solvent a colorless resin was obtained which was dried in a vacuum desiccator. After three days' standing, it had solidified to a yellowish crystalline mass. It was allowed to stand for a time with some ether and was then filtered. More crystalline crops were secured by concentrating the mother liquor. The first three crops totalled 78.1 mg.; the melting points were between 168.5° and 175°. A fourth crop (3.1 mg.) melted between 185° and 195° (unchanged starting material?). The first three crops were combined, dissolved in a rather large volume of ether, and then concentrated to a lower volume. A total of 65.4 mg. of crystals melting at 174–176° was obtained. Somewhat lower-melting

material was secured from the mother liquor; $[\alpha]_D^{26.7}$ +153.5° (20.0 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{21}H_{28}O_4$: C, 73.21; H, 8.20.
Found: C, 73.01; H, 8.17.

Pregnane-(5,6)(α)-oxide-20-one-3(β),21-diol 21-monoacetate (XIX). The 21-acetoxypregnenonol [5-pregnene-20-one-3(β),21-diol 21-monoacetate] (XVIII) used for this experiment had a melting point of about 180°. Steiger and Reichstein (14) record 184–185°.

To a solution of 900 mg. of 21-acetoxypregnenonol in 18 cc. of chloroform was added in the cold-room 7.5 cc. of a chloroform solution containing approximately 20% excess of perbenzoic acid (412 mg.). The mixture was allowed to stand in the cold-room for about one day and thereafter at room temperature for three more days. It was then washed with *N* sodium carbonate solution and with water. After drying with sodium sulfate it was brought to dryness; weight of the crystalline white residue 945 mg.

In a preliminary experiment the crude oxide had been subjected to purification by means of chromatographic adsorption. As a result of this experiment it was learned that the mixture of the two stereoisomeric oxides consisted to a very large extent of the α-isomer, which crystallized from acetone in needles and melted at 195–197°. In the main experiment, purification by means of chromatographic adsorption was abandoned because mere crystallization of the above residue (945 mg.) from acetone furnished about 660 mg. of material melting at 194–195°. More of fairly pure α-oxide could be obtained by repeatedly recrystallizing the material contained in the mother liquor. Optical rotation and analysis refer to the purest crystalline fraction (m.p. 195–197°) of the above mentioned preliminary experiment; $[\alpha]_D^{26.1}$ + 15.6° (9.6 mg. in 2.0 cc. of acetone).

Anal.[8] Calc'd for $C_{23}H_{34}O_5$: C, 70.72; H, 8.78.
Found: C, 70.96; H, 9.03.

Acetolysis of pregnene-(5,6)(α)-oxide-20-one-3(β),21-diol 21-monoacetate (XIX); *preparation of pregnane-20-one-3(β),5,6*(trans),*21-tetraol 3,6,21-triacetate* (XXI) *and of pregnane-20-one-3(β),5,6*(trans),*21-tetraol 6,21-diacetate* (XX). In a preliminary experiment, 200 mg. of the above α-oxide (XIX) was refluxed with 6.0 cc. of glacial acetic acid for 105 minutes. From this, 227 mg. of a crude product was obtained. This was subjected to chromatographic adsorption which furnished a total of about 95 mg. of "crystalline material" consisting mainly of pregnane-20-one-3(β),-5,6(*trans*),21-tetraol 3,6,21-triacetate (XXI) (melting point after purification 176–177.5°). About 105 mg. of "non-crystalline material" was obtained which represented the crude pregnane-20-one-3(β),5,6(*trans*),21-tetraol 6,21-diacetate (XX). Since we were mainly interested in the latter compound, it was decided to shorten the refluxing with glacial acetic acid in the hope that this would improve the yield of the 6,21-diacetate (XX). This was actually the case and therefore this experiment will be described in full.

A solution of 440 mg. of pregnane-(5,6)(α)-oxide-20-one-3(β),21-diol 21-monoacetate (XIX) in 13.2 cc. of glacial acetic acid was refluxed (temperature of metal-bath about 125°) for 45 minutes. Immediately thereafter the acetic acid was removed *in vacuo*. The residue was a viscous oil, which, on adding water and kneading for several hours, became eventually crumbly. It was filtered and washed with water the next day; dry weight, 493 mg. This material was subjected to chromatographic adsorption, for which it was dissolved in 55 cc. of benzene and 25 cc. of petroleum

[8] Microanalysis by Mr. Lyon Southworth, Harvard University, Cambridge, Mass.

ether; this solution was filtered through a properly prepared column of 15.5 g. of aluminum oxide (Brockmann).

Chromatographic Fractionation

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE (MG.)	APPEARANCE OF RESIDUE
1	55 cc. benzene + 25 cc. petroleum ether	1.0	Resinous
2	70 cc. benzene + 10 cc. petroleum ether	5.0	Resinous
3	80 cc. benzene	12.2	Resinous
4	60 cc. benzene + 20 cc. ether	58.6	Resinous
5	40 cc. benzene + 40 cc. ether	35.1	Resinous
6	20 cc. benzene + 60 cc. ether	2.5	Resinous with centers of crystallization
7	160 cc. ether	357.2	Partly resinous; partly crystalline?
8	60 cc. ether + 20 cc. chloroform	12.0	Resinous
9	40 cc. ether + 40 cc. chloroform	2.5	Resinous
10	20 cc. ether + 60 cc. chloroform	1.4	Resinous
11	120 cc. chloroform	2.0	Resinous
12	75 cc. chloroform + 5 cc. methanol	17.5	Resinous
13	70 cc. chloroform + 10 cc. methanol	1.2	Resinous
14	60 cc. chloroform + 20 cc. methanol	0.8	Resinous
Total		509.0	

Pregnane-20-one-3(β),5,6(trans),*21-tetraol 3,6,21-triacetate* (XXI). When the residues of fractions 4 and 5 respectively were treated with ether, the material went into solution. Crystallization set in soon and furnished fair yields of crystals melting at 170–173° and 172–174° respectively. Recrystallization was from ether, to which some petroleum ether was added. This raised the melting point to 176–177.5°; $[\alpha]_D^{26.1}$ + 3.5° (17.2 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{27}H_{40}O_8$: C, 65.81; H, 8.19.
Found: C, 65.68; H, 8.23.

Ten milligrams of the above substance was treated with 0.5 cc. of pyridine and 0.35 cc. of acetic anhydride at room temperature for two days. Working up of the reaction mixture in the usual manner furnished material which yielded from a mixture of ether and petroleum ether prisms of m.p. 175.5–176°. There was no depression of the melting point when this substance was mixed with the above recorded analytical sample.

Pregnane-20-one-3(β),5,6(trans),*21-tetraol 6,21-diacetate* (XX). When the residue of fraction 7 of the chromatographic separation (357.2 mg.) was treated with a little ether, only part of the material went into solution.

Examination of the "ether-insoluble" part (7a: 232.4 mg.): This white, solid material melted between 120° and 135°. It was dissolved in a rather large volume of ether. On concentrating this solution to a low volume, a turbidity suddenly appeared. Glistening scales of a rather irregular shape (7a′: 20.2 mg.) separated from this solution when it was allowed to stand overnight; m.p. between 114° and 120°. This substance was once more recrystallized from ether to which a trace of petroleum ether was added. Irregular-shaped, rather stout plates, partly in rosette arrange-

ment, separated overnight (7a″: 14.5 mg.). The melting point was not yet sharp; real melting took place at about 118°, however the molten substance did not become transparent before 126°.

Anal. Calc'd for $C_{25}H_{38}O_7$: C, 66.62; H, 8.50.
Found: C, 66.62; H, 8.46.

All mother liquors which originated from the "ether-insoluble" part (fraction 7a) were combined and brought to dryness. Weight of residue: 203.6 mg. The analysis of this material indicated that it represented the same substance as recorded above; $[\alpha]_D^{26.1} + 16.7°$ (6.0 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{25}H_{38}O_7$: C, 66.62; H, 8.50.
Found: C, 66.25; H, 8.22.

Examination of the "ether-soluble" part (7b: 124.8 mg.): This material represented a brittle, white foam. Its analysis (Found: C, 67.71; H, 8.10) indicated that it was probably a mixture.

When the residue of fraction 12 of the chromatographic separation (17.5 mg.) was treated with ether, crystals separated after a few days' standing; weight 11.8 mg.; m.p. between 185° and 200°. This substance may consist of unchanged 5,6-oxide.

Pregnane-20-one-3(β),5,6(trans),*21-tetraol 3,6,21-triacetate* (XXI) *by acetylating pregnane-20-one-3(β),5,6*(trans),*21 tetraol 6,21-diacetate* (XX). The starting material for this acetylation was a crude preparation of pregnane-20-one-3(β),5,6(trans),-21-tetraol 6,21-diacetate (XX) which had been obtained in a preliminary experiment ("non-crystalline material" of first paragraph of experiment describing the acetolysis of XIX). This substance corresponded to the residue of fraction 7 of the foregoing chromatographic fractionation. To a solution of 77.7 mg. of such starting material in 1.5 cc. of pyridine was added 1.0 cc. of acetic anhydride. This mixture was allowed to stand overnight. It was then brought almost completely to dryness. When the resinous residue was treated with water it soon became crumbly. After washing with water and drying (dry weight 82.6 mg.) it was recrystallized from ether to which some petroleum ether was added. A first crop (51.8 mg.) of m.p. 175–176° and a second crop (17.2 mg.) of m.p. 172–173° was obtained. Neither sample showed a depression of the melting point when mixed with an authentic sample of pregnane-20-one-3(β),-5,6-(*trans*),21-tetraol 3,6,21-triacetate.

Pregnane-3,20-dione-5,6(trans),*21-triol 6,21-diacetate* (XXII). To a solution of 45 mg. (0.1 millimole) of pregnane-20-one-3(β),5,6(*trans*),21-tetraol 6,21-diacetate (XX) in 1.5 cc. of glacial acetic acid was added 2.3 cc. (the equivalent of 1.15 atoms of O) of a solution of 333 mg. of chromium trioxide in 100 cc. of 90% acetic acid. The mixture was allowed to stand at room temperature for 24 hours. After the addition of 1.5 cc. of alcohol it was brought almost to dryness *in vacuo*. After the addition of water to the sticky residue, the latter was taken up in ether. The ether phase was washed with *N* sodium carbonate and water, and was finally dried with sodium sulfate. After the removal of the solvent, 44.1 mg. of a dry residue was obtained. On dissolving it in ether and then concentrating to a low volume, beautiful needles crystallized in rosette arrangement. Various crops totalling 36.9 mg. and all of them melting above 159° were obtained. After repeated crystallization the constant melting point was at 163.5–164.5°; long, flat rectangular crystals in rosette arrangement. On repeating the experiment with 143 mg. of the starting substance a total of 107 mg. of crystalline material melting above 159° was obtained; $[\alpha]_D^{26.1} + 21.5°$ (9.3 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{25}H_{36}O_7$: C, 66.92; H, 8.09.
Found: C, 66.76; H, 7.84.

4-Pregnene-3,20-dione-6(α),21-diol diacetate [*6(α)-hydroxy-11-desoxycorticosterone*

diacetate] (XXIII). Sixty milligrams of pregnane-3,20-dione-5,6(*trans*),21-triol 6,21-diacetate (XXII) was dissolved in 10.0 cc. of chloroform. A moderate stream of dry hydrogen chloride was passed through this solution for three hours; cooling with ice, temperature not above +2°. The solution was then poured into ice-cold *N* sodium carbonate and shaken in a separatory funnel. The chloroform phase was washed three times with water and thereafter dried with sodium sulfate overnight. After the removal of the solvent a very slightly yellow resin was obtained which was dried in a vacuum desiccator. When it was treated with some acetone, crystallization began immediately; this was intensified by the addition of some petroleum ether. The first crop (48.2 mg.) had the melting point 84–88°, the second crop (1.5 mg.) melted slightly lower. This material was recrystallized from acetone to which petroleum ether was added until turbidity appeared; sheaves of huge dagger-shaped crystals; the melting point remained unchanged; $[\alpha]_D^{27.2}$ + 114.3° (11.2 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{25}H_{34}O_6$: C, 69.72; H, 7.96.
Found: C, 69.30; H, 8.11.

SUMMARY

1. It is proposed that what was formerly (2) designated androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate be called androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate and the previously (2) designated androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate be called androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate.

2. It is proposed that the oxide of dehydroisoandrosterone first described by Ouchakov and Lutenberg (4) as well as by Miescher and Fischer (5) which was previously (2) designated β-oxide of dehydroisoandrosterone henceforth be called α-oxide of dehydroisoandrosterone.

3. With the above proposed changes uniformity is ensured regarding certain reactions which are obtained with (5,6)(α)-oxides and (5,6)(β)-oxides in the cholestane and androstane series respectively.

4. By treatment with glacial acetic acid androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate (VIII) is transformed into androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (X). The latter substance yields by vigorous acetylation (acetic anhydride and dry hydrogen chloride) androstane-17-one-3(β),5,6(*trans*)-triol triacetate (XII). By treatment with glacial acetic acid androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate (IX) is converted into androstane-17-one-3(β),5,6(*trans*)-triol 3,5-diacetate (XI). The latter substance yields by mild acetylation (acetic anhydride) androstane-17-one-3(β),5,6(*trans*)-triol triacetate (XII).

5. When dehydroisoandrosterone (XIII) is treated with perbenzoic acid the main product is androstane-(5,6)(α)-oxide-17-one-3(β)-ol (XIV). Proper treatment of the latter substance with glacial acetic acid furnishes a mixture of androstane-17-one-3(β),5,6(*trans*)-triol 6-monoacetate (XV) and androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (X) in which the former (XV) prevails. When treated with acetic anhydride, the 6-mono-

acetate (XV) is transformed into the 3,6-diacetate (X). The 6-monoacetate (XV) yields with chromic acid androstane-3,17-dione-5,6(*trans*)-diol 6-monoacetate (XVI). The latter substance can be dehydrated to 4-androstene-3,17-dione-6(α)-ol acetate [6(α)-acetoxy-4-androstene-3,17-dione] (XVII).

6. In the capon comb growth test, 6(α)-acetoxy-4-androstene-3,17-dione (XVII) is one-fifth as active as androsterone or 4-androstene-3,17-dione.

7. When 5-pregnene-20-one-3(β),21-diol 21-monoacetate [21-acetoxy-4-pregnene-20-one-3(β)-ol] (XVIII) is treated with perbenzoic acid the principle product is pregnane-(5,6)(α)-oxide-20-one-3(β),21-diol 21-monoacetate (XIX). Proper treatment of the latter substance with glacial acetic acid furnishes a mixture of pregnane-20-one-3(β),5,6(*trans*),21-tetraol 6,21-diacetate (XX) and pregnane-20-one-3(β),5,6(*trans*),21-tetraol 3,6,21-triacetate (XXI) in which the former prevails. When treated with acetic anhydride and pyridine the 6,21-diacetate is transformed into the 3,6,21-triacetate. The 6,21-diacetate yields with chromic acid pregnane-3,20-dione-5,6(*trans*),21-triol 6,21-diacetate (XXII). The latter compound can be dehydrated to 4-pregnene-3,20-dione-6(α),21-diol diacetate [6(α)-hydroxy-11-desoxycorticosterone diacetate] (XXIII).

8. The diacetate of 6(α)-hydroxy-11-desoxycorticosterone (XXIII) produces no diabetogenic action and has no influence upon the work performance of adrenalectomized rats. The daily dosage required for the maintenance of life of adrenalectomized rats was not established with certainty. At any rate the new compound is definitely less active in this respect than 11-desoxycorticosterone acetate.

PHILADELPHIA, PA.

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REACTIONS INVOLVED IN THE LIQUID-PHASE ALKYLATION OF ISOPARAFFINS WITH OLEFINS

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The commercial development of the sulfuric acid alkylation process has gone forward very rapidly upon the basis of relatively simple and empirical assumptions and it has been estimated that by the fall of 1940, plants had been installed capable of producing over 7,200,000 barrels per year of 92–94 octane number fuel (unleaded) from C_4 olefins and isobutane alone (1). While the practical aspects of the process are well known, the underlying reaction-mechanism is apparently rather complex and thus far no entirely satisfactory theory has been presented which would account for the products obtained. These differ greatly from those that would be predicted if the isoparaffin had added to the double bond in the expected manner. Furthermore, hydrocarbons of molecular weight both lower and higher than those to be expected are obtained. There remains, therefore, considerable incentive for further study.

Birch *et al.* (2) have presented considerable data which would indicate that no single reaction-mechanism will account for all the products and they conclude that isomerization of the primary products is at least partially responsible for the structure of the hydrocarbons of the expected molecular weight.

As the result of our study of a wider variety of isoparaffins and olefin feed stocks we have come to a somewhat different view of the reaction-mechanism. This view envisages both carbon-to-carbon cleavage and dehydrogenation of the primary isoparaffins as taking place in the alkylation reaction.

A discussion of the experimental data which lead to this view follows.

EXPERIMENTAL

Both batch and continuous operation were employed in the experiments about to be discussed.

The batch experiments were made in a high-speed mechanical mixer; the olefin was added slowly to a mixture of acid and excess isoparaffin. A similar reactor with the addition of a separator was used in the continuous experiments. A high isoparaffin-olefin ratio is obtained in the reaction zone by first blending the olefin with an excess of isobutane and then feeding this mixture into a reactor containing an

emulsion of acid and reacted hydrocarbon which is rich in isoparaffin but substantially olefin-free. A portion of the emulsion is continuously withdrawn to a separator, the acid is returned to the mixer and the hydrocarbon is withdrawn and stabilized to remove the excess isobutane and then fractionally distilled to identify the products obtained.

Where sufficient hydrocarbon feed was available, continuous operation was used because it has the advantage over batch in that the concentration of the reactants in the reaction zone is constant and a more uniform product results. Furthermore, the relative reactivity of the different feeds can be determined by comparing the rate at which the titratable acidity of the sulfuric acid declines owing to side reactions such as olefin polymerization or hydropolymerization. As has been pointed out in previous publications, absorption of the olefin in the acid and the presence of impurities in the feeds lead to a loss of activity of the acid for alkylation. This is evidenced by a drop in the titratable acidity of the acid, and an increase in high-boiling material in the reaction-product, until a point is reached where the acid must be discarded.

Experiments have been made with a wide variety of isoparaffin and olefin feeds. In order to compare the reactivity of the different isoparaffins a common olefin, butene-2, was used under similar reaction conditions. For comparison of the different olefins a common isoparaffin, isobutane, was used but in this case the reaction conditions were adjusted to those which have been found to give a reasonable catalyst life.

The experimental conditions and the results obtained with the isoparaffin series are given in Table I. The compositions of the products are shown in Figures 1–4. The corresponding data for the olefin series are given in Table II and in Figures 5–15.

In order to determine whether isomerization of the primary products could occur under the conditions of alkylation as proposed by Birch *et al.*, experiments were made with pure isooctane (2,2,4-trimethylpentane) and trimethylbutane, which would be the products expected from the reaction of isobutylene with isobutane, and propylene with isobutane, if direct addition of the isoparaffin to the double bond had occurred.

Reactions of isoparaffins with butene-2. From the data given in Table I it will be seen that, based upon the amount of product per unit of acid used, the activity of the isoparaffin decreases as the length of the chain increases. Likewise the octane number of the product decreases.

The fact that methylcyclohexane yielded considerable quantities of saturated C_{11} hydrocarbons is of particular interest, since previous investigators (2) reported that the reaction did not occur and upon the basis of their findings discarded the reaction-mechanism suggested by the work of Ingold and his co-workers, who postulate the formation of an intermediate complex between the paraffin and acid (5).

A comparison of the activity of neohexane, which did not react, and isohexane (Table I), is of particular interest because it demonstrates the role played by the hydrogen attached to the tertiary carbon atom. It would appear that the first step may involve the replacement of the hydrogen by an acid sulfate radical, which then so weakens the adjacent C—C bond that fission occurs.

The composition of the product which is obtained from isobutane and butene-2 does not agree entirely with that previously reported by Birch *et al.* They report the presence of 2,5- and 2,4- dimethylhexane, which we have not been able to substantiate. They also state that the presence of 2,3,4- and 2,3,3- trimethylpentane in the reaction-mixture is suspected but has not been confirmed. On the other hand,

TABLE I

ALKYLATION OF REPRESENTATIVE ISOPARAFFINS WITH BUTENE-2

ISOPARAFFIN USED	ISOBUTANE	ISOPENTANE	ISOHEXANE (2- & 3-METHYL PENTANE)	METHYLCYCLOHEXANE*	NEOHEXANE*
Conditions:					
Mole ratio of isoparaffin to olefin	5.0	5.1	5.5	1.6	2
Strength of acid, wt. % H_2SO_4	100.0	100.0	99.8	100.0	100.0
Volume ratio of acid/hydrocarbon	0.7	0.7	0.7	1.0	0.6
Temperature, °C	10	10	10	20	10
Contact time, minutes	20	20	20	60	60
Results:					
Volumes of alkylate/volume of acid	20	11	5	—	—
Wt. % yield of alkylate, based on olefin used	200	264	206	106	none
Per cent of aviation fraction (E.P. 150° C.) in alkylate after stabilizing from original isoparaffin	93	83	78 (E.P., 165°C.)	78 (E.P., 200°C.)	—
Br_2 No. of alkylate, g./100 cc.	<1	<1	<1	<1	—
Octane No. (A.S.T.M.-C.F.R.) of aviation fraction of alkylate	94	86.5	76.5	—	—

* Batch experiments.

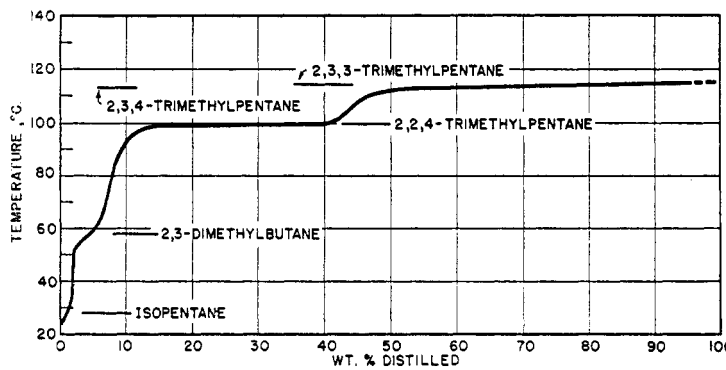


FIGURE 1. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH BUTENE-2

PHYSICAL DATA FOR PRODUCTS				LITERATURE VALUES	
B. range, °C.	R.I. 20/D	Sp.gr. 20/4	Probable identity	R.I. 20/D	Sp.gr. 20/4
99–100	1.391	0.692	2,2,4-Trimethylpentane	1.392	0.691
114–115	1.404	.720	2,3,4-Trimethylpentane	1.404	.720
			2,3,3-Trimethylpentane	1.407	.725

our distillation curve shows a definite flat coinciding with the boiling point of either 2,3,4- or 2,3,3- trimethylpentane.

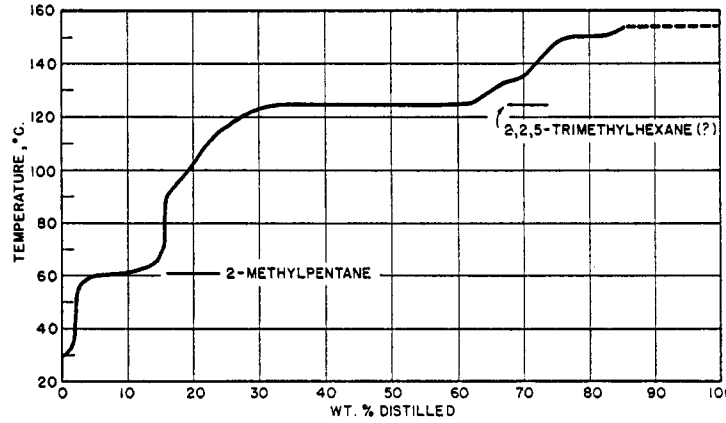


FIGURE 2. PRODUCT FROM ALKYLATION OF ISOPENTANE WITH BUTENE-2

PHYSICAL DATA FOR PRODUCTS					LITERATURE VALUES	
B. range, °C.	Mol. wt.	R.I. 20/D	Sp.gr. 20/4	Probable identity	R.I. 20/D	Sp.gr. 20/4
60–62	87	1.373	0.657	2-Methylpentane	1.371	0.653
124–125	119	1.400	.707	2,2,5-Trimethylhexane (?)	1.399	.708
130–135	124	1.406	.720	Dimethylheptane (?)	—	—
148–152	134	1.410	.729	Decanes	—	—

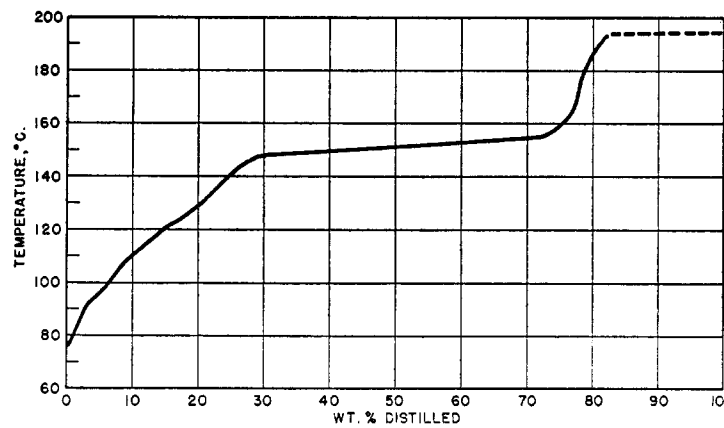


FIGURE 3. PRODUCT FROM ALKYLATION OF ISOHEXANE WITH BUTENE-2

Also, for isopentane and butene-2, our results indicate that the low-boiling fraction is 2-methylpentane rather than 2,3-dimethylbutane, because the material boiling

below 95° had an octane number of only 81.5 whereas if 2,3-dimethylbutane were present, a much higher octane number would have been found.

In the case of isopentane an appreciable amount of isobutane was also formed which is not included in the weight yield shown in Table I. Despite this, the yield based on the olefin is higher than theoretical, and would certainly indicate that either isopentane itself or one of its reaction-products splits to give an olefin and paraffin of lower molecular weight than the starting material (*i.e.*, secondary cleavage).

The identification of the isomers present in the case of isohexane and methylcyclohexane is rendered difficult by a lack of physical data in the literature by which to distinguish them. However, it will be seen that a saturated product of the expected molecular weight was obtained.

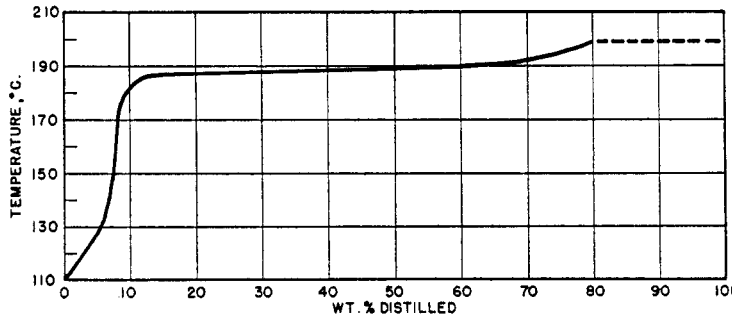


FIGURE 4. PRODUCT FROM ALKYLATION OF METHYLCYCLOHEXANE WITH BUTENE-2

Mol. wt. of 185–192°C. Fraction	= 147 (C_{11})
Br. No.	"	"	"	= 0.23 g./100 g.
Sp. gr. 20/4	"	"	"	= 0.799
R.I. 20/D	"	"	"	= 1.441

Alkylation of isobutane with various olefinic feeds. If a comparison is made of the reaction-products from the normal olefins and the tertiary olefins, it will be seen that the percentage of lighter-boiling materials is much greater with the branched olefins. This is most strikingly apparent with the pentenes, where only 28% of the product boils below the nonane range with a pentene-2 feed, whereas 50% boils below the nonane range with 2-methylbutene-2 as the olefinic feed.

Considerable work has already been presented by others on the use of isobutylene polymers as olefinic feeds, and it has been shown that the product is quite similar to that obtained with isobutylene itself. Our study of the alkylation of co-polymers of isobutylene and butene-1 formed by Hot Acid polymerization in general confirms the previous work of Birch *et al.*, in that the reaction-products are the same as those obtained with isobutylene polymers. This is not surprising when it is remembered that the reaction-products obtained from the normal butylenes are quite similar to those obtained from isobutylene except for the amount of light ends formed, and that diisobutylene and Hot Acid dimer are of almost equivalent branching as evidenced by their respective octane numbers.

However, when a dimer fraction from the U.O.P. polymerization of butene-2 was

TABLE II

ALKYLATION OF ISOBUTANE WITH REPRESENTATIVE OLEFINS

TYPE OF OLEFIN USED	NORMAL			TERTIARY			OLEFIN POLYMERS					CYCLIC
Olefin Used	Propylene	Butene-2	Pentene-2	Isobutylene	2-Methyl-butene-2	Octylenes from 2-ethylhexanol-1	Propylene trimer (U.O.P. Polymer)	Butylene dimer (Hot Acid Polymer)	Butylene trimer (Hot Acid Polymer)	Butene-2 dimer (U.O.P.)	Diisoamylene	Cyclohexene
Conditions:												
Mole ratio of isoparaffin to olefin	6.7	5.0	10.0	7.1	10.0	10.0	15.8	10.7	20.3	10.6	20	10.0
Acid strength used, wt. % H_2SO_4	98.0	100.0	98.0	98.2	98.0	98.0	100.0	98.0	100.0	97.8	100.0	100.0
Vol. ratio of acid to hydrocarbon	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	1.0	1.0
Temperature, °C	30	10	10	20	10	10	20	10	10	10	10	10
Contact time, minutes	40	20	20	10	20	20	20	20	20	20	20	20
Results:												
Volumes of alkylate per volume of acid	6	20	15 (extrap.)	12.5	14 (extrap.)	14	10.5	15 (extrap.)	11	12.5 (extrap.)	14	3
Wt. % yield of total alkylate, based on olefin	213	200	185	180	192	150	193	185	166	188	203	152
Per cent of aviation fraction (E.P. 150°C.) in total alkylate	90	93	92	81	86	75	93	83	77	83	78	86 (E.P.) (180°C.)
Bromine No. g./100 cc. of aviation fraction	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Octane No. (A.S.T.M.-C.F.R.) of aviation fraction of alkylate	88.5	94.0	91.0	91.5	93.0	—	78.5	93.0	93.0	88.0	91.0	—

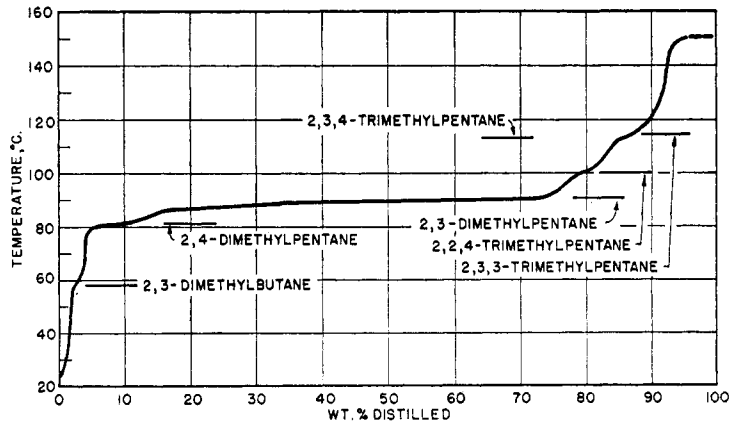


FIGURE 5. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH PROPYLENE

PHYSICAL DATA FOR PRODUCTS				LITERATURE VALUES	
B. range, °C.	R.I. 20/D	Sp.gr. 20/4	Probable identity	R.I. 20/D	Sp.gr. 20/4
58–61	1.374	0.661	2,3-Dimethylbutane	1.375	0.662
81–83	1.383	.676	2,4-Dimethylpentane	1.382	.673
90	1.392	.695	2,3-Dimethylpentane	1.392	.694
97–100	1.391	.694	2,2,4-Trimethylpentane	1.392	.692
113–115	1.403	.716	2,3,4-Trimethylpentane	1.404	.720
			2,3,3-Trimethylpentane	1.407	.725

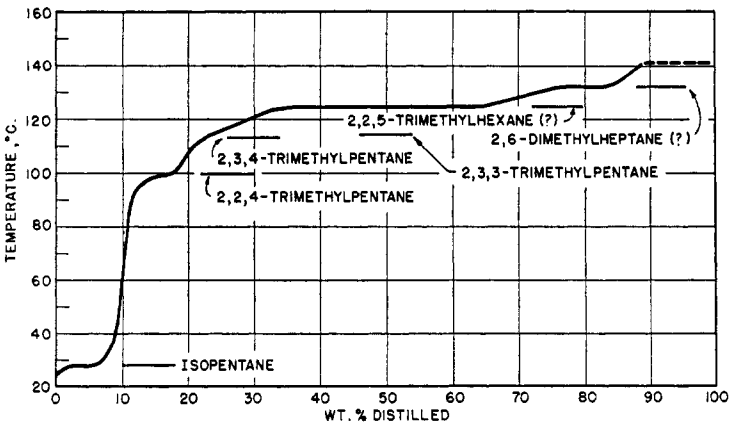


FIGURE 6. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH PENTENE-2

PHYSICAL DATA FOR PRODUCTS		
B. range, °C.	Mol. wt.	Probable identity
27.5–28	—	Isopentane
98–100	—	2,2,4-Trimethylpentane
113–115	—	2,3,3- or 2,3,4-Trimethylpentane
124–125	122	Nonanes
131–132	123	Nonanes

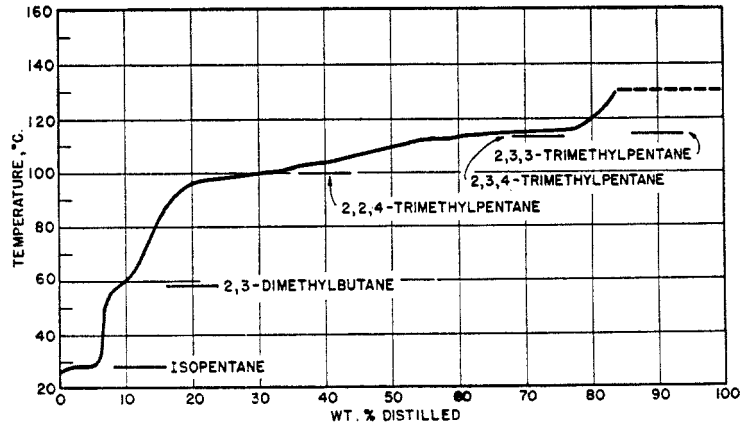


FIGURE 7. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH ISOBUTYLENE

PHYSICAL DATA FOR PRODUCTS				LITERATURE VALUES	
B. range, °C.	R.I. 20/D	Sp.gr. 20/4	Probable identity	R.I. 20/D	Sp.gr. 20/4
99–100	1.391	0.692	2,2,4-Trimethylpentane	1.392	0.692
113–115	1.404	.719	2,3,4-Trimethylpentane	1.404	.720
			2,3,3-Trimethylpentane	1.407	.725

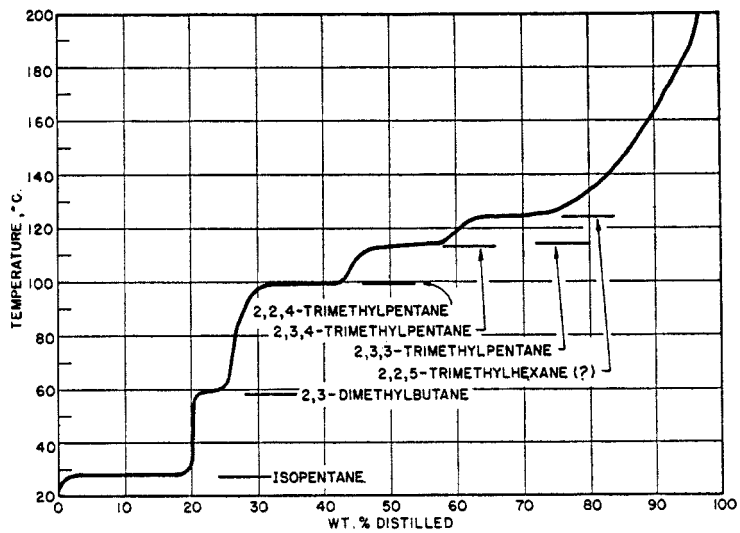


FIGURE 8. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH 2-METHYLBUTENE-2

PHYSICAL DATA FOR PRODUCTS				LITERATURE VALUES	
B. range, °C.	R.I. 20/D	Sp.gr. 20/4	Probable identity	R.I. 20/D	Sp.gr. 20/4
28	1.354	0.619	Isopentane	1.355	0.619
99–100	1.392	.692	2,2,4-Trimethylpentane	1.392	.692
113–115	1.405	.720	2,3,4-Trimethylpentane	1.404	.720
			2,3,3-Trimethylpentane	1.407	.725
124–125	1.399	.708	2,2,5-Trimethylhexane (?)	1.399	.708

substituted for diisobutylene or Hot Acid octylenes, we find that the alkylation product is of lower octane number. This might seem contradictory, but further light is obtained when propylene polymer is used as the feed (Table II). Upon alkylation with propylene trimer, we find that a product is obtained which is composed of nonanes and octanes. This product was carefully distilled and the nonanes compared with hydrogenated trimer fraction. It will be seen (Figure 10) that the physical constants throughout the nonane cut correspond closely with those of the hydro-

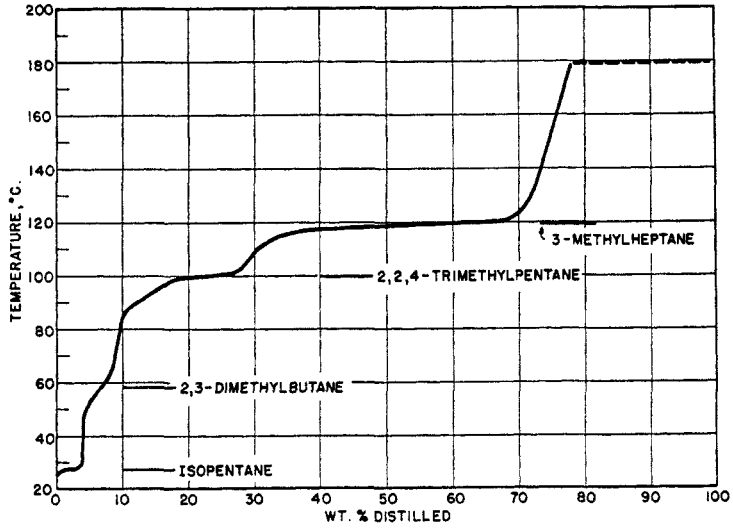


FIGURE 9. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH OCTYLENES FROM DEHYDRATION OF 2-ETHYL HEXANOL-1

PHYSICAL DATA FOR PRODUCTS				LITERATURE VALUES	
B. range, °C.	R.I. 20/D	Sp.gr. 20/4	Probable identity ·	R.I. 20/D	Sp.gr. 20/4
27–28	1.353	0.618	Isopentane	1.355	0.620
99–100	1.391	.691	2,2,4-Trimethylpentane	1.392	.692
119–120	1.398	.705	3-Methylheptane	1.400	.706

genated trimer cut, and the composition of the octane cut is similar to that obtained with butylene and isobutane. Only a negligible amount of heptanes was found whereas if the trimer had depolymerized, it would, by analogy with diisobutylene, have resulted in a product similar to that obtained from propylene. Further, the relative proportion of octanes to nonanes is in the molal ratio which would be expected if the propylene trimers had accepted hydrogen from isobutane, and the isobutylene thus formed had in turn reacted with excess isobutane to form octanes. This would explain in part the results obtained with butene-2 dimer and could be applied to the reactions of the simpler olefins.

Hydrogenation was also the main reaction that occurred in alkylation with diisoamylene. Although some depolymerization took place, which resulted in an appre-

ciable amount of isopentane in the product, Figure 14 shows the main constituents of the product to be isopentane, octanes, and isodecanes. There was no evidence of C_9 isoparaffins being formed.

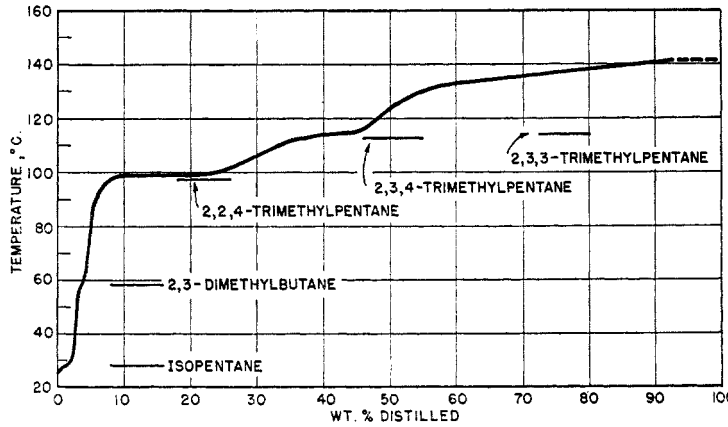


FIGURE 10. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH PROPYLENE TRIMERS

PHYSICAL DATA FOR PRODUCTS				LITERATURE VALUES	
B. range, °C.	R.I. 20/D	Sp.gr. 20/4	Probable identity	R.I. 20/D	Sp.gr. 20/4
99–100	1.392	0.695	2,2,4-Trimethylpentane	1.392	0.692
113–115	1.402	.715	2,3,4-Trimethylpentane	1.404	.720
			2,3,3-Trimethylpentane	1.407	.725

COMPARISON OF HYDROGENATED TRIMER WITH C_9 FRACTION OF ALKYLATION PRODUCT

B. RANGE, °C.	ALKYLATION PRODUCT		HYDROGENATION PRODUCT	
	R.I. 20/D	Sp.gr. 20/20	R.I. 20/D	Sp.gr. 20/20
131–133	1.404	0.717	1.404	0.717
133–134	1.405	.718	1.404	.718
134–135	1.404	.718	1.405	.719
135–136	1.404	.720	1.406	.720
136–137	1.405	.720	1.405	.722
137–138	1.406	.722	1.407	.724
138–139	1.407	.725	1.408	.726
139–140	1.408	.726	1.410	.729

The reaction of isobutane with a cyclic olefin is of interest, for the product obtained shows clearly that both hydrogen transfer and alkylation readily occur. The presence of cyclohexane in the product from alkylation with cyclohexene is evidence of the hydrogen transfer, and the presence of methylcyclopentane is evidence of isomerization as an accompanying reaction. In the case of the cyclohexene, how-

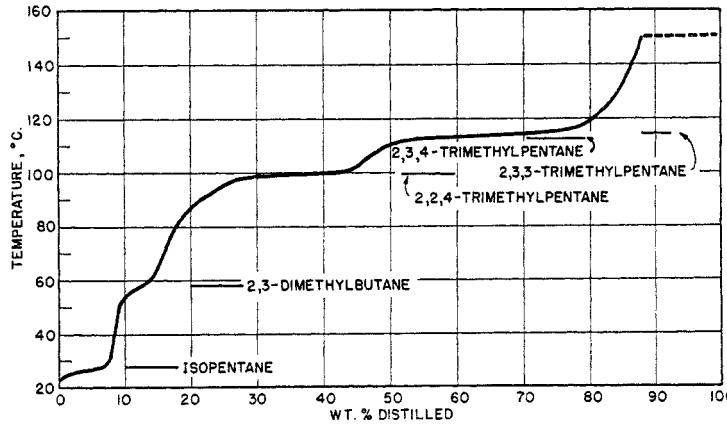


FIGURE 11. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH BUTYLENE DIMERS

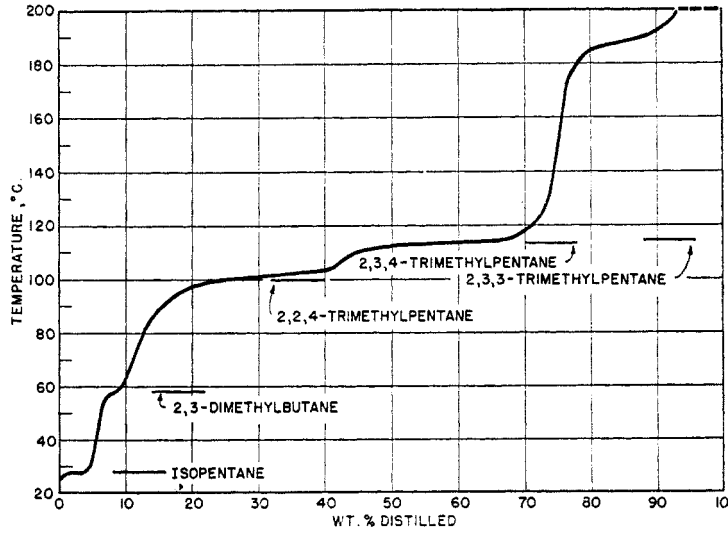


FIGURE 12. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH BUTYLENE TRIMERS

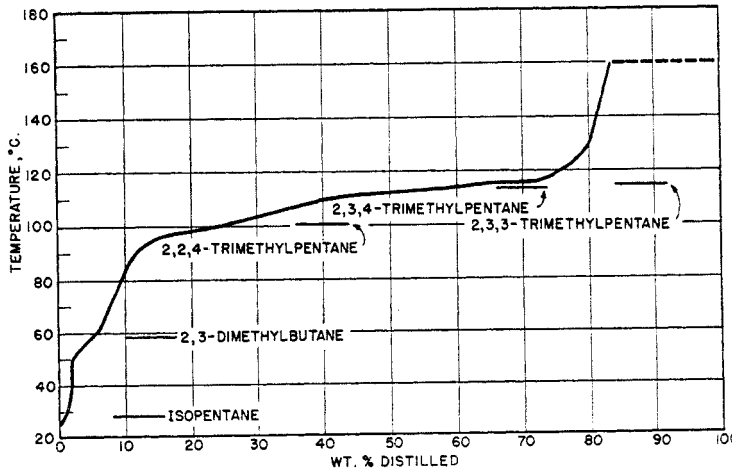


FIGURE 13. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH *n*-BUTYLENE DIMERS

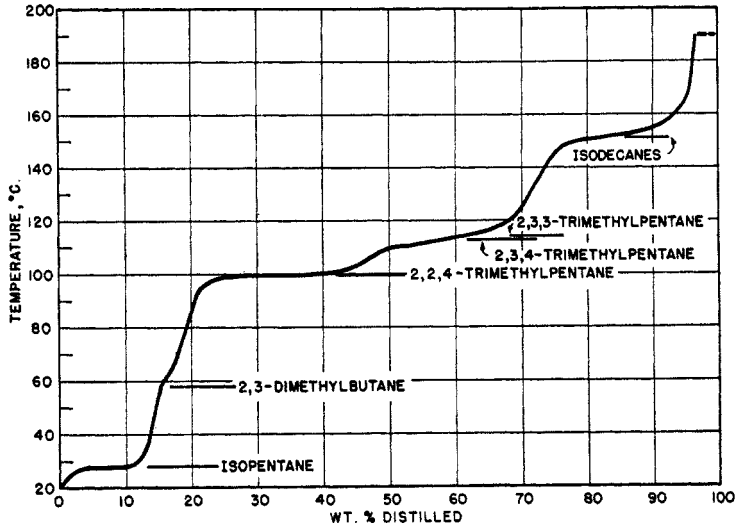


FIGURE 14. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH DIISOAMYLENE

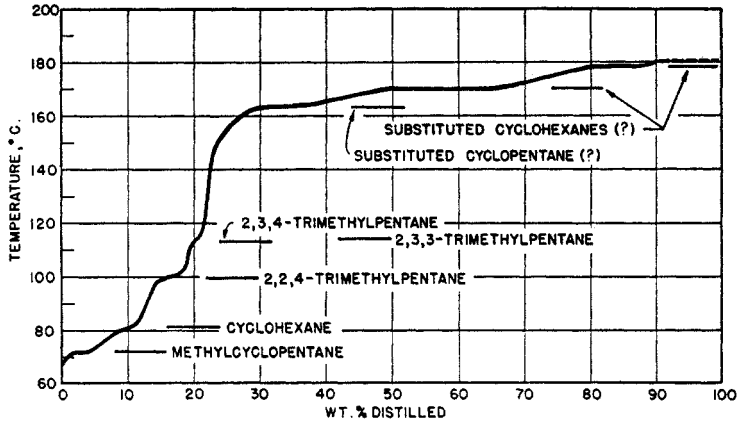


FIGURE 15. PRODUCT FROM ALKYLATION OF ISOBUTANE WITH CYCLOHEXENE

PHYSICAL DATA FOR PRODUCTS				LITERATURE VALUES	
B. range, °C.	R.I. 20/D	Sp.gr. 20/4	Probable identity	R.I. 20/D	Sp.gr. 20/4
71.5–73.5	1.409	0.747	Methylcyclopentane	1.410	0.749
79– 81	1.418	.760	Cyclohexane	1.426	.778
94–100	1.394	.698	2,2,4-Trimethylpentane	1.392	.691
113–114	1.405	.719	2,3,4- (2,3,3-) Trimethylpentane	1.404(1.407)	.720(.725)
163–164	1.436	.791	Substituted cyclopentane (?)	—	—
170–171	1.440	.798	Substituted cyclohexane (?)	—	—
178	1.451	.823	" " "	—	—

ever, a large proportion of the olefin was absorbed into the acid; thus the yield based on olefin input was rather poor.

Attempt to isomerize the expected primary products. Experiments have been made with isooctane and other branched chain paraffins to see if structural changes could occur under the conditions of the alkylation reaction. There was some evidence of the formation of lower- and higher-boiling fractions but little or no change of the structure of the isooctane was noted despite the drastic conditions used (Figure 16). Similar results were also obtained with 2,2,3-trimethylbutane, the expected product from propylene alkylation. On the basis of these data, it is somewhat unlikely that structural rearrangement after alkylation will provide a satisfactory explanation for the fact that the main products from alkylation are not those usually expected.

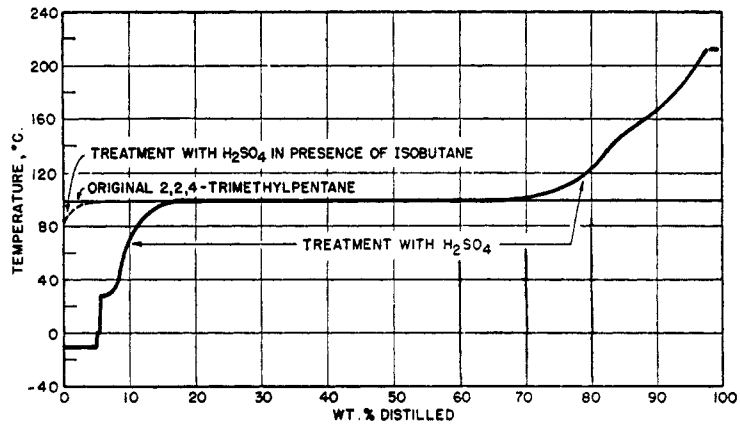


FIGURE 16. DISTILLATION OF 2,2,4-TRIMETHYLPENTANE BEFORE AND AFTER TREATMENT WITH 100% H_2SO_4 FOR ONE HOUR

Examination of the data definitely shows that no one reaction-mechanism will as yet account for all the products obtained. However, the products might be broadly classified on the basis of the type of reactions which produce them. This has been done in Table III.

POSSIBLE REACTION-MECHANISMS

Direct alkylation. Broadly speaking, direct alkylation could be defined as the coupling of the olefin and the isoparaffin to form a product of the expected molecular weight. This should not involve any structural rearrangement within the hydrocarbons themselves. However, the products obtained on alkylation with sulfuric acid are not those expected from simple addition of the isoparaffin to the double bond, although they may have the expected molecular weight.

With the normal olefins, paraffins of the expected molecular weight do constitute the principal portion of the product. With the isoolefins and with the olefin polymers this is not the case.

Hydrogenation (alkylation and dealkylation). Considerable evidence has been presented to show that this reaction occurs to some extent in most

TABLE III

Composition of Alkylation Products

Reactants	Products obtained, wt. %		Products to be expected from direct alkylation	Products to be expected from hydrogenation	Products to be expected from secondary alkylation
Isobutane and propylene	2,4-Dimethylpentane 2,3- " " 2,2,4-Trimethylpentane 2,3,4- or 2,3,3-Trimethylpentane Propane also formed	8–12 62–66 5–9 6–10	2,4-Dimethylpentane 2,3- " "	Propane	2,2,4-Trimethylpentane 2,3,3- " "
Isobutane and butene-2	Isopentane 2,3-Dimethylbutane 2,2,4-Trimethylpentane 2,3,4- or 2,3,3-Trimethylpentane Isobutane probably also formed	Trace 4–6 34–38 51–55	2,2,4-Trimethylpentane 2,3,4- " " 2,3,3- " "	n-Butane (not found) Isobutane	2,2,4-Trimethylpentane 2,3,3- " "
Isobutane and pentene-2	Isopentane 2,2,4-Trimethylpentane 2,3,4- or 2,3,3-Trimethylpentane Isononanes	6–8 6–10 8–12 55–65	Isononanes	n-Pentane (not found) Isopentane	2,2,4-Trimethylpentane 2,3,3- " "
Isobutane and isobutylene	Isopentane 2,3-Dimethylbutane 2,2,4-Trimethylpentane 2,3,4- or 2,3,3-Trimethylpentane Isobutane probably also formed	7–9 8–10 24–28 30–34	2,2,4-Trimethylpentane 2,3,3- " "	Isobutane	2,2,4-Trimethylpentane 2,3,3- " "
Isobutane and 2-methylbutene-2	Isopentane 2,3-Dimethylbutane 2,2,4-Trimethylpentane 2,3,4- or 2,3,3-Trimethylpentane Isononanes	18–20 5–7 14–16 15–17 15–20	Isononanes	Isopentane	2,2,4-Trimethylpentane 2,3,3- " "

Isobutane and octylenes from 2-ethylhexanol-1	Isopentane	3–5	Isododecanes	3-Methylheptane	2,2,4-Trimethylpentane
	2,3-Dimethylbutane	3–5			2,3,3- " "
	2,2,4-Trimethylpentane	12–16			
	2,3,3-Trimethylpentane	(?)			
	3-Methylheptane	35			
	Isododecanes	(?)			
Isobutane and propylene trimers	Isopentane	2–3	Isotridecanes (not found)	Hydrogenated trimers	2,2,4-Trimethylpentane
	2,3-Dimethylbutane	1–2			2,3,3- " "
	2,2,4-Trimethylpentane	15–20			
	2,3,4- or 2,3,3-Trimethylpentane	18–20			
	Hydrogenated trimers	45			
Isobutane and butylene dimers	Isopentane	6–7	Isododecanes	Hydrogenated dimers	2,2,4-Trimethylpentane
	2,3-Dimethylbutane	5–6	2,2,4-Trimethylpentane*		2,3,3- " "
	2,2,4-Trimethylpentane	60–65	2,3,4- " " *		
	2,3,3 or 2,3,4-Trimethylpentane		2,3,3- " " *		
	Hydrogenated dimers (?)				
	Isododecanes (?)	(?)			
Isobutane and butylene trimers	Isopentane	5–6	Isohexadecanes (not found)	Hydrogenated trimers	2,2,4-Trimethylpentane
	2,3-Dimethylbutane	3–5	2,2,4-Trimethylpentane*		2,3,3- " "
	2,2,4-Trimethylpentane	60–65	2,3,4- " " *		
	2,3,4- or 2,3,3-Trimethylpentane		2,3,3- " " *		
	Hydrogenated trimers	10–15			
Isobutane and diisoamylene	Isopentane	10–12	Isotetradecanes (not found)	Isodecanes	2,2,4-Trimethylpentane
	2,3-Dimethylbutane	2–3	Isononanes (not found)	Isopentane*	2,3,3- " "
	2,2,4-Trimethylpentane	20–25			
	2,3,4- or 2,3,3-Trimethylpentane	20–25			
	Isodecanes	16–20			
Isobutane and cyclohexene	Methylcyclopentane	5–6	C_{10} (substituted cyclohexanes)	Cyclohexane	2,2,4-Trimethylpentane
	Cyclohexane	4–5			2,3,3- " "
	2,2,4-Trimethylpentane	4–6			
	2,3,4- or 2,3,3-Trimethylpentane	4–5			
	C_{10} (substituted cyclopentanes (?))	15–20			
	C_{10} (substituted cyclohexanes (?))	50–55			

* From depolymerization and subsequent alkylation.

alkylations. With propylene trimers and butene-2 dimer it may constitute the major reaction. The presence of propane in the product from isobutane plus propylene and of 2-methylbutane in the product from 2-methylbutene-2 plus isobutane can be readily explained in this manner. A similar hydrogenation reaction explains the formation of 3-methylheptane during the alkylation of isobutane with the octylenes obtained by dehydration of 2-ethylhexanol-1. Whether or not the hydrogenation transfer actually occurs through alkylation followed by dealkylation is still a question.

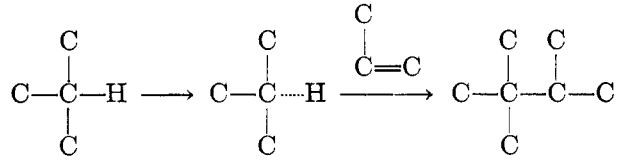
Polymerization and depolymerization. This reaction has been discussed in detail by others. The fact that a large proportion of octanes are obtained upon alkylation of isobutane with butylene trimers is evidence that this reaction can occur in the case of highly-branched olefins, and this is not surprising, as both diisobutylene and triisobutylene are known to be depolymerized by the usual polymerization catalysts. Hydrogenation of the trimers is also an accompanying reaction.

With the Hot Acid dimers it is difficult to say whether hydrogenation or depolymerization predominates, but for butene-2 dimer from U.O.P. polymerization, hydrogenation is at least a large factor.

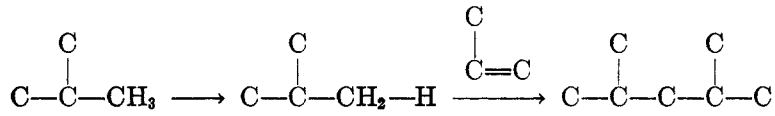
Rearrangement of primary products. There is some evidence that isomerization or structural rearrangement may account for some of the products obtained. For example, in the alkylation of isobutane with cyclohexene, methylcyclopentane is obtained, indicating that hydrogenation and isomerization had occurred. However, ring contraction is known to take place more readily than paraffin isomerization, and the experimental data would tend to show that isomerization of the primary products is at least of secondary importance.

Possible mechanism of formation of products of expected molecular weight. Two mechanisms have been proposed in the past to try to explain the primary alkylation products which are obtained. Both of these theories assume that the isoparaffin, because of its branched structure, contains labile hydrogen atoms, which under the influence of the acid are removed to give radicals or ions which will add to the olefin to form a saturated paraffin. One theory proposes that the tertiary hydrogen atom of the isoparaffin is the more labile (3), while the other assumes that a hydrogen atom attached to a methyl group (2) is the more readily removed. Simple schematic diagrams of these mechanisms which do not include the electronic shifts which were postulated may be represented as follows:

(a) Labile hydrogen on tertiary carbon atom



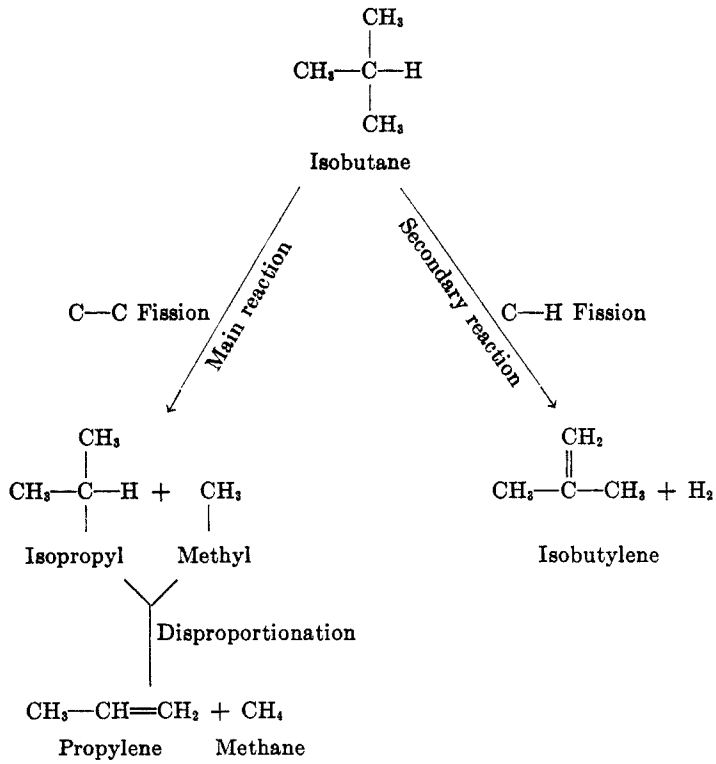
(b) Labile hydrogen on methyl group



However, neither of these mechanisms can explain the products that are actually obtained unless it is assumed that isomerization of the primary products of alkylation occurs, and in view of our results this seems unlikely.

However, if we assume that the isoparaffin undergoes dehydrogenation, then carbon-to-carbon cleavage is even more plausible on the basis of the bond energies involved. For example, Pauling has calculated that the energy involved in cleaving the C—H bond amounts to 100 kg. cal. per mole, whereas the C—C linkage requires only 83 kg. cal. per mole. Furthermore, the thermal decomposition of isobutane is known to take place in two directions, C—C fission and C—H fission, as shown below.

THERMAL DECOMPOSITION OF ISOBUTANE (4)



Assuming that alkyl fragments are formed by cleavage of the isoparaffin during the alkylation reaction,[1] then the addition of these fragments to the

[1] This possibility was first suggested by S. A. Ballard.

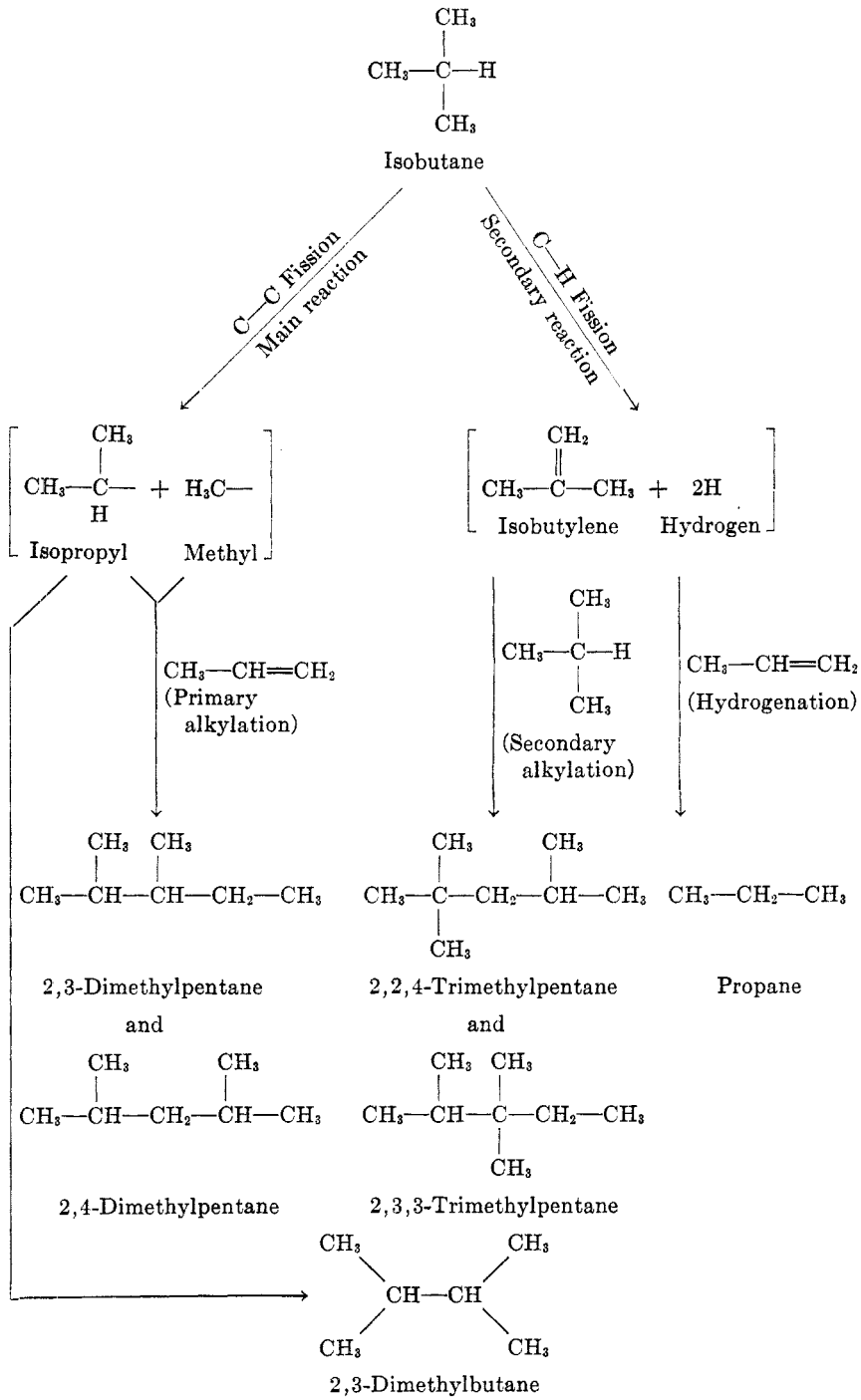
olefin double bonds would give products of the expected molecular weight and, in most cases, give the structures actually obtained.

It might be said that upon the same basis *n*-butane should react the same as isobutane. In thermal alkylation it apparently does. However, isobutane would be expected to be more active than normal butane, for Ziegler (7) and others have shown that the substitution of methyl radicals for hydrogen tends to weaken the adjacent C—C linkage in the paraffin chain.

This view of C—C cleavage is also held by Kline and Drake (6) to be the explanation for the products of polymerization of olefins.

With isobutane, the carbon-to-carbon cleavage would yield an isopropyl and a methyl fragment which would then react with the same or with different olefin molecules. For example, with isobutane and propylene the following series of reactions could occur.

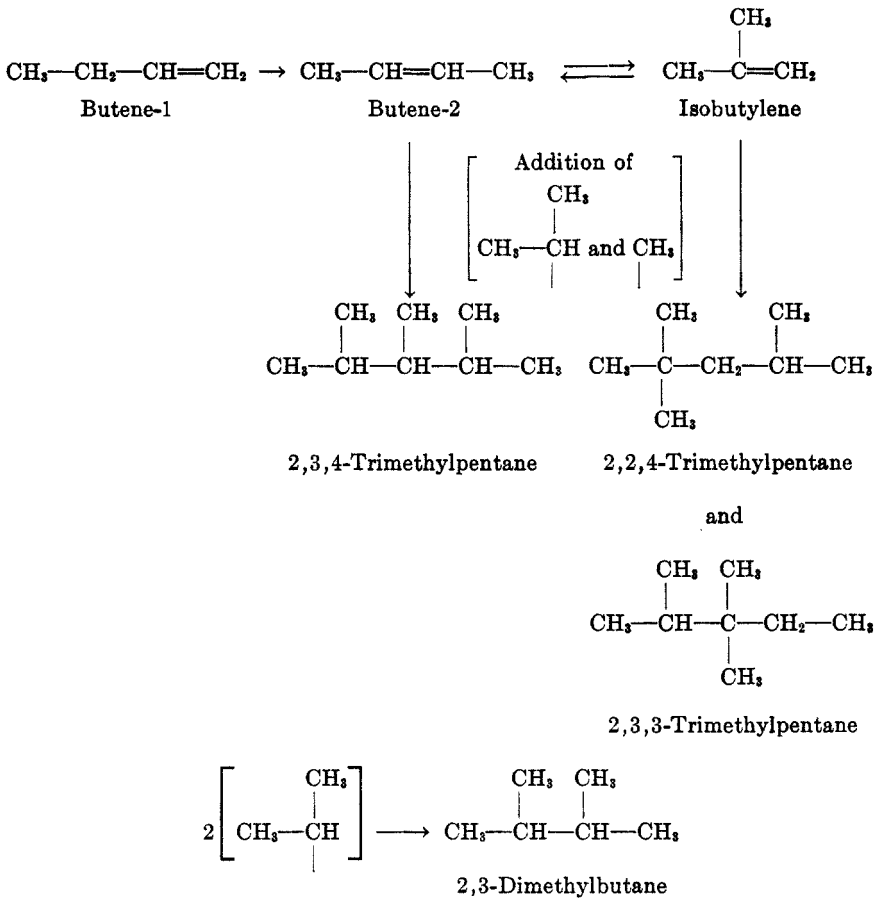
ALKYLATION OF ISOBUTANE WITH PROPYLENE



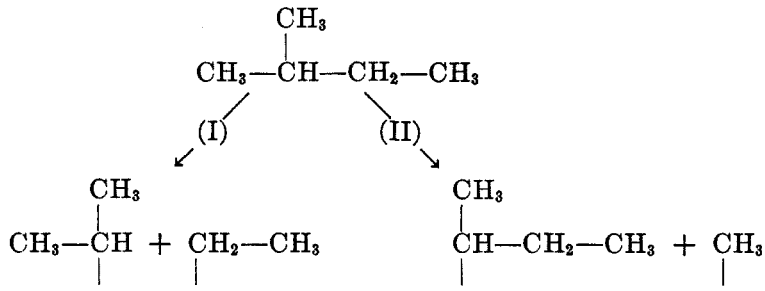
It will be seen from Table III and Figure 5 that these are the products actually obtained and not those which would be expected if the addition of the isoparaffin occurred at the double bond in the accepted manner.

With isobutane and the butylenes, following the same scheme, the products listed below would be obtained.

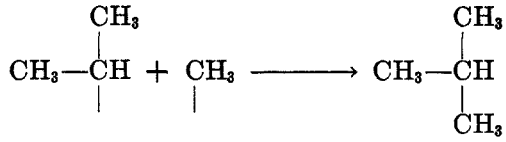
ALKYLATION OF ISOBUTANE WITH BUTENE-1, BUTENE-2, OR ISOBUTYLENE



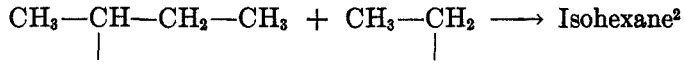
Similarly, in the alkylation of isopentane with olefins, it is found that isobutane is almost invariably produced along with some isohexane. This could be readily explained by the following scheme if it is assumed that isopentane can split in two ways, *e.g.*:



The fragments might then recombine to give isobutane and isohexane in the following fashion,



Isobutane

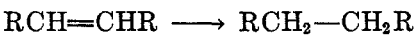


Similar examples might be worked out for the other isoparaffins and olefins used, but the exact identification of the isomers present in many cases would involve a very large amount of additional work. This was not within the scope of our investigation, which was directed primarily toward commercial application. It is hoped that the presentation of these data will stimulate academic study along these lines and will lead to a further clarification of the reaction-mechanisms involved.

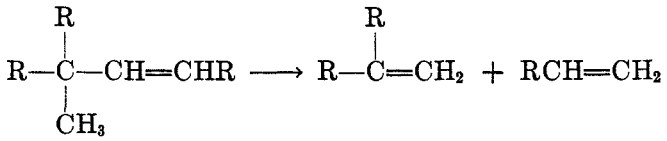
SUMMARY

The structures of the products obtained in the alkylation reaction indicate that the following types of reactions occur.

1. Hydrogenation.

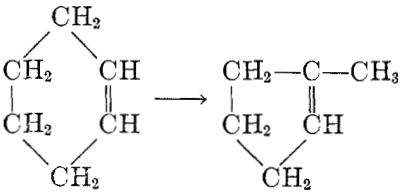


2. Depolymerization.

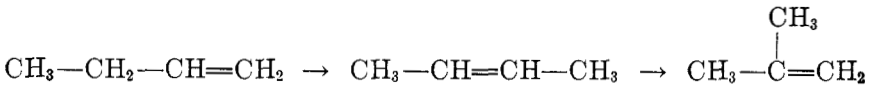


[2] The actual formula of the isohexane cannot be predicted because of the possible shifting of bonds.

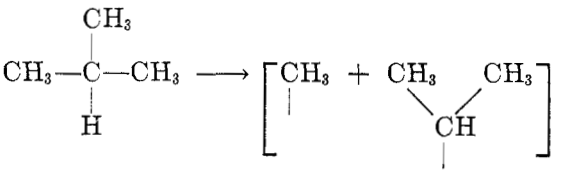
3. Ring isomerization.



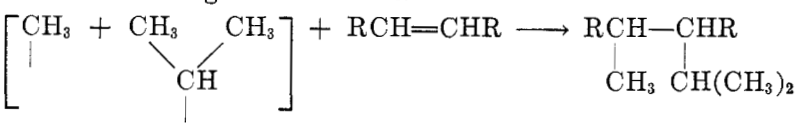
4. Olefin isomerization.



5. Carbon-to-carbon cleavage.



6. Addition of fragments to olefins.



ACKNOWLEDGMENT

The authors wish to thank Shell Development Company for permission to publish this paper outlining their personal views of the reaction-mechanisms involved in alkylation, and to thank the members of their laboratory who so ably assisted in the experimental work.

EMERYVILLE, CALIF.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE OPTICAL ISOMERS OF *cis*-9-METHYL-1-DECALONE

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The synthesis of compounds possessing the carbon skeleton of steroids has been the object of many important publications in recent years. In all cases except the total synthesis of the four possible equilenin isomers by Bachmann, Cole, and Wilds (1), the question of optical isomerism was either ignored or postponed to a later stage in the proposed synthesis.

Inasmuch as the aim of all these investigations was without exception the comparison of some one synthetic steroid with the corresponding natural compound and, since the natural compounds in all cases are optically active, the ultimate comparison, which at the same time would represent an absolute structure proof, can never be achieved unless the synthetic compound is a pure substance stereochemically. This concerns not only *cis-trans* isomerism in rings and substituents, but also optical isomerism with respect to every center of asymmetry. The stereochemical problem is simplified if the syntheses are performed on stereochemically homogeneous perhydronaphthalenes.

It was therefore attempted to synthesize such an optically active perhydronaphthalene derivative containing an angular methyl group and possessing a structure that would permit further synthetic operations. The compound chosen for this purpose was 9-methyl-1-decalone, reported in impure form as its semicarbazone by Chuang, Tien, and Ma (2), and as relatively pure, probably *cis* form, by Elliot and Linstead (3). The reason for choosing this particular compound was twofold: firstly, the angular methyl group at C_9 gives dissymmetry to the molecule, in addition to being a general characteristic of all steroids and, secondly, its method of synthesis outlined in flow-sheet A, as well as the method reported by Elliot and Linstead, can be repeated using 9-methyl-1-decalone, instead of methylcyclohexanone as starting material. The procedure could thus be applied to the synthesis of perhydrophenanthrenes or cyclopentenophenanthrenes.

Since rather large amounts of 9-methyl-1-decalone were necessary for the steps outlined in flow-sheet B, it was decided to check all methods re-

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ported in the literature and, if possible, improve them, since good yields were of utmost importance.

All reported methods center around the preparation of methylcyclohexenylbutyric acid (VI), which is cyclized according to the Darzens reaction as modified by Cook and Lawrence (4) to the corresponding chloro ketone (VII) which, after removal of hydrochloric acid, yields the unsaturated ketones (VIII) and (X). The yields in this cyclization are very good and the problem is therefore primarily the preparation of the substituted butyric acid. Since the method outlined by Elliot and Linstead (3) for the preparation of this acid proved to be the most economical, an attempt was made to improve the over-all yields in those reactions. According to this method methylcyclohexenylbutyric acid is prepared by a Grignard reaction of pentenyl bromide (5-bromo-1-pentene) with methylcyclohexanone, permanganate oxidation of the resulting tertiary alcohol and dehydration of the hydroxy acid. Linstead's 60 to 70% yield in the Grignard reaction could not be duplicated, and considerable amounts of methylcyclohexanol were found in the reaction mixture. This formation of carbinols by Grignard reagents is in agreement with earlier observations that aliphatic magnesium bromides with moderately long chains have reducing properties (8, 9, 10). As noted by Elliot and Linstead (3), the dehydration of the hydroxy acid proceeds with formation also of a spirolactone, some of which isomerizes to the unsaturated acid on distillation. This spiro-lactone need not be discarded, since it can be converted into ethyl methyl cyclohexenylbutyrate in very good yield, by boiling with thionyl chloride in benzene solution and pouring the mixture into absolute ethyl alcohol. This procedure, usually applied to the splitting of γ-lactones (13), apparently is also applicable to δ-lactones. The resulting ester can be quantitatively saponified to the acid.

Simultaneously with the study of the reported methods, a new synthesis of this acid was attempted, which proved to be superior in ease of preparation as well as yield. The method developed consists mainly in an elongation of the side chain of methylcyclohexenylacetic acid by two successive Arndt-Eistert rearrangements.

Starting with methylcyclohexenylacetic acid, the ethyl ester of which was prepared as described by Chuang *et al.* (2), its acid chloride was reacted with diazomethane to give a liquid diazo ketone (IIa). Rearrangement of this diazo ketone with concentrated ammonium hydroxide solution in the presence of silver oxide gave an amide in yields not exceeding 20%. When rearranged in ethyl alcoholic solution, the ester (IV) was obtained in 40% yield, which did not represent any improvement over the direct rearrangement to the acid (III), using thiosulfate in aqueous solution as medium. In the former case, the yield of the final product (III) after saponification

would hardly have exceeded 35%, the yield obtained in the direct rearrangement.

Methylcyclohexenylpropionic acid (III) was prepared by Chuang, Tien, and Ma (2), in their synthesis of 8-methyl-1-hydrindanone but, since these authors failed to report any physical constants other than the boiling point, the acid prepared by the Arndt-Eistert rearrangement was analyzed and the values found to correspond to the formula $C_{10}H_{10}O_2$. The dibromo compound reported by Chuang, Tien, and Ma (2) could not be obtained in crystalline form. The next higher homolog of this acid, the desired methylcyclohexenylbutyric acid (VI) was prepared from the propionic acid by a second diazo ketone rearrangement without isolation of any intermediates. Rearrangement to the amide or ester in this case was not tried, since the rearrangement to the acid proceeded easily with quite satisfactory yield.

In the ring closure to the chloro ketone (VII), the original procedure of Cook and Lawrence (4) was followed. These authors applied the reaction to the cyclization of cyclohexenylbutyric acid to 10-chloro-1-octalone. The subsequent removal of hydrochloric acid required more extensive investigation, since there was some doubt as to the purity of the product. The question of purity at this stage required particular attention since the success of all later steps was dependent on the purity of the starting material. Cook (4) reported the formation of an octalone and identified it as $\Delta^{9,10}$-1-octalone, originally reported by Hueckel and Naab (5). Their product was uniform, and it seems natural that removal of hydrochloric acid should proceed as indicated by them. Since in the case of methylcyclohexenylbutyric acid the formation of a C_9—C_{10} double bond is impossible, the product must be either $\Delta^{4,10}$ (VIII)- or $\Delta^{5,10}$ (IX)-9-methyl-1-octalone. With the exception of the carbonyl group, the chloro ketone is perfectly symmetrical, the latter group being too far removed to have any particular influence on the course of the reaction. One would therefore expect both octalones to be formed in this reaction.

Frequent distillations of the product failed to give consistent refractive indices, though correct analytical figures were obtained. Chuang, Tien, and Ma (2) reported the melting point 226–227° for the semicarbazone and left the question of the double bond open. They also reported an oxime melting at 99–100°. These constants could not be verified in this laboratory, and these derivatives were identified as mixtures of two semicarbazones and two oximes. Chuang's semicarbazone was found to be a mixture of semicarbazones melting at 228–229° and 168°, from which the octalones could be regenerated. The oximes formed by the usual procedure from the pure octalones, melted at 105° and 120° respectively. All attempts to determine the exact position of the double bond in the

pure octalones failed. Oxidative cleavage of the double bond would produce, in either case, diketocarboxylic acids with the same empirical formulas. Oxidation of the octalones to dicarboxylic acids, followed by cleavage of the double bond should permit differentiation, but the two dicarboxylic acids could not be prepared.

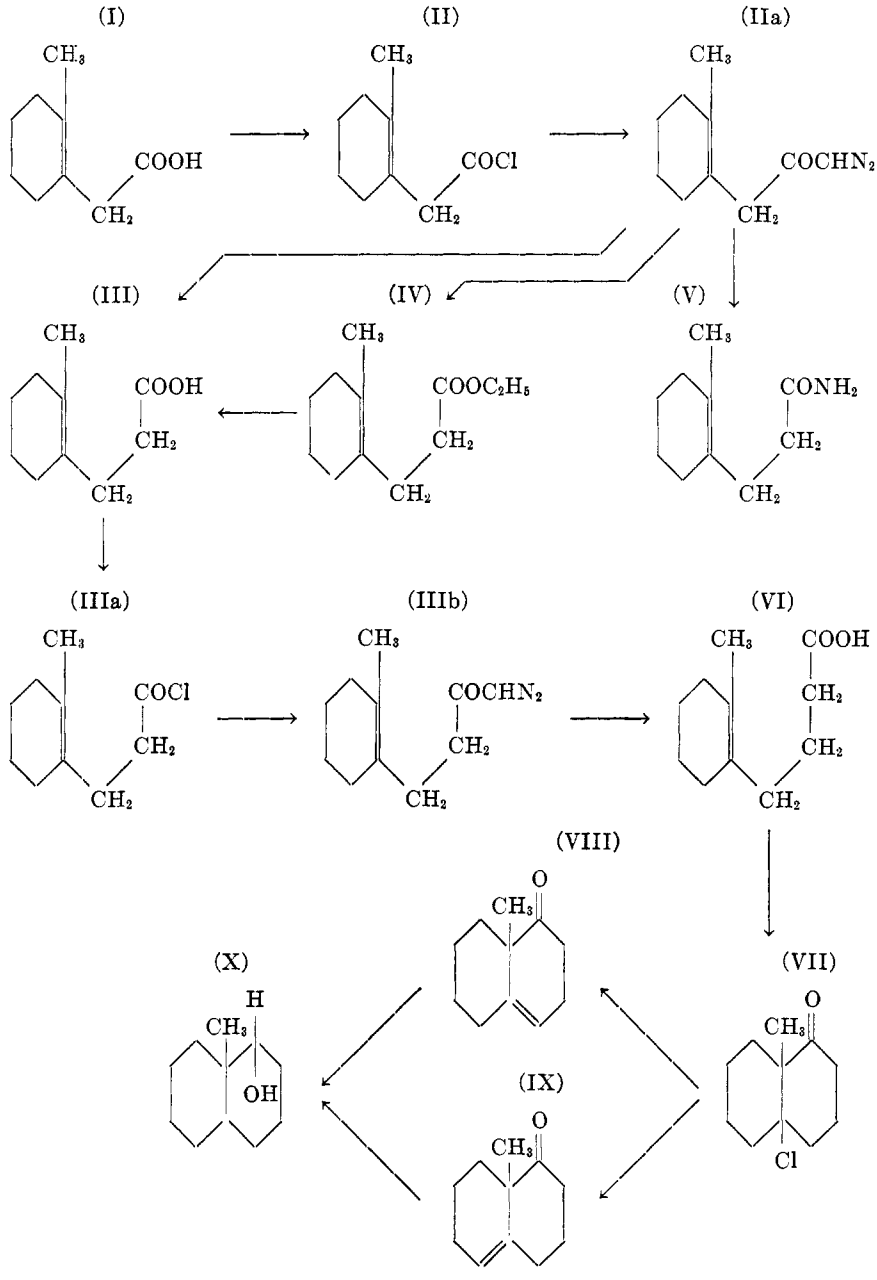
Hydrogenation of both octalones gave either 9-methyl-1-decalol (X) or 9-methyl-1-decalone (XI), depending on the quantity of catalyst used. With platinum oxide in acetic acid, in quantities exceeding one-tenth the amount of octalone, the hydrogenation could not be stopped at the ketone stage. Reduction of the carbonyl group seemed to take place at the same time. In order to ensure uniformity of the product, all the octalone was hydrogenated to the alcohol (X) which, after purification, was oxidized to the ketone (XI).

Purification of this ketone was effected by regeneration from its semicarbazone, m.p. 225°, which agrees with the value reported by Elliot and Linstead (3) for what they call the *cis* form. The next step, the conversion to the oxime, was somewhat complicated by the fact that the reaction of hydroxylamine hydrochloride yielded two oximes, m.p. 106° and 88°, probably the *syn* and *anti* forms (XII and XIII). Both oximes, when reduced in alkaline solution, similar to the procedure of Leroux (6), gave an amine which, on the basis of its analogy to decalylamine, we have designated as *cis*-9-methyl-1-decalylamine-B, for want of a better nomenclature (15). The exact position of the NH_2 group, or the hydrogen atom with respect to the angular methyl group is uncertain in either case (11). The epimeric amine, *cis*-9-methyl-1-decalylamine-A, was obtained by catalytic reduction of the two oximes of m.p. 105° and 120°.

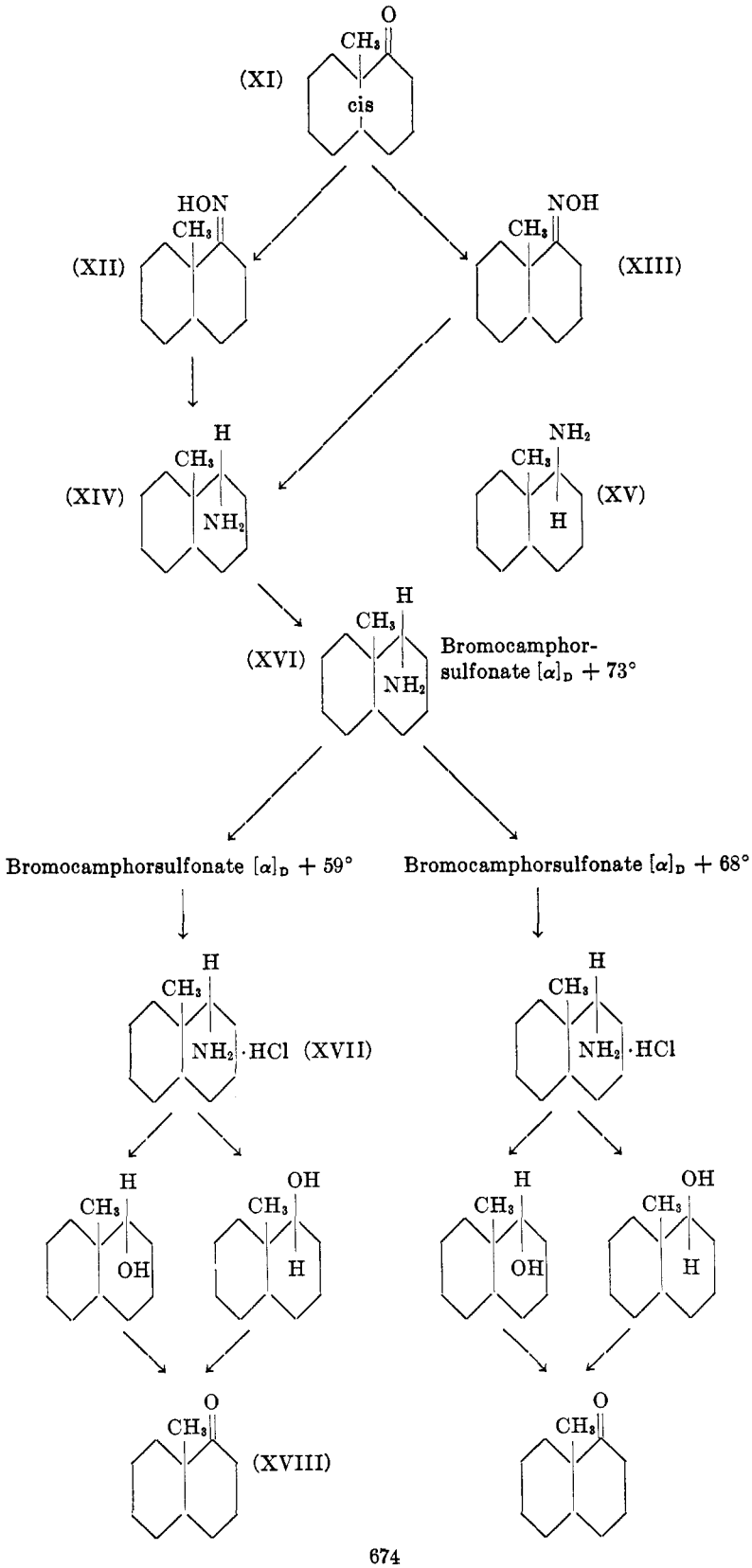
The latter route, although shorter, was found to be less satisfactory than the reduction of the saturated oxime, since the product, due to incomplete hydrogenation, was less uniform than in the former case. In either case, the products were purified through their benzoyl derivatives, melting at 158° and 142° respectively. The procedure followed in the preparation of the benzoyl derivatives, and the regeneration of the amines, was essentially the one described by Hueckel *et al.* (14).

Only the purest fraction of this *cis*-9-methyl-1-decalylamine-B (XIV) was used for the subsequent resolution into its optical isomers. Hueckel and Kuehn (7) reported a similar resolution of β-decalylamine using camphorsulfonic acid (Reychler's acid) as the optically active reagent. This acid was found to be unsuitable for the resolution of XIV, because of the excessive solubility of its salts. α-Bromo-π-camphorsulfonic acid, on the other hand, was found to form salts which were sufficiently difficultly soluble in dilute ethyl alcohol to be separated by a reasonable number of crystallizations.

Flow-Sheet A


(I)
(II)
(IIa)
(III)
(IV)
(V)
(IIIa)
(IIIb)
(VI)
(VII)
(VIII)
(IX)
(X)
CH3
COOH
COCl
COCHN2
CH2
COOC2H5
CONH2
H
OH
O
Cl

Flow Sheet B


(XI)
cis
(XII)
(XIII)
(XIV)
(XV)
(XVI)
Bromocamphor-sulfonate $[\alpha]_D$ + 73°
Bromocamphorsulfonate $[\alpha]_D$ + 59°
Bromocamphorsulfonate $[\alpha]_D$ + 68°
·HCl (XVII)
(XVIII)

The amines, regenerated from the bromocamphorsulfonates were reacted with nitrous acid, to give a mixture of hydrocarbon and partially inverted alcohol. The hydrocarbon in each case was probably $\Delta^{1,2}$-9-methyloctalin and was not further investigated. The conversion to the alcohols seemed to proceed under partial inversion at C_1, since the mixtures obtained from the *d*- and *l*-amines could not be brought to equal and opposite rotation. However, the fact that oxidation of the dextro and levo mixture yielded *d*, and *l*-9-methyl-1-decalone in reasonably pure condition, indicated that the Walden inversion was confined to C_1 as indicated in flow-sheet B.

This fact is quite in agreement with the observations of Hueckel (15), that in the α B series inversion of the product takes place to a limited extent, although he was unable to isolate the inverted alcohol in pure form. The optical data herein reported do not necessarily prove that inversion has taken place, but certainly support Hueckel's statement. Furthermore, it may be taken as additional confirmation that the ring configuration is *cis* and not *trans*, since in the α B-*trans* series no inversion whatsoever occurred (15).

After oxidation of the alcohol mixture, the products were purified by means of their semicarbazones. These derivatives were found to have the same melting point, which was higher than that of the semicarbazone of the inactive ketone. Mixed melting points of these compounds in varying ratios indicated that the semicarbazone of the inactive ketone was a racemic mixture.

ACKNOWLEDGMENTS

Our thanks are due to Professor Charles O. Beckmann, of this University, for the use of his polarimeter; and to Mr. Saul Gottlieb, who carried out the analytical work herein recorded.

EXPERIMENTAL

(All melting points recorded are corrected.)

2-Methylcyclohexenylacetic acid (I). The ethyl ester of this acid was prepared according to the procedure of Chuang, Tien, and Ma (2). When saponified and worked up in the usual way, the acid boiled at 137–139°/10 mm. Previously reported boiling point is 151°/28 mm. (17).

2-Methylcyclohexenylacetylchloride (II). Fifty grams of cyclohexenylacetic acid was added drop by drop to 70 cc. of thionyl chloride over a period of one-half hour. The mixture was then heated to boiling on the steam-bath and refluxed for one-half hour. The excess of thionyl chloride was removed under reduced pressure and the residue distilled from a 200 cc. Claisen flask (the large flask was necessary because of strong foaming). The distillate was redistilled from a 50 cc. Claisen flask equipped with a short fractionating column. The fraction boiling at 86–89°/10 mm. was collected. Yield: 36 g.; d_4^{25} 1.065; n_D^{25} 1.4852; R_L found: 46.00, calc'd: 45.98.

Anal. Calc'd for $C_9H_{13}ClO$: Cl, 20.4. Found: Cl, 20.3.

β-(2-Methylcyclohexenyl)propionamide (V). An ether solution of diazomethane was prepared from 74 g. of nitrosomethylurea in the usual manner, using 500 cc. of absolute ether as solvent. This solution was cooled in ice and, while efficiently stirred, 35 g. of cyclohexenylacetyl chloride was added. As soon as the evolution of gases had ceased, the flask was placed in the ice-box overnight. The following day the precipitated polymethylenes were removed by filtration and the solution concentrated under reduced pressure. The residual diazo ketone (IIa) could not be crystallized and, due to its instability to light and heat, was worked up immediately.

Approximately 10 g. of the diazo ketone was dissolved in 75 cc. of dioxane, 30 cc. of 20% ammonium hydroxide solution, and 5 cc. of a 10% silver nitrate solution added, and the mixture heated on the steam-bath. After a few minutes the solution became cloudy and nitrogen was given off. The heating was continued for another hour, the reaction mixture decanted from the precipitated silver, poured upon ice and the product extracted with ether. The ether was dried, filtered, and evaporated. The residue crystallized on standing in the ice-box overnight. The crude crystalline material was purified by crystallization from benzene-petroleum ether mixtures; m.p. 135°.

Anal. Calc'd for $C_{10}H_{17}NO$: C, 71.9; H, 10.3.
Found: C, 72.0; H, 10.4.

Ethyl β-(2-methylcyclohexenyl)propionate (IV). Ten grams of the diazo ketone, prepared as described above, was dissolved in 150 cc. of absolute ethyl alcohol, a suspension of 10 g. of silver oxide added, and the mixture refluxed on the steam-bath. After refluxing for one hour, the solution became clear and the precipitated silver was filtered off. The alcohol in the filtrate was removed under reduced pressure and, after elimination of a small amount of water, the product was distilled under reduced pressure, b.p. 95-97°/10 mm.; yield, 4.5 g.

Anal. Calc'd for $C_{12}H_{20}O_2$: C, 73.4; H, 10.2.
Found: C, 73.2; H, 10.2.

β-(2-Methylcyclohexenyl)propionic acid (III). Thirty-two grams of diazo ketone, prepared as described above, was dissolved in 50 cc. of pure dioxane and added to a vigorously stirred solution of 35 g. of sodium thiosulfate in 400 cc. of water containing 30 g. of silver oxide in suspension. After stirring for one hour at room temperature, the reaction mixture was filtered through cotton, the filtrate acidified with nitric acid and the product isolated in the usual manner; b.p. 112–113°/14 mm.; yield, 33%.

Anal. Calc'd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.5.
Found: C, 71.2; H, 9.5.

A lower-boiling fraction in this distillation was identified as the ethyl ester of this acid. Its formation was probably due to hydrolysis of the dioxane.

γ-(2-Methylcyclohexenyl)butyric acid (VI). Nine and two-tenths grams of methylcyclohexenylpropionic acid (III) was dissolved in 60 cc. of anhydrous ether, 4.5 g. of anhydrous pyridine added and the mixture cooled in ice. One molar equivalent of thionyl chloride (4.2 cc.) was then slowly added to the mixture. The pyridine hydrochloride first separated in white crystals, and later congealed to a yellow semi-solid mass. After all the thionyl chloride had been added, a little anhydrous ether saturated with dry hydrogen chloride was added, to precipitate the excess of pyridine. The pyridine hydrochloride was centrifuged and washed once more with anhydrous ether. The ether solution was concentrated under reduced pressure at room temperature, and the residual acid chloride, a slightly yellow liquid, was brought into reaction with excess of diazomethane in the manner described above. The rearrangement to the butyric acid proceeded smoothly without the use of silver oxide. The product, 3.5 g., boiled at 166–167°/10 mm. and solidified in the side arm.

It was recrystallized from petroleum ether, and then melted at 43°. Elliot and Linstead reported the melting point 44°. Chuang, Tien, and Ma (2) do not give a melting point.

Ethyl γ-(2-methylcyclohexenyl)butyrate. Eleven grams of the pure spiro-lactone, b.p. 102–105°/1 mm., obtained as by-product in the dehydration of Linstead's hydroxybutyric acid, was dissolved in 50 cc. of dry benzene and refluxed on the steam-bath. Fourteen grams of thionyl chloride, dissolved in 25 cc. of dry benzene, was added from a dropping-funnel and the refluxing continued for 2 hours, the reaction mixture allowed to cool to room temperature and then poured into 200 cc. of absolute alcohol. This alcohol-benzene solution was warmed on the steam-bath for about 10 minutes, the solvents removed under reduced pressure and the residue distilled using a small fractionating column. Eight grams of pure ester, b.p. 77–78°/0.5 mm., was collected; n_D^{25} 1.4671; d_4^{25} 0.9680.

Anal. Calc'd for $C_{13}H_{22}O_2$: C, 74.3; H, 10.5.
Found: C, 74.5; H, 10.4.

If the refluxing of the reaction mixture was stopped after one hour, the resulting product was a mixture of about 30% unsaturated and 70% saturated ester.

The ester prepared by this procedure was saponified with 20% alcoholic potassium hydroxide solution and worked up in the usual manner. The acid distilled at 132–135°/2 mm. and, after recrystallization from petroleum ether, had the melting point of 43°, and was identical with the acid obtained by the diazo ketone rearrangement, dehydration of the hydroxy acid according to Linstead, as well as the acid obtained by isomerization of the spiro-lactone itself.

9-Methyl-1-octalone (VIII or IX). The cyclization of methylcyclohexenylbutyric acid was carried out exactly as described by Cook and Lawrence (4), without isolation of the intermediate chloro ketone (VII). All attempts to distill this ketone, contrary to the experience of Elliot and Linstead (3), failed since the compound decomposed even at 0.1 mm. pressure. The crude chloro ketone was therefore heated with dimethylaniline at 180° for 3 hours and the product distilled under reduced pressure. Repeated distillations failed to give a pure product as indicated by inconsistent refractive indices.

The first crude product, b.p. 85-95°/0.5 mm., dissolved in solvent alcohol, was added to a mixture of 2 parts of anhydrous sodium acetate and 1.5 parts of semicarbazide hydrochloride, with the requisite amount of water. After a period of about 10 or 15 minutes, a precipitate began to form. The reaction was brought to completion by heating the mixture on the steam-bath for about one hour and allowing it to stand in the ice-box overnight. The following day the semicarbazone was filtered off and recrystallized from dilute ethyl alcohol. Recrystallization was repeated until the precipitate showed the same melting point as the second crop obtained by concentration of the mother liquors. The pure compound melted at 228–229°.

Anal. Calc'd for $C_{12}H_{19}N_3O$: C, 65.2; H, 8.6.
Found: C, 65.5; H, 8.4.

Eight and two-tenths grams of the pure semicarbazone, m.p. 228–229°, was suspended in 200 cc. of 5% hydrochloric acid, stirred, and heated on the steam-bath for one-half hour. The ketone, which had formed as a colorless oil, was extracted with ether, the ether washed with sodium carbonate solution, and dried with magnesium sulfate. After filtration and removal of the solvent, the product was distilled under reduced pressure, b.p. 66–67°/0.5 mm.; n_D^{25} 1.5065; d_4^{25} 1.0054; R^L calc'd: 48.16, found: 48.6; yield, nearly that calculated.

Anal. Calc'd for $C_{11}H_{16}O$: C, 80.5; H, 9.75.
Found: C, 80.4; H, 9.88.

The product was a camphoraceous-smelling oil and exhibited all the properties of unsaturation. On standing for a month, it polymerized to a yellow resin. Since there existed the possibility of a shift of the double bond, a small sample of the compound was converted into its semicarbazone by the usual procedure; the crude derivative had the melting point 228°, indicating that no isomerization had taken place under the influence of hydrochloric acid.

Oxime. Eight hundred milligrams of the ketone was dissolved in 6 cc. of methanol and to this solution was added 1 g. of hydroxylamine hydrochloride and 1 g. of sodium acetate, dissolved in 3 cc. of water. Methanol was then added to the mixture until a clear solution was obtained. After a few minutes, a precipitate formed and, on standing overnight, the reaction was complete as indicated by the absence of the characteristic odor of the ketone. The oxime was filtered and recrystallized from dilute methyl alcohol; m.p. 105°.

Anal. Calc'd for $C_{11}H_{17}NO$: C, 73.7; H, 9.5.
Found: C, 73.9; H, 9.8.

There was some evidence of an isomeric oxime in the mother liquor, but it could not be isolated in pure form.

Isomeric 9-methyl-1-octalone (VIII or IX). The combined mother liquors of the semicarbazone (m.p. 228–229°) were diluted with water until cloudy, left standing for about a week, and the precipitate filtered off. After frequent recrystallization, from Skellysolve D (77–116° ligroin), a semicarbazone m.p. 168° was isolated.

Anal. Calc'd for $C_{12}H_{19}N_3O$: C, 65.2; H, 8.6.
Found: C, 65.5; H, 8.6.

This semicarbazone was decomposed as described for its isomer. The product distilled at 70–71°/0.5 mm.; n_D, 1.5084; d_4^{25} 1.0081. It was a colorless oil, in its properties and odor similar to the isomer (b.p. 66–67°/0.5 mm.).

Anal. Calc'd for $C_{11}H_{16}O$; C, 80.5; H, 9.7.
Found: C, 80.4; H, 9.9.

Oxime. This derivative was prepared from the ketone, using the same procedure as described above; m.p. 120° (from alcohol).

Anal. Calc'd for $C_{11}H_{17}NO$: C, 73.7; H, 9.5.
Found: C, 73.6; H, 9.8.

Oxidation experiments. (a) *Oxidation with hypobromite in pyridine solution.* The procedure followed was that described by Ladenburg, Chakravorty, and Wallis (18), for the oxidation of *i*-cholestanone-6 to α_1-*i*-cholestane-diacid-6,7.

Two grams of the octalone, freshly regenerated from its semicarbazone (m.p. 168°), was added to a solution of sodium hypobromite prepared by dissolving 10 g. of sodium hydroxide in 100 cc. of water followed by addition of 2.5 cc. of bromine. To this solution was added 75 cc. of pure pyridine and the mixture shaken for 25 hours. Two layers were formed; the upper pyridine layer was bright red and the aqueous layer colorless. The mixture was cooled in ice and slowly acidified with dilute (50%) sulfuric acid. When the mixture was acid to Congo red the red color disappeared. The acid products were then extracted with ether and attempts were made to purify the product or products in the usual way. Only resinous material could be isolated.

(b) *Nitrous acid reaction and rearrangement.* The procedure followed that reported by Levitz, Perlman, and Bogert (19) in the conversion of spirocyclohexane-1,1′-tetralone-4′ to α,α-pentamethylenehomophthalic acid.

To an ice-cold and well-stirred mixture of 1 g. of freshly regenerated octalone, 2 cc. of freshly distilled butyl nitrite, and 2 cc. of glacial acetic acid, 3 cc. of concentrated nitric acid was added from a microburette. No reaction took place cold, and

the mixture was slowly heated to 50° and allowed to remain at that temperature for 15 minutes. It was then placed in the ice-box and left standing for several days. No crystalline material formed, but the mixture separated into two layers. The lower layer was removed and a rearrangement attempted under the assumption that this material represented the crude isonitroso ketone. No definite acidic reaction product could be isolated.

The experiment was repeated and attempts made to crystallize the crude product. Standing in the ice-box for 11 months under petroleum ether, scratching, etc., did not produce crystallization.

cis-*9-Methyl-1-decalylamine-A* (XIV). The two unsaturated oximes, m.p. 105° and 120°, were reduced according to the following procedure: 200 mg. of each oxime was dissolved in 25 cc. of glacial acetic acid containing 95 mg. of reduced platinum oxide catalyst and shaken in hydrogen. The two compounds took up respectively 76.5 and 77.0 cc. of hydrogen in 9 hours. The calculated amount of hydrogen under the conditions was 82.3 cc. After removal of the catalyst by filtration, the acid was neutralized with 10% sodium hydroxide solution and the amine extracted with ether. After careful drying with anhydrous magnesium sulfate for two days, the amines were precipitated from the filtered solution with dry hydrogen chloride and recrystallized from acetone-alcohol mixtures.

Anal. Calc'd for $C_{11}H_{22}ClN$: C, 65.0; H, 10.8.
Found: C, 64.8; H, 11.0.

Benzoyl derivative. The amines were regenerated from their hydrochlorides with dilute sodium hydroxide solution and extracted with ether. The ether extracts were concentrated to about 3 cc. and 200 mg. of benzoic anhydride, dissolved in an equal amount of anhydrous ether, added. The benzoyl derivatives were crystallized by seeding, from dilute alcohol containing a little sodium bicarbonate, and then from pure alcohol. The two benzoyl derivatives showed the same melting point (142°) and gave no depression when mixed.

Anal. Calc'd for $C_{18}H_{25}NO$: C, 79.6; H, 9.2.
Found: C, 79.5; H, 9.0.

cis-*9-Methyl-1-decalol* (X). The octalone (2.133 g.), regenerated from the semicarbazone (m.p. 228–229°), was dissolved in 50 cc. of glacial acetic acid and hydrogenated using platinum oxide as catalyst. The compound took up 658.5 cc. of hydrogen in 90 minutes. No more hydrogen was taken up if the shaking was continued. The calculated amount of hydrogen for two moles under the conditions of the experiment was 651 cc. After removal of the catalyst by filtration, neutralization of the acid, and extraction with ether, drying, etc., the product was distilled under reduced pressure. The decalol was found to be a very viscous oil, with a camphoraceous odor which was even more pronounced than in the case of the ketone: b.p. 95°/1 mm.; n_D^{25} 1.5029; d_4^{25} 1.0000; R_L calc'd: 50.1, found: 49.8.

Anal. Calc'd for $C_{11}H_{20}O$: C, 78.5; H, 11.9.
Found: C, 78.6; H, 12.1.

3,5-Dinitrobenzoate. This ester was formed by interaction of the alcohol and 3,5-dinitrobenzoyl chloride in anhydrous pyridine solution. The reaction mixture was poured into ice-water, the precipitate filtered and recrystallized from 95% alcohol, m.p. 126°.

The octalone regenerated from the semicarbazone of m.p. 168° was similarly hydrogenated, and a dinitrobenzoate prepared from this product gave no depression with the ester of m.p. 126°.

Anal. Calc'd for $C_{18}H_{22}N_2O_6$: C, 59.7; H, 6.1; N, 7.7.
Found: C, 59.8; H, 6.1; N, 7.7.

Of these analytical figures, the C and H determinations were run on a dinitrobenzoate from the semicarbazone of m.p. 228-229°, and the N determination on the dinitrobenzoate from the semicarbazone of m.p. 168°.

cis-*9-Methyl-1-decalone* (XI). Five and five-tenths grams of pure *cis*-9-methyl-1-decalol was dissolved in 30 cc. of glacial acetic acid, and 2.6 g. of chromic anhydride dissolved in 10 cc. of water was added in small amounts. The solution was cooled and stirred for several hours, transferred to a larger vessel and steam distilled. Three hundred cubic centimeters of distillate was collected and the product, after extraction with ether and removal of the solvent, transformed into its semicarbazone by the usual procedure, and crystallized from alcohol, giving a product of m.p. 225°.

Anal. Calc'd for $C_{12}H_{21}N_3O$: C, 64.6; H, 9.4.
Found: C, 64.7; H, 9.5.

The ketone was regenerated from the semicarbazone by means of oxalic acid; b.p. 58.5°/0.7 mm.; n_D^{25} 1.4862; d_4^{25} 0.9820; R_L calc'd 48.63, found 48.61.

Elliot and Linstead (3) reported the following values: d_4^{15} 0.9958; n_D^{15} 1.4926; R_L calc'd 48.61, found 48.45.

Anal. Calc'd for $C_{11}H_{18}O$: C, 79.5; H, 10.8.
Found: C, 79.7; H, 11.0.

Oxime. Three and eight-tenths grams of pure *cis*-9-methyl-1-decalone was dissolved in 20 cc. of ethyl alcohol and to this solution was added 4 g. of hydroxylamine hydrochloride and 4 g. of anhydrous sodium acetate, dissolved in 10 cc. of water. Sufficient alcohol was then added to form a clear solution. After standing overnight, 2.5 g. of crystalline oxime had formed. This was filtered off and recrystallized from dilute alcohol, m.p. 106°.

Anal. Calc'd for $C_{11}H_{19}NO$: C, 72.9; H, 10.5.
Found: C, 73.1; H, 10.7.

The mother liquors of this oxime were concentrated at room temperature and the solution allowed to stand in the ice-box for several days. The crystalline precipitate was filtered off and recrystallized many times from very dilute alcohol, m.p. 88°.

Anal. Calc'd for $C_{11}H_{19}NO$: C, 72.9; H, 10.5.
Found: C, 72.7; H, 10.3.

In order to prove that these oximes were not derived from the possible presence of *trans*-9-methyl-1-decalone, both oximes were hydrolyzed by shaking with 20% oxalic acid and the products transformed into the semicarbazones. They proved to be identical, m.p. 225°, and identical with the original semicarbazone from which the ketone was prepared.

Hydrogenation of the 9-methyl octalone mixture to cis-*9-methyl-1-decalone.* Thirty grams of octalone mixture, regenerated from the mixed semicarbazones (m.p. 168° and 228-229°), was hydrogenated using 1 g. of reduced platinum oxide in 100 cc. of glacial acetic acid. Hydrogen was rapidly taken up during the first hour, at the end of which time 4500 cc. had been absorbed, and the shaking was continued for another 12 hours. A total of 4840 cc. of hydrogen was taken up. The calculated amount for one double bond was 4835 cc. The mixture was freed from the catalyst by filtration, the acetic acid neutralized with sodium hydroxide and sodium bicarbonate solutions, and the ketone isolated by steam distillation. The product was converted into its semicarbazone by the usual procedure, and proved to be identical with the compound obtained by oxidation of *cis*-9-methyl-1-decalol (X). After regeneration from its semicarbazone, 24.5 g. of the pure *cis*-9-methyl-1-decalone was obtained.

cis-*9-Methyl-1-decalylamine-B* (XIV). One and eight-tenths grams of the oxime,

m.p. 106°, was dissolved in 40 cc. of absolute alcohol. To this solution was added 4 g. of metallic sodium in small pieces over a period of 2 hours, and the mixture was then heated under reflux until all the sodium had gone into solution. When cooled to room temperature, the solid mass was dissolved in water and the amine extracted with ether. After drying and removal of the ether, the amine was distilled under reduced pressure, b.p. 65-68°/1 mm. Determination of the density and refractive index, as well as an analysis, was omitted because of the strong tendency of this compound to take up carbon dioxide from the air with formation of carbonates.

The hydrochloride was prepared by precipitation from anhydrous ether solution with dry hydrogen chloride, and crystallization from acetone-alcohol mixtures.

Anal. Calc'd for $C_{11}H_{22}ClN$: C, 65.0; H, 10.8.
Found: C, 64.8; H, 10.9.

Benzoyl derivative. This derivative was prepared in exactly the same manner as already described for its epimer. Recrystallized from dilute ethyl alcohol, m.p. 158–159°.

Anal. Calc'd for $C_{18}H_{25}NO$: C, 79.6; H, 9.2.
Found: C, 79.7; H, 9.2.

The same procedure was repeated with the oxime m.p. 88°, and found to give the same amine as indicated by the identity of the benzoyl derivatives.

α-Bromo-π-camphorsulfonic acid. This acid was prepared according to the procedure of Regler and Hein (16), and purified through its ammonium and silver salts; yield 60%. A solution of 0.069 g. in 5 cc. water, 1 dm. tube, showed α_D + 1.08, $[\alpha_D^5]$ + 78.5°.

Resolution of the amines. Six and five-tenths grams of purest *cis*-9-methyl-1-decalylamine-B purified through its benzoyl derivative, m.p. 158–159°, according to the procedure of Hueckel (14), was dissolved in 20 cc. of absolute ethyl alcohol, and 12.1 g. of α-bromo-π-camphorsulfonic acid dissolved in 50 cc. of absolute ethyl alcohol was added. The solution was cooled in ice during the addition, since otherwise considerable ammonia was given off, indicating decomposition of the amine. The solution was allowed to stand in the ice-box overnight and was then concentrated under reduced pressure until the salt began to crystallize, when the mixture was transferred to a crystallizing dish and the solvent evaporated at room temperature. The crude salt had the specific rotation +73.5°.

This salt was recrystallized and fractionated in the usual triangle procedure. Both salts crystallized in long needles. The less soluble salt was first obtained in pure condition and was rather easily brought to constant rotation, yield 7.4 g; 0.392 g. in 5 cc. solution, 1 dm. tube, α_D +5.37°; $[\alpha_D]_{H_2O}$ + 68.8°.

The more soluble salt was obtained in pure form only after a great number of crystallizations and repeated seeding of its saturated solution with the less soluble salt; yield, 6.1 g; 0.277 g. in 5 cc. solution, 1 dm. tube, α_D +3.28°; $[\alpha_D]_{H_2O}$ + 59.2°.

The salts were dissolved in 10% sodium hydroxide solution and the free amine extracted with ether. After careful washing and drying with magnesium sulfate, the amines were precipitated as their hydrochlorides and excess of hydrochloric acid removed in a vacuum desiccator containing soda lime.

(+)cis-*9-Methyl-1-decalylamine-B.* Regenerated from the bromocamphorsulfonate, $[\alpha_D]_{H_2O}$ + 68.5°, it was transformed into its hydrochloride according to the procedure outlined above; 0.3532 g. in 5 cc. solution, 1 dm. tube, α_D +0.45°; $[\alpha_D]_{H_2O}$ +7.0°.

(−)cis-*9-Methyl-1-decalylamine-B.* Regenerated from the bromocamphorsulfonate, $[\alpha_D]_{H_2O}$ +59.2°, it was transformed into its hydrochloride as outlined above; 0.459 g. in 5 cc. solution, 1 dm. tube, α_D −0.59°; $[\alpha_D]_{H_2O}$ −6.9°.

(+)cis-*9-Methyl-1-decalone.* Two grams of the (+) amine, regenerated from its hydrochloride, was dissolved in 25 cc. of 10% acetic acid and 1 g. of sodium nitrite, dissolved in 3 cc. of water, added. The resulting green solution was kept at 50° until the reaction had died down and then heated on the steam-bath for about 3 hours. When cooled to room temperature, the product was extracted with ether, the ether extracts washed, and the ether removed on the steam-bath. The residual mixture of alcohol, hydrocarbon, and ester was saponified by refluxing on the steam-bath with alcoholic potassium hydroxide solution for 2 hours. The neutral constituents were worked up in the usual way and distilled under reduced pressure. The first fraction, consisting mostly of hydrocarbon, was neglected, and only the main fraction, boiling at 95-97°/1 mm., was collected. Its specific rotation was about +8° and, in the redistilled product, went up to about +11°; yield, 1.2 g. All this material was dissolved in 20 cc. of glacial acetic acid, and 600 mg. of chromic anhydride dissolved in 1 cc. of water was added. The mixture was allowed to stand at room temperature for an hour and was then steam distilled. Alcohol was added to the distillate until a clear solution was obtained, and the ketone was precipitated as the semicarbazone in the usual way. After repeated recrystallizations, this derivative melted at 228°. A mixed melting point with the inactive ketone in a ratio of 5:1 gave the melting point 226–227° and in a ratio of 1:1, 225–227°; 920 mg. of pure semicarbazone was obtained; 0.391 g. in 5 cc. solution, 1 dm. tube; α_D +0.09°; $[\alpha_D]_{EtOH}$ +1.1°.

The ketone was regenerated from the semicarbazone in the manner described above, and its boiling point was approximately 60°/1 mm.; 0.341 g. in 5 cc. solution, 1 dm. tube; α_D +0.29°; $[\alpha_D]_{EtOH}$ +4.2°.

(−)cis-*9-Methyl-1-decalone.* The conversion of the amine to the alcohol and the oxidation of this alcohol to the ketone, was carried out exactly as described for its epimer. The semicarbazone was much more difficult to bring to constant melting point, but reached the same value, 228°, after about 10 recrystallizations. Four grams of amine gave 1.1 g. of pure semicarbazone; 0.5440 g. in 5 cc. solution, 1 dm. tube, α_D −0.10°; $[\alpha_D]_{EtOH}$ −0.90°.

The ketone regenerated from the semicarbazone had approximately the same boiling point as its antipode, 60°/1 mm.; 0.4240 g. in 5 cc. solution, 1 dm. tube; α_D −0.33°; $[\alpha_D]_{EtOH}$ −3.9°.

SUMMARY

1. β-(2-Methylcyclohexenyl)propionic acid (III) and γ-(2-methylcyclohexenyl)butyric acid (VI) were prepared by a new method.

2. Removal of hydrochloric acid from 9-methyl-10-chloro-1-decalone (VII) proceeds with formation of two isomers: $\Delta^{4,10}$-, and $\Delta^{5,10}$-9-methyl-1-octalone (VIII and IX), both of which were isolated and characterized by derivatives. The exact position of the double bond in each of these ketones was not determined.

3. The two possible epimeric forms (XIV and XV) of *cis*-9-methyl-1-decalylamine were prepared and characterized by derivatives.

4. One of these amines (XV) was resolved into its optical antipodes (XVII) by means of α-bromo-π-camphorsulfonic acid.

5. The conversion of the *d*-, and *l*-amine with nitrous acid, was found to proceed with partial Walden Inversion at C_1, as indicated by the fact that

oxidation of the resulting mixture of alcohols yielded an optically pure ketone in each case (XVIII).

6. The semicarbazone of the inactive *cis*-9-methyl-1-decalone proved to be a racemic mixture, as shown by mixed melting points in varying ratios.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE REACTIONS AND ENOLIZATION OF CYCLIC DIKETONES. VI. 2,4,5-TRIPHENYLCYCLOPENTENE-4-DIONE-1,3 AND 2,4,5-TRIPHENYLCYCLOPENTANEDIONE-1,3[1]

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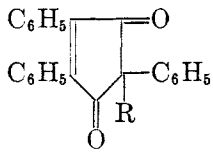
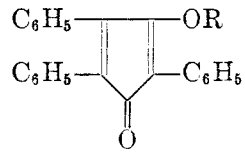
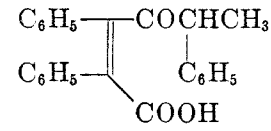
It has been suggested (1) that the enolization of α-diketones derived from cyclopentane is greatly suppressed when a double bond is present in the five-membered ring. For example 3,4-diphenylcyclopentanedione-1,2 reacts immediately with bromine and is readily soluble in aqueous sodium carbonate, while 3,4-diphenylcyclopentenedione-1,2 is not affected by bromine is boiling carbon tetrachloride and is insoluble in cold aqueous sodium hydroxide. The research described in the present paper was undertaken to determine if the enolization of β-diketones with the same five-membered ring system is likewise suppressed by a double bond in the ring. The results indicate that such is the case.



I, R = H
III, R = Br
IV, R = COC_6H_5
VI, R = CH_3



II, R = H
V, R = COC_6H_5



VII

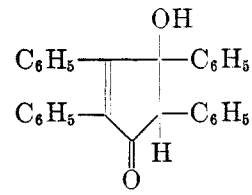
2,4,5-Triphenylcyclopentenedione-1,3 can be prepared readily by the action of sodium methoxide on benzaldiphenylmaleid.[2] It is yellow, and this fact indicates that it is ketonic (I) for if it existed in the enolic form (II) it would be red, as are all substances containing the fulvene nucleus. It does not react with bromine in chloroform, but it can be brominated in acetic acid containing a little hydrogen bromide, giving 2-bromo-2,4,5-

[1] Abstracted from a thesis presented by S. Wawzonek in partial fulfillment of the requirements for the Ph.D. degree, July, 1939.

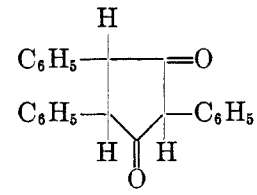
[2] A paper describing the diketone and a different method for its preparation was published by Allen, Massey, and Nicholls (2) after the present research had been completed.

triphenylcyclopentenedione-1,3 (III). It dissolves slowly in aqueous alcoholic sodium hydroxide, forming a purple sodium salt, but acidification of a solution of this salt even at low temperatures causes the yellow diketone to precipitate.[3] Sodium nitrite converts the diketone into a biscyclopentyl derivative, a substance which also results when the diketone is treated with chromic acid (2).

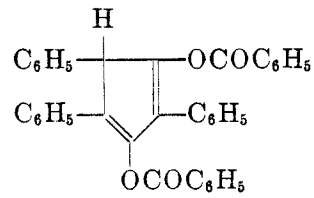
When 2,4,5-triphenylcyclopentenedione-1,3 is treated with benzoyl chloride in aqueous alkali, a yellow C-benzoyl derivative (IV) is obtained. But when the benzoylation is carried out with benzoyl chloride in pyridine, there is formed a mixture of the C-compound with a red O-benzoyl derivative (V). Alkylation of the diketone with methyl sulfate and aqueous alkali yields only a yellow methyl compound (VI), which must be a C-derivative since it is not affected by long boiling with hydrogen bromide in acetic acid or by hydroxylamine; it is cleaved by alcoholic alkali with the formation of an acid $C_{24}H_{20}O_3$, probably VII.



VIII



IX



X

When treated with phenylmagnesium bromide, 2,4,5-triphenylcyclopentenedione-1,3 is enolized immediately. Further interaction leads to the formation of only a small amount of VIII, the compound to be expected if the behavior (3) of 2-phenylindandione-1,3 towards phenylmagnesium bromide is considered. The main product is 2,4,5-triphenylcyclopentanedione-1,3 (IX).

[3] Acidification of a solution of the red sodium salt of indandione-1,3 at ordinary temperatures yields a colorless precipitate consisting of the diketone; but if the acidification is carried out at about 0°, the precipitate is dark red and becomes colorless only after it stands for a few minutes.

The saturated diketone[4] is best obtained by the action of zinc dust on an alkaline solution of 2,4,5-triphenylcyclopentene-4-dione-1,3. It is a colorless substance, not only easily soluble in aqueous sodium carbonate, but also so acidic that it can be titrated using phenolphthalein. It reacts immediately at room temperature with bromine in acetic acid, yielding a bromo compound (III) identical with the one obtained from the unsaturated diketone. With benzoyl chloride and alkali, 2,4,5-triphenylcyclopentanedione-1,3 reacts to form a colorless dibenzoate (X).

The data obtained indicate that the marked tendency to enolize of β-diketocyclopentane derivatives is almost completely absent in β-diketocyclopentene derivatives. Since the same phenomena are found in similar α-diketonic compounds, the behavior may be generalized by the statements that (a) there is a tendency for one double bond to enter a five-membered ring (enolization of a saturated diketone), and (b) there is a resistance to the entry of a second double bond (enolization of an unsaturated diketone). The inconsistency of the second of these statements with the results of Kistiakowsky, Ruhoff, Smith, and Vaughan (4) cannot yet be explained without resorting to pure speculation.

EXPERIMENTAL

The method used for the preparation of large quantities of diphenylmaleic anhydride involved the condensation of potassium benzoylformate with phenylacetic acid. The filtered solution from the oxidation of mandelic acid (375 g., 2.5 moles) by the procedure of Corson, Dodge, Harris, and Hazen (5) was evaporated to a small volume and then cooled. The potassium benzoyl formate was filtered with suction; the filtrate was evaporated, cooled, and filtered as long as potassium benzoylformate separated. The combined portions of moist potassium salt were then dissolved in $\left(\frac{\text{wt. K salt} - 470}{18} + 5\right)$ moles of acetic anhydride containing 340 g. of phenylacetic acid, and the mixture was boiled for twelve hours. Water (200 ml.) was then added to decompose the acetic anhydride, and the product was filtered and recrystallized from acetic acid. By working up all the filtrates there was obtained 212–270 g. of diphenylmaleic anhydride which melted at 157–158°.

Before this method for the preparation of diphenylmaleic anhydride was developed, considerable work was done in attempting to check syntheses which have been described in the literature, but no satisfactory one was found. The addition of sodium methoxide (2 moles) to an ether solution of benzyl cyanide (1 mole) and iodine (1 mole) gave dicyanostilbene in a yield of at best 30% (literature (6) 90%). Adding iodine to benzyl cyanide and sodium methoxide in ether, or adding benzyl cyanide together with sodium methoxide to iodine in ether, or adding sodium methoxide and iodine simultaneously to benzyl cyanide in ether gave no better results. Substitution of the ether by methanol, or by methanol containing a little acetone, or by methanol saturated with sodium iodide; or the use of magnesium methoxide at 0°

[4] This compound was also prepared by Allen, Massey, and Nicholls (2), but its acidic character led them to formulate it as α,β,δ-triphenylpentene-γ-oic acid.

or at the boiling point of the solution; or the use of sodamide in liquid ammonia gave a poor yield or none at all. The action of sodium methoxide on α,β-diphenylsuccinonitrile (7) and iodine in methanol-ether gave 44% of dicyanostilbene. Boiling dicyanostilbene with alcoholic potash for twenty-four hours gave diphenylmaleic anhydride in 75% yield, while the use of sulfuric acid for the hydrolysis (8) led only to the formation of bright red substances (indones?).

Treatment of phenylbromoacetic ester with sodium in dry ether followed by alkaline hydrolysis (9) gave only a trace of diphenylmaleic anhydride. The thermal decomposition of mandelic acid (10) (15.2 g.) under a slight vacuum gave 0.4 g. of diphenylmaleic anhydride. The action of sodium hypobromite on 3,4-diphenylcyclopentenone (11) gave only small amounts of the desired substance. Condensation of benzoylformic ester with phenylacetic acid by the use of acetic anhydride and sodium acetate followed by alkaline hydrolysis gave 4% of diphenylmaleic anhydride.

2,4,5-Triphenylcyclopentene-4-dione-1,3 (I). A mixture of diphenylmaleic anhydride (175 g.), phenylacetic acid (140 g.), potassium acetate (1.5 g.), and sodium acetate (5.5 g.) was heated for one and one-half hours at 220–225° (12). The resulting benzaldiphenylmaleid was cooled, pulverized, and washed with methanol; yield 213 g. It was then boiled for four hours in methanol (400 ml.) in which 50 g. of sodium had been dissolved. The purple solution was cooled, poured into water (500 ml.), and acidified. The crude diketone (213 g.) was crystallized from acetic acid, from which it separated in the form of yellow needles (180 g.) that melted at 167–168°. The diketone was not affected by aqueous alkali, but it gave a purple solution in aqueous-alcoholic sodium hydroxide.

Anal. Calc'd for $C_{23}H_{16}O_2$: C, 85.2; H, 4.9.
Found: C, 85.3; H, 5.1.

Boiled for fourteen hours with hydroxylamine hydrochloride (2 g.) and sodium carbonate (0.5 g.) in aqueous ethanol, the diketone (1 g.) yielded an oxime (0.79 g.). This compound melted at 223–226° (decomp.) after crystallization from acetic acid; it was soluble in alkali.

Anal. Calc'd for $C_{23}H_{17}NO_2$: C, 81.4; H, 5.0.
Found: C, 78.0, 81.4; H, 5.1, 5.7.

Bromination. A mixture of the diketone I (1 g.), bromine (0.3 ml.), hydrobromic acid (2 drops), and acetic acid (15 ml.) was boiled for thirty minutes and then poured into water. The product III (1.2 g.), crystallized from acetic acid and then from ligroin, formed yellow needles that melted at 133–134°.

Anal. Calc'd for $C_{23}H_{15}BrO_2$: C, 68.5: H, 3.7.
Found: C, 68.4; H, 3.8.

Benzoylation. (a) In aqueous alkali. A solution of the diketone I (3.2 g.) in 10 ml. of benzene was shaken with water while 10% potassium hydroxide and benzoyl chloride were added alternately as long as the addition of alkali caused the development of a purple color. Crystallized from acetic acid, the resulting 2-benzoyl-2,4,5-triphenylcyclopentene-4-dione-1,3 (IV) formed yellow needles that melted at 175–176°.

Anal. Calc'd for $C_{30}H_{20}O_3$: C, 84.1; H, 4.7.
Found: C, 84.1; H, 4.8.

(b) In pyridine. A solution of the diketone I (1.1 g.), pyridine (9 ml.), and benzoyl chloride (1.1 ml.) in chloroform (20 ml.) was dark red. After it had been allowed to stand for fifteen minutes it was poured into water and ether, and the resulting ether solution was washed with dilute acid and dilute base. The product, a red

solid (0.72 g.) which melted unsharply at 151°, was separated by crystallization from acetic acid into two compounds. One was yellow and melted at 175–176° alone or mixed with a sample of the C-benzoyl derivative IV. The other, 3-benzoyloxy-2,4,5-triphenylcyclopentadienone (V), formed dark red plates that melted at 180–180.5°.

Anal. Calc'd for $C_{30}H_{20}O_3$: C, 84.1; H, 4.7.
Found: C, 83.9; H, 4.7.

Methylation. To a suspension of the diketone I (13 g.) in a mixture of 20 ml. of ethanol and 60 ml. of water at the boiling point were added alternately dimethyl sulfate and sodium hydroxide as long as a purple color was developed by the alkali. Crystallized from alcohol, the resulting 2-methyl-2,4,5-triphenylcyclopentenedione-1,3 (VI) formed yellow plates (11.6 g.) that melted at 106–108°.

Anal. Calc'd for $C_{24}H_{18}O_2$: C, 85.2; H, 5.3.
Found: C, 85.1; H, 5.5.

The methylated compound was insoluble in alkali and did not react with bromine in carbon tetrachloride. It was recovered unchanged after it had been boiled with hydrobromic acid in acetic acid, or after it had been boiled for one hundred hours with hydroxylamine in alcohol.

Boiled for three hours in ethanol (30 ml.) containing 15 ml. of 10% potassium hydroxide, the methylated diketone (4.1 g.) was converted into γ-keto-α,β, δ-triphenyl-Δ-α-hexenoic acid (VII) which formed white platelets (3 g.) that melted at 169–170.5°, after it had been crystallized from acetic acid.

Anal. Calc'd for $C_{24}H_{20}O_3$: C, 80.9; H, 5.6; N. E., 356.
Found: C, 80.8; H, 5.9; N. E., 389.

Reaction with phenylmagnesium bromide. A solution of 16.2 g. of the diketone I in 125 ml. of benzene was added to a Grignard reagent prepared from 40 g. of bromobenzene. The mixture became purple at once, but after it had been boiled for nine hours it was orange. It was decomposed with iced ammonium chloride, and the biphenyl was removed with steam. The residue was taken up in ether and extracted with alkali; acidification of the extract gave 8.7 g. of 2,4,5-triphenylcyclopentanedione-1,3 (IX) which melted at 202–204°. Recrystallized from toluene this substance formed fine white crystals that melted at 203–205°.

Anal. Calc'd for $C_{23}H_{18}O_2$: C, 84.7; H, 5.5; N.E., 326.
Found: C, 84.8; H, 5.6; N.E., 328.

The alkali-insoluble portion (0.8 g.) of the product was 2,3,4,5-tetraphenylcyclopentene-2-ol-4-one (VIII), a colorless substance that melted to a red liquid at 196–198° (literature (13) 210°). This compound was not analyzed; on boiling with acetic acid containing a drop of sulfuric acid it was converted into tetraphenylcyclopentadienone, which melted at 212–213° alone or mixed with an authentic sample.

2,4,5-*Triphenylcyclopentanedione-1,3* (IX). A solution of the diketone I (1 g.) in 25 ml. of 10% potassium hydroxide containing 5 ml. of ethanol was boiled with zinc dust until the purple color had disappeared. The solution was filtered and acidified, and the white precipitate was crystallized from toluene. The product (0.64 g.) then melted at 203–205° alone or mixed with the acidic substance obtained from the Grignard reaction previously described.

Benzoylation. A solution of the saturated diketone IX (1 g.) in 50 ml. of 10% potassium hydroxide was shaken with 6 ml. of benzoyl chloride. After the acid chloride had all reacted, the product was taken up in ether, and finally crystallized from acetic acid. The resulting 2,5-dibenzoyloxy-1,3,4-triphenylcyclopentadiene (0.65 g.) formed white needles that melted at 138–139°.

Anal. Calc'd for $C_{37}H_{26}O_4$: C, 83.1; H, 4.9.
Found: C, 82.8, 82.7; H, 5.4, 5.3.

The dibenzoate (0.5 g.) gave only benzoic acid (0.27 g.) when it was oxidized in aqueous acetone with potassium permanganate (0.63 g.).

Bromination. A solution of the saturated diketone (1 g.) and bromine (0.2 ml.) in acetic acid (24 ml.) was allowed to stand for five hours, during which it gave off hydrogen bromide. The solution was then poured into water and the yellow product was removed with ether. It weighed 0.96 g. and melted at 131–133°. After crystallization from acetic acid and then from ligroin it formed yellow needles that melted at 134–135° alone or mixed with the compound III obtained from the bromination of the unsaturated diketone.

SUMMARY

It is shown that 2,4,5-triphenylcyclopentene-4-dione-1,3 exists entirely in the ketonic state, while 2,4,5-triphenylcyclopentanedione-1,3 is entirely enolic. These results support a conclusion reached previously from studies of related α-diketones that there is a tendency for one double bond to enter a cyclopentane ring, while there is a resistance to the entry of a second.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING AT THE UNIVERSITY OF PENNSYLVANIA, AND THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

THE MICHAEL CONDENSATION.[1] VI. THE INSTABILITY OF SOME ADDITION PRODUCTS[2]

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Received April 4, 1941

In discussions (1) of the influence of structure upon reactivity in the Michael condensation it has been shown that, except in rare cases, the yields of addition products decrease as either the addenda or the acceptors become more highly substituted. In some cases there are unusual differences in reactivity between a substituted active methylene compound and its next higher homolog. For example, benzalacetophenone gave an 80% yield of addition product with ethyl methylmalonate (2) but none with ethyl ethylmalonate (1a). If these differences are a result of spatial

$$\begin{matrix} C_6H_5CH{=}CHCOC_6H_5 \\ + \\ RCH(COOC_2H_5)_2 \end{matrix} \xrightarrow{NaOC_2H_5} \begin{matrix} C_6H_5CHCH_2COC_6H_5 \\ | \\ RC(COOC_2H_5)_2 \end{matrix}$$

I, R = CH_3—, 80%
II, R = C_2H_5—, 0%

interference with addition by the larger substituent, it might be expected that II, once prepared, would be stable. This paper describes experiments which might be expected to give II[4] but which gave other results. These data show that it is sterically possible for ethyl ethylmalonate to add to benzalacetophenone, but that II is unstable in the presence of sodium ethoxide and undergoes retrogression.

The literature contains abundant examples of the alkylation of addition products from the Michael condensation and it was hoped that this might be a useful method for the synthesis of II and related compounds. The

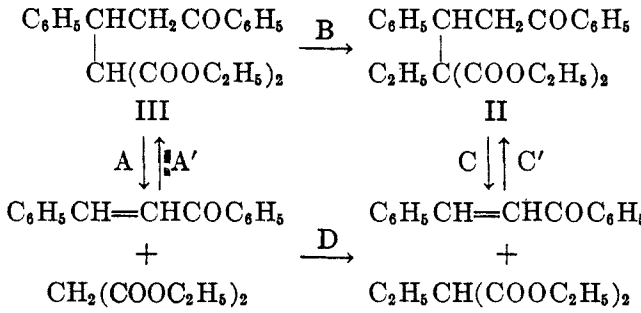
[1] For the fifth paper in this series, see Connor and McClellan (1).

[2] Presented before the Organic Division of the American Chemical Society at the Baltimore meeting, April 3, 1939.

[3] A portion of this communication is constructed from the thesis submitted by Miss Dorothy Dyott in partial fulfilment of the requirements for the degree of Master of Science at Cornell University in June, 1935.

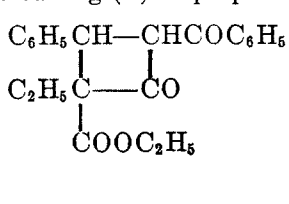
[4] The discussion deals with II as an example; data which are described in the experimental part and which might lead to other compounds not obtained from the Michael condensation, might be interpreted similarly.

general results can be shown by considering the alkylation of ethyl α-carbethoxy-β-phenyl-γ-benzoylbutyrate (III); other examples are described in the experimental part. Methylation of III gave ethyl α-carbethoxy-α-methyl-β-phenyl-γ-benzoylbutyrate (I), as well as some cleavage (25%) to ethyl methylmalonate and benzalacetophenone. Alkylation of III with other alkyl halides gave only cleavage products; ethylation, for example, gave benzalacetophenone and ethyl ethylmalonate.

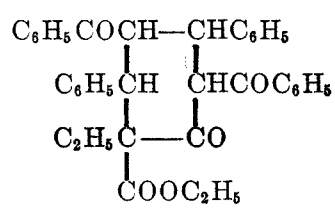


These results indicate that if ethylation of III occurs (step B), the product (II) is unstable in the presence of sodium ethoxide and undergoes retrogression (step C). The results could also be explained by assuming that the initial reaction is the retrogression of III (step A) followed by alkylation (step D) to give ethyl ethylmalonate; if this is the case, the failure of ethyl ethylmalonate to condense with benzalacetophenone might be due to steric hindrance or to the instability of II.

Explanation based on steric hindrance seems improbable in view of the results obtained (1a) by the reaction of the sodium derivative of ethyl ethylmalonate with benzalacetophenone in dry benzene. Under these conditions, which are favorable for bringing about further reaction of the initial addition product, the products are ethyl α-ethylcinnamate and ethyl benzoylacetate. These products *must* result from a Michael condensation, regardless of whether the subsequent reaction is the formation of a four-membered ring (IV) as proposed by Holden and Lapworth (3) or a six-membered ring (V) as proposed by Michael and Ross (2). It is therefore



IV



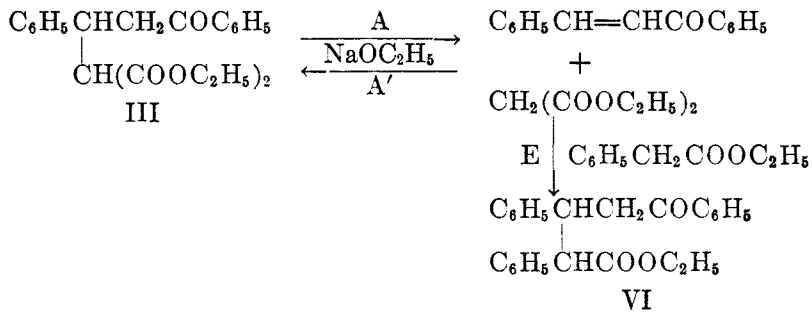
V

sterically possible for ethyl ethylmalonate to add to benzalacetophenone, (step C′); even ethyl benzylmalonate (1a) undergoes some addition. It then follows that some addition products, such as II, undergo retrogression so readily that they may not be isolated.

The difference between the results of methylation and ethylation of III probably depends upon the relative rates of the alkylation reactions (step B) and the retrogression reactions (step C). Methylation occurs rapidly enough to remove the alkoxide before I undergoes complete retrogression, although I is completely cleaved (2) with an equivalent of catalyst. Ethylation, on the other hand, does not occur rapidly enough to permit II to be isolated.

Since it has been shown (4) that retrogression is favored at higher temperatures, an investigation of the reaction at −78° was carried out in the hopes that the temperature coefficients (of steps C and C′) might be different enough to permit the isolation of II. However, no addition products could be isolated from the reaction at −78° of benzalacetophenone with ethyl ethylmalonate, ethyl α-phenylbutyrate, or ethyl phenylmalonate. The retrogression reaction, therefore, occurs readily over a wide temperature range.

It was also found that III undergoes retrogression more readily than might be expected from the high yields obtained in its preparation. Under conditions similar to those used for the alkylation, except that ethyl phenylacetate was added instead of the alkyl halide, over 50% of III was converted to ethyl α,β-diphenyl-γ-benzoylbutyrate (VI).



The total cleavage of III must have been considerably more than 50%, since step E is irreversible (as shown by the failure of VI to react with ethyl malonate under these conditions) and since the reaction of benzalacetophenone with ethyl malonate is more rapid than with ethyl phenylacetate. (The last conclusion is reached because the same results were obtained when ethyl phenylacetate reacted with III as when it reacted with a mixture of benzalacetophenone and ethyl malonate. In both cases,

therefore, it appears that the retrogression of III governs the rate of the reactions.)

These data show that in some cases the addition products that might be expected from the Michael condensation are so readily cleaved by sodium ethoxide that they cannot be isolated and that steric hindrance does not prevent addition. It cannot be decided whether the results obtained by the alkylation of addition products such as III are due to retrogression of III followed by alkylation (path AD), or to alkylation followed by retrogression (path BC), or to both reactions.

Acknowledgment. The authors are grateful to the Faculty Research Committee of the University of Pennsylvania for a grant to aid this investigation and to Dr. V. H. Wallingford of the Mallinckrodt Chemical Works for liberal supplies of ethyl α-phenylbutyrate and ethyl phenylmalonate.

EXPERIMENTAL PART

1. Alkylation Studies

The alkylations were carried out by two general methods. A. To a solution of sodium ethoxide prepared by dissolving 1.3 g. (0.057 gram atom) of sodium in 100 ml. of absolute ethanol was added 0.06 mole of the compound to be alkylated and 0.06 mole of alkyl halide. The mixture was refluxed on the steam-bath for forty-two hours, cooled, diluted with water, and acidified with acetic acid. The product was extracted with ether, dried over magnesium sulfate, and distilled under reduced pressure.

B. The procedure was like that described above except that the reaction period was three weeks at room temperature.

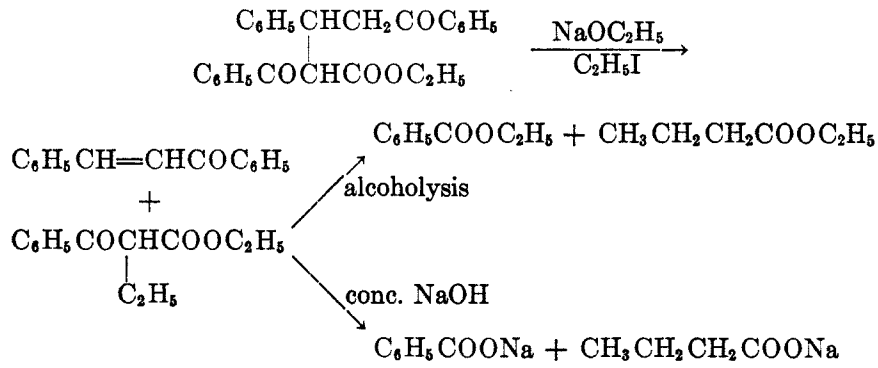
Reaction of ethyl α-carbethoxy-β-phenyl-γ-benzoylbutyrate (III) with methyl iodide. Method A gave 2.4 g. (26%) of ethyl methylmalonate, b.p. 82° (12 mm.) The residue was difficult to purify (an indication of the presence of benzalacetophenone) but finally gave from ether-ligroin crystallization ethyl α-methyl-α-carbethoxy-β-phenyl-γ-benzoylbutyrate, (I) m.p. 90–93° (2). Method B gave practically identical results.

Reaction of ethyl α-carbethoxy-β-phenyl-γ-benzoylbutyrate (III) with ethyl iodide. Method A gave 7.6 g. (75%) of ethyl ethylmalonate, b.p. 115–123° (30 mm.) which was identified by conversion to 5-ethylbarbituric acid. The residue was 11.0 g. Method B gave 7.6 g. (65%) of ethyl ethylmalonate, b.p. 115–123° (30 mm.). The absence of any rearrangement-retrogression products (1) was shown by the negative reaction with ferric chloride. The distillation residue weighed 12.5 g. (theory for benzalacetophenone, 10.8 g.) but the absence of II or of unreacted III was shown by hydrolysis with dilute sulfuric acid. The hydrolysis mixture was made alkaline, the benzalacetophenone removed by ether extraction and the aqueous layer acidified. No insoluble acid was present.

Reaction of ethyl α-carbethoxy-β-phenyl-γ-benzoylbutyrate (III) with benzyl chloride. Method A gave 3.1 g. (44%) of benzyl ethyl ether, b.p. 60° (9 mm.) and 1.1 g. (8%) of ethyl benzylmalonate, b.p. 75° (9 mm.). The residue was refluxed with 20% sodium hydroxide solution, extracted with ether, and acidified. There was obtained

5.2 g. (25%) of benzylmalonic acid, which after recrystallization melted at 116–117° [the reported (5) melting point is 117°].

Reaction of ethyl α,γ-dibenzoyl-β-phenylbutyrate (I) with ethyl iodide. Method A gave 2.4 g. (30%) of ethyl benzoate, b.p. 89–99° (9 mm.), and a residue of 14.8 g. from which benzalacetophenone crystallized after chilling in an ice-salt-bath. The benzalacetophenone, after repeated recrystallizations, melted at 54°. The 9.6 g. remaining was shown to contain ethyl α-ethyl-α-benzoylacetate by refluxing for three hours with 20% sodium hydroxide solution, extraction with ether, and acidification of the aqueous layer. Benzoic acid precipitated and butyric acid was indentified by distillation of the filtrate and conversion to the *p*-bromophenacyl ester m.p. 59–60°. The reaction products presumably are formed as follows:



2. Attempted Condensations at Various Temperatures

A solution of 20.8 g. (0.1 mole) of benzalacetophenone and 0.1 mole of the active methylene compound in 100 ml. of dry ether was added to a solution of sodium ethoxide prepared by dissolving 2.3 g. (0.1 gram atom) of sodium in the minimum amount of absolute alcohol. The mixture was allowed to stand for seventy-two hours in an insulated box containing solid carbon dioxide. At the end of this period an excess of glacial acetic acid was added, the mixture then allowed to come to room temperature, poured into ice-water, separated, and the ethereal layer dried over anhydrous magnesium sulfate. The ether was removed by distillation and unchanged active methylene compound distilled under reduced pressure. With ethyl ethylmalonate, ethyl phenylmalonate, and ethyl α-phenylbutyrate the recovery of starting material was good and there were found no indications of condensation except traces of very high-melting solids which may have been trimolecular compounds (2); the latter were not obtained in quantities large enough for examination. Ethyl α-phenylbutyrate was also used with one-sixth equivalent (0.4 g.) of sodium but the results were similar to those described above.

Attempts to obtain condensation at higher temperatures and the experiments in which the sodio derivatives were used in dry benzene have been reported earlier (1a).

3. Retrogression Studies

Ethyl α-carbethoxy-β-phenyl-γ-benzoylbutrate (2) (III) with ethyl phenylacetate. A sodium ethoxide solution was prepared by dissolving 1.04 g. (0.045 gram atom) of sodium in 100 ml. of absolute alcohol. To this was added 16.6 g. (0.045 mole) of III and 7.38 g. (0.045 mole) of ethyl phenylacetate and the mixture allowed to

stand three weeks at room temperature. At first a homogeneous solution was formed, but within two days a solid appeared. The reaction mixture was poured into cold water containing an excess of acetic acid, filtered, and dried. The weight of crude material was 15.4 g. This was crystallized from alcohol and gave 7.72 g. of ethyl α,β-diphenyl-γ-benzoylbutyrate, m.p. 148–150°. Concentration of the filtrate gave 0.58 g., m.p. 140–146°, and 0.30 g., m.p. 135–145°. Calculated as pure VI, the total of 8.6 g. represents a 51% conversion. A check run gave 8.0 g. (48%). Concentration of the mother liquors gave oils which did not crystallize.

Ethyl α,β-diphenyl-γ-benzoylbutyrate (6) (VI) with ethyl malonate. A sodium ethoxide solution was prepared by dissolving 0.69 g. (0.03 gram atom) of sodium in 100 ml. of absolute alcohol. To this was added 11.1 g. (0.03 mole) of VI and 4.8 g. (0.03 mole) of ethyl malonate and the reaction mixture treated as described in the preceding paragraph. Recrystallization of the product gave 9.40 g., m.p. 152–152.7° and 0.95 g., m.p. 151–152°. The total (10.35 g.) represents a recovery of VI of 93.5%. The additional solid formed by dilution of the mother liquor with water appeared to be entirely VI but was not pure.

Benzalacetophenone with ethyl malonate and ethyl phenylacetate. A sodium ethoxide solution was prepared by dissolving 1.04 g. (0.045 gram atom) of sodium in 100 ml. of absolute alcohol. To this was added 9.36 g. (0.045 mole) of benzalacetophenone, 7.38 g. (0.045 mole) of ethyl phenylacetate, and 7.2 g. (0.045 mole) of ethyl malonate. The reaction mixture was treated as previously described. Recrystallization of the product gave 6.47 g., m.p. 141–144°. Concentration of the filtrate gave 0.52 g. of a sticky material with no definite melting point. Calculated as pure VI, the total of 6.99 g. represents a yield of 41.7%. Further concentration of the mother liquor gave an oil which would not crystallize.

SUMMARY

It has been shown that in some cases the addition products which might be expected from the Michael condensation are so readily cleaved that they cannot be isolated in the presence of sodium ethoxide; failure to isolate the addition products cannot be attributed solely to steric hindrance.

PHILADEPHILA, PENNA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING AT THE UNIVERSITY OF PENNSYLVANIA]

THE MICHAEL CONDENSATION.[1] VII. ACTIVATION OF THE METHYLENE GROUP BY CARBON—CARBON UNSATURATION[2]

ROBERT S. TAYLOR[3] AND RALPH CONNOR

Received April 19, 1941

In discussing (1) the structure of addenda in the Michael condensation, the statement was made that $L_2—CH_2—L_3$ is known to react in cases where the labilizing groups (L_2 and L_3) are —COOR, —COR, —$CONH_2$, —CN, —NO_2, —SO_2R, and —CHO and that *one* of the groups may be an aryl group. It has been reported (2) that fluorene adds to mesityl oxide in the presence of potassium hydroxide, but the reaction has apparently not been extended. This paper describes the results of an investigation to determine if *both* L_2 and L_3 may be aromatic and if they may be olefinic.

Fluorene, cyclopentadiene, and pentadiene-1,4 were the compounds selected for study. Fluorene is known to undergo several reactions which are considered typical of active methylene compounds: condensation with aldehydes (3), the Claisen condensation with esters (4), formation of metallic derivatives by reaction with sodamide (5) or the Grignard reagent (6), and condensation with aromatic nitroso compounds (7). Exchange reactions with ethoxydeuterium (8) and a study of the acid strength (9) of fluorene also suggested that this might be a fairly active substance to study as an example of a compound containing a methylene group attached to two aromatic rings. Cyclopentadiene also condenses with aldehydes (3) and reacts with sodamide (5) and the Grignard reagent (6). It was therefore chosen as a representative compound containing a methylene group attached to two olefinic groups. Cyclopentadiene, however, is a conjugated system, and some of its reactions [*e.g.*, the reaction with diazonium salts (10)] may be attributed to this structure or a resonance hybrid (11) rather than to the activity of the methylene group. For this reason it seemed advisable to test the behavior of pentadiene-1,4. While

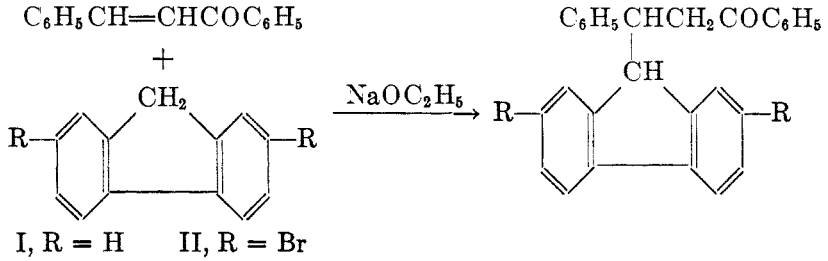
[1] Presented before the Division of Organic Chemistry at the St. Louis meeting of the American Chemical Society, April 8, 1941.

[2] This communication is constructed from a thesis submitted by Robert S. Taylor in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Pennsylvania in June, 1940.

[3] Harrison Fellow in Chemistry, 1939–1940.

Grignard and Lapayre (6) have found that allylacetylenes react with sodamide and the Grignard reagent, it appears that no previous study has been made of the reactions of a methylene group attached to two non-conjugated olefinic bonds.

In the presence of one equivalent of sodium ethoxide, fluorene (I) reacted (2–27%) with benzalacetophenone, benzal-*p*-bromoacetophenone, and benzalacetone. Since no condensation occurred with piperidine or one-sixth of an equivalent of sodium ethoxide (1), fluorene must be considered as a relatively weak addendum. 2,7-Dibromofluorene (II) gave similar results but was somewhat more reactive (11–48% of the adducts).

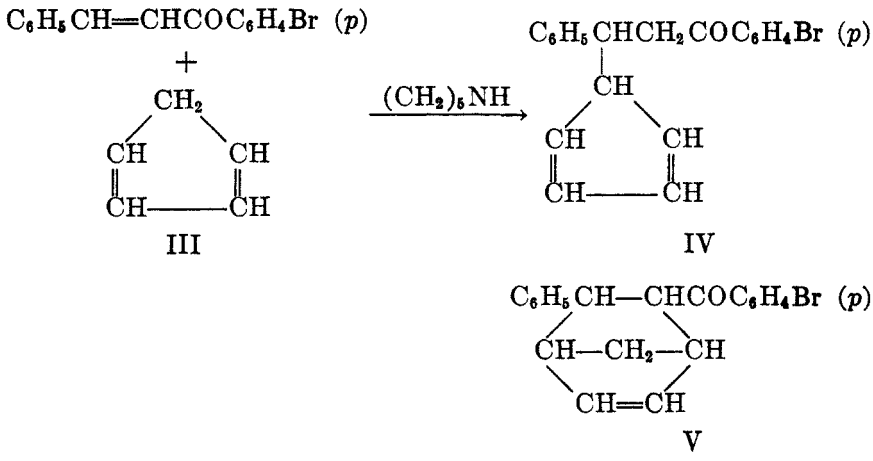


I, R = H II, R = Br

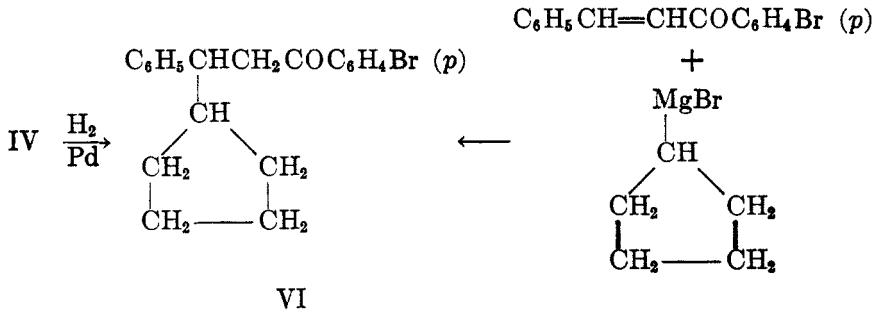
Even in the presence of an equivalent of sodium ethoxide, fluorene and 2,7-dibromofluorene did not react with α, β-unsaturated esters or with *m*- or *p*-nitrobenzalacetophenone. It has previously been noted (1) that nitro groups decreased the activity of acceptors in the Michael condensation.

Cyclopentadiene (III) reacted with α,β-unsaturated ketones when piperidine was used as a catalyst. This fact is worthy of special emphasis, since it appears to place cyclopentadiene in a class of highly active compounds; several substances (*e.g.*, ethyl phenylacetate) which are commonly regarded as typical active methylene compounds do not add (1) to benzalacetophenone under these conditions. While some addition product was obtained by refluxing a benzene solution of cyclopentadiene, unsaturated ketone, and piperidine, better yields (25–30%) were obtained by carrying out the reaction under pressure to prevent the loss of cyclopentadiene. The adduct from benzalacetophenone did not crystallize and was isolated as the oxime; the adduct from benzal-*p*-bromoacetophenone was isolated.

Since cyclopentadiene undergoes the Diels-Alder reaction with vinyl phenyl ketone (12), the product obtained from the reaction of the diene with benzal-*p*-bromoacetophenone might be expected to have the structure IV or V, depending upon whether the Michael condensation or Diels-Alder reaction occurred.

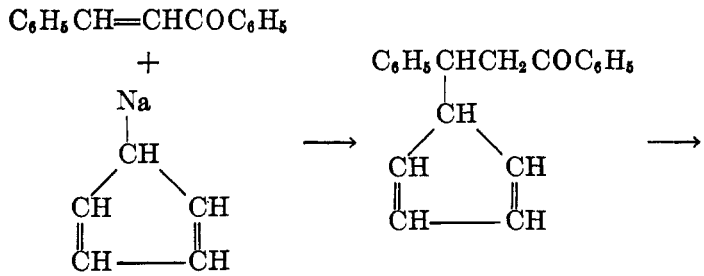


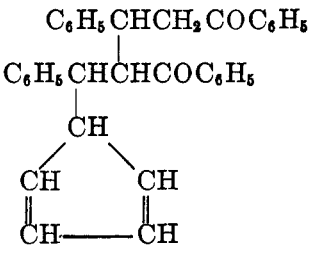
The adduct isolated absorbed two moles of hydrogen and gave a product (VI) identical with that obtained by the reaction of cyclopentylmagnesium bromide with benzal-*p*-bromoacetophenone. This establishes the structure of the adduct as that (IV) obtained from a Michael condensation.



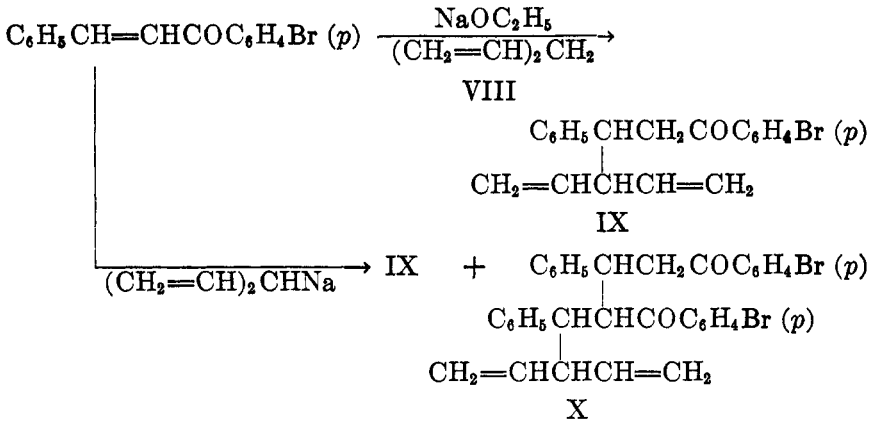
Attempts to carry out the condensation of cyclopentadiene with unsaturated ketones in the presence of sodium ethoxide gave deep red tars, possibly because of fulvene formation. When the sodium derivative of cyclopentadiene, prepared by the use of sodamide in liquid ammonia, was allowed to react with benzalacetophenone, tars were also produced, but it was possible to isolate a "trimolecular" product (VI), from the reaction of two moles of the ketone with one of the diene.

Pentadiene-1,4 (VIII) reacted with benzal-*p*-bromoacetophenone in the presence of an equivalent of sodium ethoxide. The same product (IX) was obtained using the sodium derivative of the hydrocarbon, prepared by the action of sodamide in liquid ammonia; in this case a small amount of "trimolecular" product (X) was also obtained.





VII

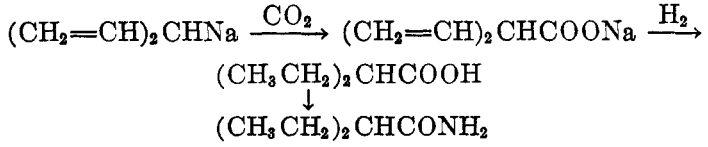


VIII

IX

X

In order to establish that the action of sodamide did not cause a shift in the double bonds of pentadiene-1,4, the sodium derivative of the latter was treated with carbon dioxide, hydrogenated, and the acid converted to the amide. This was identified as diethylacetamide by comparison with an authentic sample.



Acknowledgment. The authors are indebted to Dr. N. K. Chaney of the United Gas Improvement Company for a liberal supply of cyclopentadiene dimer.

EXPERIMENTAL PART

Michael Condensation with Fluorene (I) and 2,7-Dibromofluorene (II)

Table I summarizes the results of the experiments using fluorene and 2,7-dibromofluorene with an equivalent of sodium ethoxide at room temperature in dry benzene [conditions previously (1) designated as D]. The reaction mixture was neutralized

TABLE I

MICHAEL CONDENSATIONS[a] WITH FLUORENE AND 2,7-DIBROMOFLUORENE

ADDENDUM	ACCEPTOR	TIME (HRS.)	YIELD[b] (%)
I[c]	Benzalacetophenone	20	10
I	Benzalacetophenone	168	27
I	Benzalacetophenone	336	17[d]
I	*m*-Nitrobenzalacetophenone[e]	168	0
I	*p*-Nitrobenzalacetophenone[f]	168	0
I	Benzal-*p*-bromoacetophenone	168	15
I	Benzalacetone	168	2[g]
I	Ethyl cinnamate	168	0
I	Ethyl benzalmalonate	168	0
II[h]	Benzalacetophenone	20	22
II	Benzal-*p*-bromoacetophenone	168	48[i]
II	Benzalacetone	168	11
II	Ethyl cinnamate	216	0
II	Ethyl crotonate	168	0
II	Ethyl benzalmalonate	168	0

[a] These reactions were carried out in the presence of an equivalent of sodium ethoxide as described elsewhere in the experimental part.

[b] The yields reported are those of purified products. The crude condensation products weighed one and one-half to three times as much as the quantities indicated in the table. In the experiments for which the yields are listed at 0%, 80% to 95% of unchanged addendum was recovered.

[c] Eastman's technical grade of fluorene was recrystallized from glacial acetic acid and from alcohol.

[d] This reaction was carried out with half as much of the reagents as in the other experiments. The mechanical losses are therefore relatively higher.

[e] Prepared by the method of Sorge (13).

[f] Prepared by the method of Wieland (14).

[g] A "trimolecular" product.

[h] Prepared by the method of Sieglitz (4).

[i] The "trimolecular" product (12% based on II) was also formed.

with dilute acetic acid, washed three times with water, and the benzene layer dried over sodium sulfate. After distillation of the benzene, alcohol was added to the residue and the product crystallized. This crude material was recrystallized from an appropriate solvent.

β-(9-Fluorenyl)-β-phenylpropiophenone, m.p. 127–128° (corr.), was obtained from the reaction of benzalacetophenone and I. It was purified by repeated recrystallization from alcohol.

Anal. Calc'd for $C_{28}H_{22}O$: C, 89.9; H, 5.93; Mol. wt., 374.
Found: C, 89.3, 89.4; H, 6.03, 6.02; Mol. wt., 368, 369.

*β-(9-Fluorenyl)-β-phenyl-*p*-bromopropiophenone*, m.p. 159–160° (corr.), was obtained from the reaction of fluorene with benzal-*p*-bromoacetophenone, and recrystallized from a mixture of benzene and ligroin (1:1).

Anal. Calc'd for $C_{28}H_{21}BrO$: C, 74.2; H, 4.63; Br, 17.6.
Found: C, 73.9, 74.0; H, 4.73, 4.78; Br, 17.4, 17.4.

A "trimolecular product", m.p. 250° with decomposition, was obtained from the reaction of fluorene with benzalacetone, and recrystallized from a mixture of ether and ligroin (1:1). The exact structure was not established, but from previous work (15) it would be expected that in the initial condensation product the methylene adjacent to the carbonyl would be the reactive group in further addition; the product is therefore considered to be *4,6-diphenyl-5-acetyl-6-(9-fluorenyl)hexanone-2*.

Anal. Calc'd for $C_{33}H_{30}O_2$: C, 86.4; H, 6.59; Mol. wt., 458.
Found: C, 86.4, 86.5; H, 6.38, 6.58; Mol. wt., 435, 430.

β-[9-(2,7-Dibromo)fluorenyl]-β-phenylpropiophenone, m.p. 184–185° (corr.), was obtained from the reaction of 2,7-dibromofluorene with benzalacetophenone, and was recrystallized from glacial acetic acid.

Anal. Calc'd for $C_{28}H_{20}Br_2O$: C, 63.1; H, 3.79; Br, 30.1.
Found: C, 62.9, 63.1; H, 4.01, 4.03; Br, 29.7, 29.8.

*β-[9-(2,7-Dibromo)fluorenyl]-β-phenyl-*p*-bromopropiophenone*, m.p. 170–171° (corr.), was obtained from the reaction of II with benzal-*p*-bromoacetophenone, and was recrystallized from a mixture of alcohol and benzene (3:1) and then from benzene-ligroin (1:1).

Anal. Calc'd for $C_{28}H_{19}Br_3O$: C, 55.0; H, 3.11; Br, 39.3.
Found: C, 54.8, 55.1; H, 3.43, 3.48; Br, 38.9, 38.9.

From the same reaction there was obtained a small amount of a trimolecular compound (m.p. 255° with decomposition) which, for the reason noted above, is probably *α-(α-phenyl-β-*p*-bromobenzoylethyl)-β-phenyl-β-[9-(2,7-dibromo)fluorenyl]-*p*-bromopropiophenone*.

Anal. Calc'd for $C_{43}H_{29}Br_4O_2$: C, 57.2; H, 3.3; Br, 35.4.
Found: C, 57.1, 57.3; H, 3.51, 3.52; Br, 35.1, 35.0.

4-Phenyl-4-[9-(2,7-dibromo)fluorenyl]butanone-2, m.p. 159–160° (corr.), was obtained from the reaction of II with benzalacetone and recrystallized from a mixture of alcohol and benzene (3:1).

Anal. Calc'd for $C_{23}H_{18}Br_2O$: C, 58.8; H, 3.62; Br, 34.1.
Found: C, 58.8, 58.9; H, 3.80, 3.81; Br, 33.9, 33.8.

Using one-sixth of an equivalent of sodium ethoxide, I did not react with benzalacetophenone or ethyl cinnamate after twenty hours at room temperature. Refluxing for seventy-two hours with piperidine as a catalyst caused no condensation with I or II and benzalacetophenone. These conditions are described in more detail in an earlier paper (1) and are there referred to as B and A, respectively.

Michael Condensation with Cyclopentadiene (III) using Piperidine as a Catalyst

1. A solution of 6.6 g. (0.1 mole) of III, 20.8 g. (0.1 mole) of benzalacetophenone and 2 ml. of piperidine in 50 ml. of alcohol was refluxed for seventy-two hours. No product could be crystallized from the alcohol. Twelve grams of hydroxylamine

hydrochloride and 20 g. of potassium hydroxide were dissolved in water, added to the alcoholic reaction mixture, and refluxed for one hour. Most of the alcohol was removed by distillation, the residue dissolved in benzene and washed three times with water. The benzene was removed by distillation, and the residue crystallized from alcohol. The first fraction that crystallized (4.0 g., 14%, m.p. 149–156° uncorr.) was recrystallized twice from alcohol. The product was *β-phenyl-β-cyclopentadienylpropiophenone oxime*, m.p. 165.5–166.5° (corr.).

Anal. Calc'd for $C_{20}H_{19}NO$: C, 83.0; H, 6.63; N, 4.84.
Found: C, 83.2, 83.1; H, 6.72, 6.74; N, 4.91, 4.93.

Concentration of the mother liquor gave 1.0 g. of the dioxime of dibenzoylmethane, m.p. 208–209°, formed by the reaction of hydroxylamine with unreacted benzalacetophenone (16). The identity of this was confirmed by analysis and by a mixed melting point with an authentic sample.

The reaction of III with benzal-*p*-bromoacetophenone under conditions similar to those described above gave, from 0.025 mole of the reactants, 0.4 g. (5%) of *β-phenyl-β-cyclopentadienyl*-p-*bromopropiophenone* (IV), m.p. 107–108°. The product was recrystallized from alcohol.

Anal. Calc'd for $C_{20}H_{17}BrO$: C, 68.1; H, 4.83; Br, 22.6.
Found: C, 68.1, 68.2; H, 5.01, 4.96; Br, 22.4, 22.4.

2. A mixture of 20.8 g. (0.1 mole of benzalacetophenone, 6.6 g. (0.1 mole of III and 2 ml. of piperidine were placed in the glass liner of a high pressure bomb and heated at 180° for fifteen hours under a hydrogen pressure of 100 atmospheres. The product did not crystallize, and was isolated by conversion to the oxime as described above. The yield of β-phenyl-β-cyclopentadienylpropiophenone oxime was 9.0 g. (31%). Two grams of dibenzoylmethane dioxime was also isolated.

A solution of 9.9 g. (0.15 mole) of III, 43.1 g. (0.15 mole) of benzal-*p*-bromoacetophenone, and 6 ml. of piperidine in 150 ml. of dry benzene was heated at 80° for fifty hours under a hydrogen pressure of 100 atmospheres. From the reaction mixture was obtained 14.5 g. (27%) of β-phenyl-β-cyclopentadienyl-*p*-bromopropiophenone (IV).

Michael Condensation with Sodium Derivative of Cyclopentadiene

The sodium derivative of cyclopentadiene was prepared by adding 6.6 g. (0.1 mole) of the hydrocarbon to a solution of sodamide prepared by dissolving 2.3 g. (0.1 gram atom) of sodium in 100 ml. of liquid ammonia. The ammonia was allowed to evaporate, 100 ml. of dry ether added, and a solution of 20.8 g. (0.1 mole) of benzalacetophenone in 100 ml. of dry ether added. The reaction mixture stood for 168 hours at room temperature and was then neutralized with dilute acetic acid, washed three times with water, and the ether layer dried over anhydrous magnesium sulfate. The ether was removed by distillation and the black, tarry residue taken up in benzene. From the benzene solution was obtained 0.6 g. of *α-(α-phenyl-β-benzoylethyl)-β-phenyl-β-cyclopentadienylpropiophenone* (VII), m.p. 260° with decomposition.

Anal. Calc'd for $C_{35}H_{30}O_2$: C, 87.1; H, 6.22.
Found: C, 87.0, 87.1; H, 6.34, 6.40.

Several attempts to carry out Michael condensations with III, using one-sixth or one equivalent of sodium ethoxide or potassium hydroxide as catalysts gave deep red tars.

β-Phenyl-β-cyclopentyl-p-*bromopropiophenone (VI)*

1. A solution of 14.4 g. (0.05 mole) of benzal-*p*-bromopropiophenone in 200 ml. of dry ether was slowly added to a solution of cyclopentylmagnesium bromide pre-

pared from 8 g. (0.05 mole) of cyclopentyl bromide. After standing overnight the reaction mixture was poured over cracked ice, neutralized with dilute hydrochloric acid and the ethereal layer washed three times with water. After drying and distilling the ether, the residue was recrystallized from alcohol. The yield of pure *β-phenyl-β-cyclopentyl*-p-*bromopropiophenone* (VI) was 8.5 g. (48%), m.p. 109–110° (corr.).

Anal. Calc'd for $C_{20}H_{21}BrO$: C, 67.2; H, 5.89.
Found: C, 67.0, 67.3; H, 5.94, 5.97.

There was also obtained from this reaction 1 g. of *3-phenyl-1-*(p-*bromophenyl*)-*1,3-dicyclopentylpropanol-1*, m.p. 165–166°.

Anal. Calc'd for $C_{25}H_{31}BrO$: C, 70.3; H, 7.26.
Found: C, 69.9, 70.2; H, 7.34, 7.24.

2. A solution of 7.5 g. (0.021 mole) of IV in 50 ml. of dry ether was shaken in an Adams machine in the presence of 2.0 g. of palladium-palladium oxide catalyst (17) under an initial hydrogen pressure of 2 atmospheres. After two minutes the shaker was stopped and the mixture allowed to come to room temperature. The hydrogen absorption was about 0.05 mole. The catalyst was removed by filtration, the ether evaporated and the residue recrystallized from alcohol. The yield of pure VI was 7.0 g. (93%), m.p. 109–110°. This did not depress the melting point of the material prepared from the Grignard reagent as described above.

Michael Condensation with Pentadiene-1,4 (VII)

1. One-hundredth molar quantities of pentadiene-1,4 (18) and benzal-*p*-bromoacetophenone were treated with an equivalent amount of sodium ethoxide in the usual way (1) and allowed to stand for two weeks in a refrigerator at 0°. The product was recrystallized from alcohol and gave 0.14 g. (4%) of *γ,γ-divinyl-β-phenyl*-p-*bromo*-n-*butyrophenone* (IX), m.p. 107–108° (corr.).

Anal. Calc'd for $C_{20}H_{19}BrO$: C, 67.6; H, 5.35; Br, 22.5.
Found: C, 67.4, 67.4; H, 5.44, 5.47; Br, 22.3, 22.3.

2. The sodium derivative of pentadiene-1,4 was prepared by adding 0.68 g. (0.01 mole) of the hydrocarbon to a solution of sodamide prepared by dissolving 0.23 g. (0.01 gram atom) of sodium in 10 ml. of liquid ammonia. The ammonia was allowed to evaporate and a solution of 2.87 g. (0.01 mole) of benzal-*p*-bromoacetophenone in 100 ml. of dry ether added. The reaction mixture stood for two weeks in a refrigerator at 0° and was then neutralized with dilute hydrochloric acid. The ethereal layer was washed three times with water, dried over anhydrous sodium sulfate, and the ether removed by distillation. The residue, upon crystallization from alcohol, gave 0.39 g. (11%) of IX and 0.15 g. of a "trimolecular" product which, for the reasons mentioned above, is considered to be *α-*(*α-phenyl-β-*p-*bromobenzoylethyl*)-*β-phenyl-γ,γ-divinyl*-n-*butyrophenone* (X), m.p. 225° with decomposition.

Anal. Calc'd for $C_{35}H_{30}Br_2O_2$: C, 65.4; H, 4.71; Br, 24.9.
Found: C, 65.4, 65.4; H, 4.81, 4.74; Br, 24.7, 24.8.

Structure of the sodium derivative of pentadiene-1,4. The sodium derivative of VII was prepared by adding 3.4 g. (0.05 mole) of the hydrocarbon to 0.05 mole of sodamide in liquid ammonia. The ammonia was allowed to evaporate, 100 ml. of ether added, the flask immersed in a carbon dioxide-acetone bath, and 20 g. of pulverized solid carbon dioxide added. The flask was removed from the heating bath, allowed to come to room temperature and transferred to an Adams shaker. Two grams of palladium-palladium oxide catalyst (17) was added and the mixture shaken for seven hours under two atmospheres of hydrogen pressure. The reaction mixture was evaporated to dryness, dissolved in water, acidified with dilute sulfuric acid, and the solution

extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate and, after removal of the drying agent, treated with 15 ml. of thionyl chloride and refluxed for thirty minutes. The resulting mixture was poured into 15 ml. of concentrated ammonium hydroxide, cooled, extracted three times with ether, and the ethereal solution dried. The solid obtained after removal of the ether was recrystallized from a mixture of ligroin and benzene (3:1). The pure product weighed 1.5 g. (13%), m.p. 106–107° (corr.) and was shown to be diethylacetamide by a mixed melting point with an authentic sample.

SUMMARY

The methylene group is reactive in the Michael condensation when it is activated by two carbon-carbon double bonds. These double bonds may be parts of aromatic systems (fluorene and 2,7-dibromofluorene) or conjugated olefinic linkages (cyclopentadiene) or non-aromatic and non-conjugated (pentadiene-1,4).

PHILADELPHIA, PENNA.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE BROMINATION OF ALIPHATIC ACIDS AND THEIR ACYL DERIVATIVES

M. S. KHARASCH AND LINDSEY M. HOBBS[1]

Received April 7, 1941

Many studies of the reaction of bromine with aliphatic acids and with acyl derivatives have been recorded (1). The inconsistencies of data reported, and the conflicting conclusions drawn, however, indicate that a complete qualitative knowledge of factors governing bromination of these substances has not yet been attained. The nature and magnitude of the effects of recognized catalysts are inadequately known, in that some investigations have employed such relatively high[2] "catalyst" concentrations as to suggest that the supposed catalysts might actually be primary reactants, and further in that the effects of light and oxygen (shown by previous studies in this laboratory (2) to be highly significant in other bromination reactions) have been neglected. The present study was designed to supplement existing knowledge of the effects of catalysts, with special attention to oxygen, and of the effect of light, and to test incidentally Watson's hypothesis that certain acid brominations take place through the intermediate acyl bromides. The authors hope that the data recorded may contribute towards a sounder basis for future quantitative studies.

EXPERIMENTAL PART

Apparatus and Procedure

The procedure followed was essentially that of Watson. A solution of bromine in the acid or acyl derivative was made to approximately the desired strength, and 10-ml. portions were introduced by pipette into the reaction tubes. Great care was taken to prevent contact of the materials with atmospheric moisture; the solution was forced into the pipette by means of dry air, the reaction tubes (previously baked) were closed at all times, except during actual introduction of the sample, with calcium chloride tubes; the reaction tubes were attached to the vacuum apparatus with ground-glass joints in order to avoid the condensation of water in the reaction mixture during the making of a glass seal. For the experiments carried out *in vacuo* the reaction mixtures were degassed three times before being sealed off from the vacuum apparatus at 10^{-5} mm. of mercury. For the experiments made in the pres-

[1] du Pont Fellow, 1939. The authors wish to express their appreciation to the du Pont Company for support which made this work possible.

[2] That is, high in comparison with the bromine concentrations.

ence of oxygen the tubes were degassed as indicated above, and filled with dry oxygen at a pressure of 51 cm. of mercury at about 15–20°. The tubes were attached to a shaking device (vibrating vertically at the rate of approximately two hundred vibrations a minute, and mounted 25 cm. from a 400-watt bulb) operating so that the reaction mixtures were partly above and partly below the surface of the water of the thermostat.

The reactions were stopped by cooling of the reaction mixtures in carbon dioxide-acetone mixtures. The extent of bromination was estimated by determination of the amount of unchanged bromine in the reaction mixtures.

Purification of Materials

Bromine. Mallinckrodt's reagent bromine, treated by the method of Scott (3), was dried by two distillations from phosphoric anhydride in an all-glass apparatus, and was stored in a soft-glass bottle fitted with a ground-glass stopper.

Aliphatic acids. Eastman's C. P. propionic and *n*-butyric acids were dried with phosphoric anhydride and fractionally distilled prior to use. Acetic acid (C.P., from the Niacet Chemical Company), was purified as described later. Rüdorff (4) and Visser (5) state that 0.1% of water lowers the melting point of acetic acid by 0.2°. Pure acetic acid is stated by Hess and Haber (6) to melt at 16.625° (corr.).

Acyl derivatives. The acid chlorides and anhydrides, and the acetyl bromide (C.P., Eastman) were fractionated prior to use. From Eastman's *n*-butyryl chloride unsaturated compounds were separated (by use of a Podbielniak column) in a low-boiling fraction, while phosphorus compounds appeared in the middle fraction.[3] Pure butyryl chloride was therefore prepared from butyric acid and benzoyl chloride (7).

Bromination of Acids

Propionic acid. Propionic acid (the excess acid serving as solvent) was treated at 100° with bromine in concentrations ranging from 0.05 to 0.30 molar, both *in vacuo* and in the presence of dry oxygen. Parallel series of experiments were carried out in the dark and under illumination.

The data recorded in Tables I and II support the hypothesis that bromine molecules (*i.e.*, non-activated molecules) act as chain-breakers in a bromine-atom chain reaction, and that at relatively high bromine concentrations this effect becomes pronounced. (A similar phenomenon has been observed by Kharasch, White, and Mayo (2) in the perioxide-catalyzed side-chain bromination of toluene.)

In the course of the study thus briefly outlined it was found that apparently pure samples of propionic acid with different histories of exposure to the atmosphere (by repeated opening of stock bottles for transfer of samples) reacted at appreciably different rates. Since the experimental procedure employed seemed to preclude the presence of other significant impurities, the effect of water was investigated.

Comparison was made between samples of anhydrous acid and acid containing 2% of water. The dark reaction *in vacuo*, naturally comparatively slow, was not materially affected within the limits of experimental error. In the illuminated reaction *in vacuo*, however, the reaction rate of the aqueous acid was significantly lower than that of the anhydrous acid. Oxygen did not act as an accelerator in the presence

[3] It was found that, while the effects of light and oxygen in the bromination of the phosphorus-contaminated and the pure butyryl chloride were similar, the rate of bromination of the former was much lower.

of 2% of water; if anything, it appeared to have a slight additional inhibiting effect (Table III). These observations doubtless account for many of the discrepancies in earlier data.

TABLE I

BROMINATION OF PROPIONIC ACID AT 100°[a]

	0.097_8 *M* Br_2		0.193_8 *M* Br_2		0.293_8 *M* Br_2	
	Dark	Light	Dark	Light	Dark	Light
% Br_2 reacting:						
in vacuo	4.8	59.9 (0.586)[d]	2.5	28.7 (0.556)[d]	3.5	21.5 (0.631)[d]
Oxygen	78.7[b]	71.9[c]	32.3 (0.626)[d]	82.1 (1.59)[d]	9.5	32.8 (0.962)[d]

[a] Time 1 hr., except where otherwise indicated.

[b] Reaction stopped after 0.6 hrs.

[c] Reaction stopped after 0.2 hrs.

[d] The figures in parenthesis indicate the number of millimoles of bromine which had reacted in one hour.

TABLE II

BROMINATION OF ANHYDROUS PROPIONIC ACID AT 100°[a]

	0.0490 *M* Br_2		0.0993 *M* Br_2	
	Dark	Light	Dark	Light
% Br_2 reacting:				
in vacuo	5.5	66.3 (0.325)[d]	3.3	37.2 (0.369)[d]
Oxygen	22.6 (0.111)[d]	100[b]	33.3 (0.331)[d]	100[c]

[a] Propionic acid, of boiling point 138.7° at 756 mm., from stock bottle which had not previously been opened. Time of bromination ten minutes, except where otherwise indicated.

[b] Reaction time was five minutes.

[c] Reaction time was four minutes.

[d] The figures in parenthesis indicate the number of millimoles of bromine which had reacted in 10 minutes.

The inhibitory effect of an efficient antioxidant upon the bromination of propionic acid is striking. When 2 mole per cent of isoamyl nitrite was added to the reaction mixture in the presence of dry oxygen, no perceptible bromination took place, either in the dark or in the light, in the course of 20 minutes at 100° (Table IV).

n-Butyric acid. The effects of light and oxygen upon the bromination of normal butyric acid were found to be qualitatively similar to those observed in the bromination of propionic acid, but somewhat more pronounced (*cf.* Tables II and V).

In order to determine the position taken by bromine in the bromination of propionic and butyric acids under the experimental conditions described, large-scale runs were made, and the products were separated by careful fractional distillation. The α-bromo acids were apparently the sole products.

TABLE III

EFFECT OF WATER ON THE BROMINATION OF PROPIONIC ACID AT 100°[a]

	0.0993 *M* Br_2		0.0993 *M* Br_2	
	Dark	Light	Dark	Light
% Br_2 reacting:	Anhydrous		2% H_2O	
in vacuo	3.3	37.2	4.8	10.9
Oxygen	33.3	100[b]	1.3	10.0

[a] Reaction time 10 minutes, except where otherwise noted.
[b] Reaction complete in four minutes.

TABLE IV

BROMINATION OF PROPIONIC ACID IN PRESENCE OF ISOAMYL NITRITE

	0.150 *M* Br_2; 20 MINUTES AT 100°	
	Dark	Light
% Br_2 reacting:		
in vacuo	4.6	54.7
51 cm. O_2	96.8	96.7
O_2 + 2 mole % isoamyl nitrite	0	0

TABLE V

BROMINATION OF *n*-BUTYRIC ACID AT 100°[a]

	0.0968 *M* Br_2		0.2847 *M* Br_2	
	Dark	Light	Dark	Light
% Br_2 reacting:				
in vacuo	4.7	98.8[b]	7.0	40.4
Oxygen	100[c]	100[d]	18.2	78.0

[a] Reaction time 1 hour, except where otherwise noted.
[b] Reaction mixture became straw-colored within 20 minutes.
[c] Time of complete reaction, 7 minutes.
[d] Time of complete reaction, 3 minutes.

Acetic acid. The acetic acid used in these experiments was prepared by two somewhat different methods. In (a) the acid was purified by distillation and by partial freezing and separation as described by Hess and Haber (6). In (b) the calculated amount of acetic anhydride was added to acid (a) of freezing point 16.3–16.4° and the mixture heated for 25 hours under a reflux condenser. The mixture

was then distilled and the distillate subjected to a separation by partial freezing. The acid thus obtained froze at 16.5°. The possible impurity in (a) is presumably water and does not exceed 0.1–0.2% whereas the impurity in (b) does not exceed 0.07% and may be either water or acetic anhydride or both. In view of the possible presence of small impurities, we are not recording here the exact rate of bromination of either acid. However, our results show conclusively that the bromination of

TABLE VI

BROMINATION OF ACETIC, PROPIONIC, AND *n*-BUTYRIC ANHYDRIDES

	ACETIC ANHYDRIDE 0.0981 *M* Br_2 (0.5 HR.; 25°)		ACETIC ANHYDRIDE[b] 0.1930 *M* Br_2 (0.9 HR.; 35°)	
	Dark	Light	Dark	Light
% Br_2 reacting:				
in vacuo	12.7	11.5	91.7[a]	98.6[a]
Oxygen	11.2	13.7	81.9	80.2
	PROPIONIC ANHYDRIDE 0.0818 *M* Br_2 (35°)		*n*-BUTYRIC ANHYDRIDE 0.0618 *M* Br_2 (35°)	
	Dark (5.2 hrs.)	Light (2.0 hrs.)	Dark (2.0 hrs.)	Light (1 hr.)
in vacuo	13.5	67.4	9.6	90.5[b]
Oxygen	13.7	22.4	9.0	40.7

[a] The initial reactions *in vacuo* appeared to be more rapid in comparison with those in the presence of oxygen than is indicated by the figures given.

[b] Reaction mixture lost most of its color during the first few minutes.

TABLE VII

BROMINATION OF ACETYL, PROPIONYL, AND *n*-BUTYRYL CHLORIDES AT 35°

	ACETYL CHLORIDE 0.096 *M* Br_2		PROPIONYL CHLORIDE 0.0929 *M* Br_2		BUTYRYL CHLORIDE 0.1042 *M* Br_2	
	Dark; 3.0 hrs.	Light; 3.0 hrs.	Dark; 10.1 hrs.	Light; 1.0 hr.	Dark; 10.1 hrs.	Light; 0.55 hr.
% Br_2 reacting:						
in vacuo	65.4	72.1	30.8	81.4	25.9	100.0
Oxygen	66.3	73.8	27.7	24.8	25.6	21.6

either sample is not photochemical, and that in the dark or in the light oxygen exerts a negligible effect. Acetic acid thus occupies a unique position among the aliphatic acids. That this peculiar behavior is caused either by a trace of water in sample (a) or a trace of anhydride in sample (b) does not appear likely.

Bromination of Acyl Halides and Anhydrides

At bromine concentrations of 0.0981 and 0.1930 molar the rate of bromination of acetic anhydride was not appreciably affected either by light or oxygen. At bromine concentrations somewhat less than 0.1 molar the brominations of propionic and *n*-butyric anhydrides *in vacuo* were markedly accelerated by illumination. The dark

reactions were not appreciably affected by oxygen, but the illuminated reactions were materially retarded (Table VI).

The brominations (at bromine concentrations of *ca.* 0.1 molar) of acetyl, propionyl, and *n*-butyryl chlorides *in vacuo* were all accelerated by light, the effect increasing in the order named. The dark reactions were not materially affected by oxygen; the photobromination of acetyl chloride was substantially unaffected by oxygen, but those of propionyl and *n*-butyryl chlorides were appreciably inhibited (Table VII).

The rates of bromination of the corresponding acyl bromides were very little affected by either light or oxygen (Tables VIII and IX).

TABLE VIII

BROMINATION OF ACETYL AND PROPIONYL BROMIDES AT 25°

	ACETYL BROMIDE 0.1940 *M* Br_2		PROPIONYL BROMIDE 0.1140 *M* Br_2	
	Dark; 6.93 hrs.	Light; 6.93 hrs.	Dark; 8.0 hrs.	Light; 8.0 hrs.
% Br_2 reacting:				
in vacuo	69.3	70.1	50.7	53.8
Oxygen	68.1	68.5	47.3	48.5

TABLE IX

BROMINATION OF *n*-BUTYRYL BROMIDE AT 35° (1.5 HOURS)

	0.0476 *M* Br_2		0.1595 *M* Br_2	
	Dark	Light	Dark	Light
% Br_2 reacting:				
in vacuo	60.8	69.1	44.9	46.8
Oxygen	62.7	61.6	45.7	45.7

Discussion of Mechanism

Watson (1) has concluded that brominations of aliphatic acids, acyl halides, and acid anhydrides are similar, and that the acyl bromide is the essential reactant in each case. The production of the intermediate acyl bromide from acids, acyl chlorides, and acid anhydrides is assumed to take place by the reaction of these substances with traces of hydrogen bromide. According to Watson, the bromination of acetic anhydride takes place by two processes: (a) direct bromination of acetyl bromide (formed as suggested above), and (b) by reaction of bromine with the enol form of the anhydride, with subsequent elimination of hydrogen bromide. In the cases of acids in which the alpha hydrogen atoms have little tendency to enolize it is assumed that the acid bromide is brominated, and then reacts with more acid to form the α-bromo acid and regenerate acyl bromide. In

the cases of acyl derivatives in which the alpha hydrogen atoms have a greater tendency to enolize, it is assumed that the process thus described is accompanied by an enol-addition type of substitution.

However, the observations here recorded seem to preclude the possibility that all the reactions studied involve analogous intermediates, and proceed by essentially similar mechanisms.

It is submitted that the data recorded support the hypothesis that the bromination of propionic and butyric acids (and presumably long-chain aliphatic acids) proceeds by a chain reaction involving bromine atoms. It is further assumed that the mechanism in its essential details is similar to that proposed for the bromination of toluene (2), phenanthrene (2a), and cyclohexene (8).

On the basis of the proposed mechanism, then, some possible chain-breakers (and therefore inhibitors of these reactions) are: antioxidants, oxides of nitrogen, esters of nitrous acids, water, inactive bromine molecules, oxygen,[4] or other substances capable of reacting rapidly with bromine atoms.

The bromination of acetic acid, however, has different characteristics. It is known that neopentane reacts with bromine only with difficulty, that trimethylacetic acid is stable toward bromine in the presence of oxygen and light at 100°, and that bromination of isobutane yields almost exclusively *t*-butyl bromide. Since acetic acid has a relatively high dielectric constant, *and since all the experimental work in this laboratory indicates that primary hydrogen atoms (not in close proximity to activating group such as phenyl) are not replaced by bromine by an oxygen-catalyzed or light-accelerated reaction,* the writers believe that acetic acid does not react with bromine by a bromine-atom mechanism.

With regard to the bromination of the acyl derivatives, the situation is even more complicated. Until more data become available it seems inexpedient to advance explanations to account for the bromination of acetic acid, acid chlorides, acid bromides, and acid anhydrides. Such work is now under way in this laboratory.

SUMMARY

1*a*. The bromination of propionic and *n*-butyric acids is accelerated by light, catalyzed by oxygen, and inhibited by water.

[4] This inhibition may take place either by a primary action in which small quantities accelerate while large quantities retard the rate of bromination due to combination with bromine atoms, or by a secondary action in which oxidation products of the hydrocarbon skeleton produce an inhibition. We believe the latter effect to be the more important, and work designed to test this hypothesis is under way in this laboratory.

b. The rate of bromination of acetic acid is little affected by light or by the presence of oxygen.

2*a.* Light accelerates the bromination of propionyl and butyryl chlorides, as well as of the corresponding anhydrides. Oxygen inhibits both the dark and the illuminated reactions.

b. The effects of light and oxygen on the bromination of acetyl chloride and acetic anhydride, in comparison to those on the reactions of the higher homologs, are much smaller. The dark reactions are faster than those of the higher homologs.

3. Light and oxygen have comparatively little effect on the rate of bromination of acetyl, propionyl, and *n*-butyryl bromides.

4. On the basis of the observations here recorded, Watson's conclusion that the reactions studied have essentially a common mechanism is questioned.

CHICAGO, ILL.

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(2) See, *e.g.*, KHARASCH, WHITE, AND MAYO, (a) *J. Org. Chem.*, **2**, 574 (1938); (b) *J. Org. Chem.*, **2**, 33 (1938).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

THE RELATION BETWEEN THE ABSORPTION SPECTRA AND THE CHEMICAL CONSTITUTION OF DYES. XIX. MONO- AND POLY- AZO DYES WITH A SINGLE AUXOCHROME

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A study has been made by Funkhouser and Brode (1) showing the influence upon the absorption spectrum of the position of the azo groups of disazo dyes about a benzene ring. Further investigation by Brode and Piper (2) showed the effect upon the absorption spectra of the separation of the benzene rings bearing the azo groups. The dyes upon which these studies were made contained two or more auxochromes and it appeared worth while to continue this series of researches by studying disazo dyes containing a single auxochrome. Kuhn and Bär (3) have indicated that the structure of oxyazo compounds involves an equilibrium between the hydrazone and azoid forms of the dyes.

A study of the absorption spectra of *m*-disazo dyes containing a single auxochrome in various solvents has been made in order to clarify this situation since under these conditions only one of the azo groups can possibly exist in the hydrazone form and one must be present in the azoid state. The results confirm the deductions of Kuhn and Bär.

EXPERIMENTAL

Preparation of the dyes. 2,4,6-Trisphenylazophenol and 2,4-bisphenylazophenol were prepared by the method described by Heller (4) and by Vignon (5), and purified by washing with boiling alcohol and recrystallizing from nitrobenzene. The trisazo dye was obtained as fine needles with the sharp melting point 223° (corr.).

2,4-Bisphenylazophenol was purified by recrystallization from alcohol and acetic acid to the constant melting point 132°. The compound showed no change in its absorption spectrum after two recrystallizations.

2,6-Bisphenylazo-*p*-cresol was prepared by coupling in alkaline solution one mole of benzenediazonium chloride with one-half mole of *p*-cresol. It was purified by washing with cold 95% alcohol and recrystallizing from trichloroethylene to the constant melting point 183° (corr.).

The monoazo dyes, 2-phenylazophenol, 4-phenylazophenol, and 2-phenylazo-*p*-cresol were obtained from previous preparations in this laboratory (2).

3,5-Bisphenylazophenol was prepared by the method of Baeyer and Kochendoerfer (6), and purified by recrystallization from trichloroethylene, from which it separated in beautiful bright red needles with the constant, sharp melting point 181.5° (corr.).

3-Phenylazophenol was prepared by the method described by Jacobson and Hön-

igsberger (7) from *o*-anisidine, and purified by precipitation from alkaline solution with a stream of carbon dioxide, followed by recrystallization from water and ligroin. It was obtained as fine yellow needles with the constant melting point 116.5–117°.

2,4-Bisphenylazo-1-naphthol was prepared by the method of Bamberger and Meimberg (8). The compound was purified by recrystallization from aniline, *n*-amyl alcohol, and trichloroethylene and was obtained as a mat of fine greenish-black needles with the constant melting point 197° (corr.) as described by Bamberger.

4-Phenylazo-1-naphthol was prepared by the method of Witt and Dedichen (9), and purified by recrystallization from benzene, xylene, and acetic acid and melted sharply at 205° (corr.).

2-Phenylazo-1-naphthol was prepared from β-naphthoquinone and phenylhydrazine as described by Zincke (10), and purified by extraction and crystallization from alcohol, followed by recrystallization from glacial acetic acid to the constant melting point 138° (corr.).

Determination of absorption spectra. The solutions whose absorption spectra were measured were prepared in the manner described by Brode (11). Solutions of monoazo dyes contained about 0.0001 mole per liter while those of disazo dyes contained about 0.00004 mole per liter. Considerable variation of intensity of absorption was encountered and in order for the curve to fall completely on the plate, variations of the concentration of the solutions measured and of the cell thickness used were necessary.

Measurements in the visible portion of the spectrum were made with a Bausch and Lomb Universal Spectrophotometer while those in the ultraviolet were obtained by the use of a Bausch and Lomb medium quartz spectrograph and a modified Hilger sector photometer.

3,5-Bisphenylazophenol decomposed so rapidly in concentrated hydrochloric acid that it was necessary to take a series of readings in the visible region at intervals of 3, 5, 10, 15, etc. minutes after the solution was prepared and plot the readings so obtained against time. Extrapolation of these curves to zero time gave the approximate values that should be obtained for the undecomposed dye.

The absorption spectra of 4-phenylazophenol are taken from Brode (12).

DISCUSSION OF DATA

Phenolic derivatives in 3% sodium hydroxide. (*See Table I*)

Since a quinonoid arrangement of 3-phenylazophenol is impossible on the basis of the structural theory this dye must exist in the azoid form. 3,5-Bisphenylazophenol would be expected, therefore, to show the same absorption bands exhibited by the monoazo compound but the molecular extinction coefficients would be twice as great. In alkaline solution where the phenolic group exists as its sodium salt this relationship should be especially apparent, and such is found to be the case. The extinction values of the bands of 3-phenylazophenol are almost exactly doubled in 3,5-bisphenylazophenol.

In the *p*-cresol derivatives the effect of introducing a second phenylazo group ortho to the hydroxyl group has a hypsochromic effect upon the principal band and a bathochromic effect upon the lesser band. The values of the molecular extinction coefficients in both bands are nearly doubled in

this solvent (dilute sodium hydroxide) with the introduction of the second phenylazo group.

The value of the molecular extinction coefficient of the principal band of 2,4-bisphenylazophenol is a little less than the sum of the coefficients of the 700 f. band of the *para* derivative and the 660 f. band of the *ortho* compound. The lesser band of this disazo dye appears in the position of the high frequency band of 2-phenylazophenol and is nearly doubled in intensity.

The introduction of the third phenylazo group has nearly the same effect upon the values of the molecular extinction coefficients that was observed in the second. Thus the 650 f. band of 2,4,6-trisphenylazophenol differs from the 715 f. band of the 2,4-disazo compound in intensity by the same amount that it, in turn, differs from 4-phenylazophenol. Similarly the band at 960 f. of 2,4,6-trisphenylazophenol may be considered to be formed by the summation of the 950 f. band of the 2,4-disazo dye and the 925 f. band of 2-phenylazophenol. It is to be noted that the presence of the second phenylazo group in the ortho position to the hydroxyl of the phenol again shows a hypsochromic effect upon the high frequency band.

These data indicate that in general the absorption bands of the phenylazo derivatives of the phenols in dilute aqueous alkali are additive in character, as would be expected if they existed in the simple azoid form.

Phenolic derivatives in 95% alcohol. (*See Table I*)

The *meta*-phenylazo derivatives of phenol show a single simple absorption band in this solvent, that of the disazo dye being nearly three times as intense as the monoazo band. It should be noted that the band of 3-phenylazophenol lies in the same approximate position and has roughly the same intensity as was reported by Brode (13) for azobenzene in alcohol.

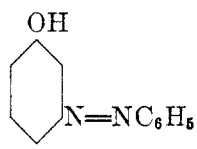
In the manner used for the demonstration of the additive character of the bands of the monoazo compounds in sodium hydroxide (11) it can be shown that the bands of the polyazo dyes, 2,4-bisphenylazophenol, 2,4,6-trisphenylazophenol, and 2,6-bisphenylazo-*p*-cresol in alcohol are also derived from those of the corresponding monoazo compounds. An exception is the slight band in the visible shown by 2,4,6-trisphenylazophenol.

In general *ortho* substituted phenylazophenols have their absorption bands at higher frequencies than *para* substituted compounds; *ortho*-phenylazo groups having a hypsochromic effect and *para*-phenylazo groups a bathochromic effect (*i.e.*, shifting the absorption toward lower frequencies). Apparently in the polyphenylazophenols this hypsochromic effect of *o*-phenylazo groups is counter to the effect noted by Nietzki (14) *i.e.*, increasing the molecular weight of a compound shifts its absorption band towards the red end of the spectrum. The bands of 2,4,6-trisphenyl-

TABLE I

POSITIONS AND INTENSITIES OF THE ABSORPTION BANDS OF THE PHENYLAZO DERIVATIVES OF PHENOL

COMPOUND	FORMULA	SODIUM HYDROXIDE		95% ETHYL ALCOHOL		CONC'D HCl	
		Molecular Extinction Coefficient ($\times 10^{-4}$)	Position (fresnel)	Molecular Extinction Coefficient ($\times 10^{-4}$)	Position (fresnel)	Molecular Extinction Coefficient ($\times 10^{-4}$)	Position (fresnel)
3-Phenylazophenol	I	0.3 1.7	690 925	1.4	950	1.8	740
3,5-Bisphenylazo-phenol	II	0.6 3.3	670 905	4.3	935	2.5	650
2-Phenylazo-p-cresol	III	0.9 1.4	620 910	.8 2.0	750 930	1.2 2.1	620 750
2,6-Bisphenylazo-p-cresol	IV	1.6 2.5	555 940	1.1 3.4	715 900	2.7 4.9	470 770
4-Phenylazophenol	V	2.3	700	.2 2.6	635 855	4.0	645
2-Phenylazophenol	VI	0.9 1.2	660 925	1.0 1.6	800 930	1.4 1.6	645 750
2,4-Bisphenylazo-phenol	VII	2.7 2.1	715 950	.5 3.6	695 895	3.5	630
2,4,6-Trisphenylazo-phenol	VIII	3.1 3.2	650 960	1.3 2.7 5.0	540 680 900	5.0 4.0	565 770



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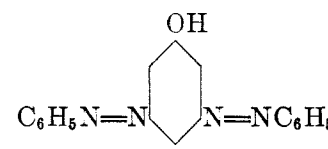

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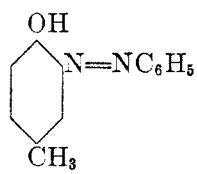

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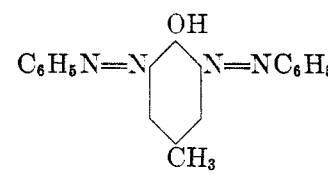

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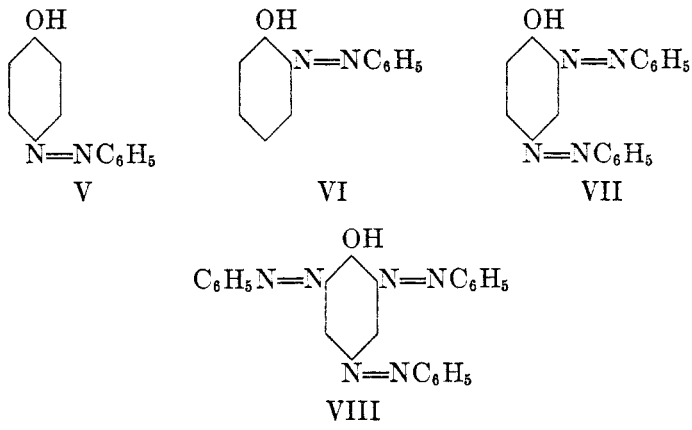

azophenol have nearly the same frequencies as those of 2,4-bisphenylazophenol. Nietzki's rule applies to the *m*-phenylazophenols, for which it holds in all solvents.

A regularity is apparent in the differences between the values of the molecular extinction coefficients at the maxima of the higher frequency absorption bands of the 2,4,6-trisphenylazophenol and the 2,4-bisphenylazophenol dyes and the values of these coefficients in monoazo compounds. The approximate constancy of this difference would indicate that this is the contribution of a single azo group to the molecular extinction coefficient unless the molecule is disturbed in some fashion.

Phenolic derivatives in concentrated hydrochloric acid. (*See Table I*)

Although in general the absorption curves of the polyphenylazophenols in concentrated hydrochloric acid may be shown to be derived from the corresponding monoazo compounds, there is less regularity, and the agreement with predicted values of the extinction coefficients is poorer than in either of the solvents previously discussed.

3,5-Bisphenylazophenol fades so rapidly in this solvent that it was impossible to measure its absorption in the ultraviolet region of the spectrum. From analogy with the alcoholic solutions it was considered probable that it possessed a single simple absorption band with a maximum at the point observed (650 f.) at the blue end of the visible region.

Again *ortho* substitution by a phenylazo group shifts the high frequency absorption band towards higher frequencies. The anomalous disappearance of the high frequency band in 2,4-bisphenylazophenol does not permit a statement as to the effect of *para* substitution upon the position of this band.

Derivatives of α-naphthol in 3% sodium hydroxide. (*See Table II*)

The double component structure of the principal band of the 2,4-bisphenylazophenol dye with maxima at 550 and 635 f. as compared with the single character of the monoazo dyes would indicate that the two chromophores remain as separate resonators, although sufficient data are not available for the assignment of the resonator structure for each of the two components.

TABLE II

POSITIONS AND INTENSITIES OF THE ABSORPTION BANDS OF THE PHENYLAZO DERIVATIVES OF α-NAPHTHOL

COMPOUND	SODIUM HYDROXIDE		95% ETHYL ALCOHOL		ACETIC ACID		CONCENTRATED HCl	
	Molecular Extinction Coefficient ($\times 10^{-4}$)	Position (fresnel)	Molecular Extinction Coefficient ($\times 10^{-4}$)	Position (fresnel)	Molecular Extinction Coefficient ($\times 10^{-4}$)	Position (fresnel)	Molecular Extinction Coefficient ($\times 10^{-4}$)	Position (fresnel)
2-Phenylazo-1-naphthol	2.2	600	1.6	600	1.7	600	2.3	555
	1.6	935	.9	845	1.1	825	1.6	695
			1.0	1029	1.5	1015	.6	985
4-Phenylazo-1-naphthol	2.1	600	1.6	745	1.9	625	1.6	545
	1.1	1035	1.4	1105	1.0	1130	.5	875
							.8	1010
2,4-Bisphenylazo-1-naphthol	2.5	550	1.7	570	1.7	570	3.8	455
	2.1	635	2.0	830	1.8	820	1.3	620
	1.9	955					1.1	850
							1.2	1110

Derivatives of α-naphthol in 95% alcohol. (*See Table II*)

The two bands of 4-phenylazo-1-naphthol in 95% alcohol (Fig. 1B) are compound bands each composed of two bands of unequal intensity. Kuhn and Bär (3) ascribe the lesser maximum of the lower frequency band to that portion of the compound in the quinoid form while the major portions of the curve with a maximum at 745 f. is due to the larger portion of the dye existing in the azoid state. The bands of 2-phenylazo-1-naphthol and of 2,4-bisphenylazo-1-naphthol appear to be simple bands.

In comparing the molecular extinction coefficients of these three compounds at the maxima of their respective absorption bands it is at once noted that the coefficient of the low frequency maximum of the disazo dye is not appreciably larger than that of either of the monoazo compounds. This would indicate that the low frequency band of these compounds is caused by an arrangement of the azo group such that only one azo group in

the molecule can exist in that state. The quinonoid formula for these azo compounds is an acceptable explanation for this fact. Furthermore the addition of the second phenylazo group has an effect upon the high frequency band of 2-phenylazo-1-naphthol nearly the same as in the phenols, where it was shown that the azo groups are additive in their intensities and

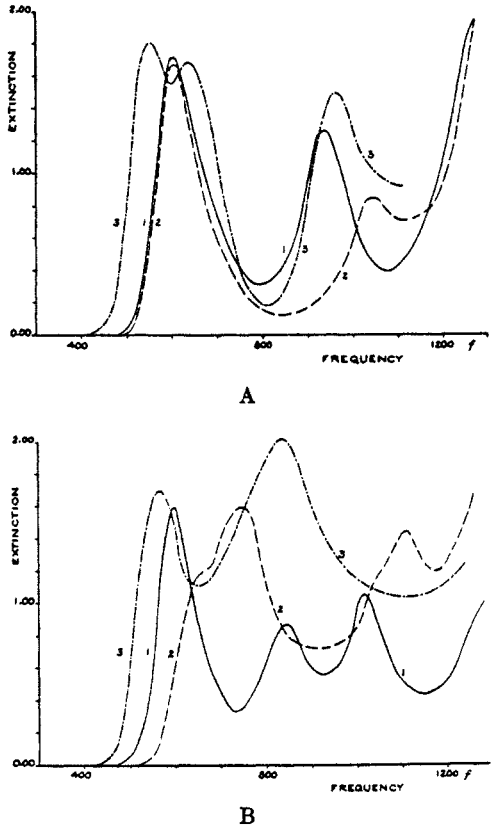

FIG. 1. The absorption spectra of (1) 2-phenylazo-1-naphthol, (2) 4-phenylazo-1-naphthol and (3) 2,4-bisphenylazo-1-naphthol in 3% aqueous NaOH (A) conc'n 0.00008 Mol. per l., cell 1.0 cm.; and in 95% ethyl alcohol (B) conc'n 0.0001 Mol. per l., cell 1.0 cm.

must exist in the azoid form. This would indicate that the entrance of the phenylazo group into the molecule does not appreciably affect the equilibrium between azoid and quinonoid forms of 2-phenylazo-1-naphthol but merely enters as an azo group which should have the absorption described.

If the disazo dye is considered as a derivative of 4-phenylazo-α-naphthol, it is seen that the principal low frequency band has shifted from 745 f. in

the monoazo dye to 570 f. with the addition of the second phenylazo group, a shift somewhat larger than would normally be expected for this change in molecular weight. If, however, the lesser simple band of this compound band is considered, the shift from roughly 640 to 600 f. is only forty units. It may be, therefore, that the quinonoid structure in the disazo dye is of the *para* type although this evidence is not conclusive.

The bands with maxima above 1000 f. in the monoazo compounds do not appear in the disazo dye.

In order to check the results given for alcoholic solutions, the absorption spectra of these compounds were measured in glacial acetic acid, in which, according to Kuhn and Bär (3), virtually all of the 4-phenylazo-1-naphthol is in the quinonoid form.

Derivatives of α-naphthol in glacial acetic acid. (*See Table II*)

The data confirm those obtained in alcohol. 2,4-Bisphenylazo-1-naphthol has a molecular extinction coefficient at its low frequency maximum no greater than that shown by the corresponding bands of either the *ortho-* or *para*-monoazo compounds, which again indicates one azo group of a different character from the other. Again the 825 f. band of the 2-phenylazo-1-naphthol is less in intensity than the 820 f. band of the disazo compound by an amount somewhat less than the difference due to a single phenylazo group in the phenol series, indicating that one of the azo groups exists in the simple azo form.

In acetic acid the absorption bands of the monoazo α-naphthols with maxima at frequencies greater than 1000 f. do not appear in the disazo dye.

Derivatives of α-naphthol in concentrated hydrochloric acid. (*See Table II*)

In this solvent the principal bands of the monoazo dyes are found added in the disazo compound, while the lesser bands of the monoazo derivatives are also found to be present in 2,4-bisphenylazo-α-naphthol. This does not permit postulation of a quinonoid structure for this dye but indicates that the azo groups are present here in the same form as they were when situated in corresponding positions in monoazo α-naphthols.

In the naphthols the addition of a second phenylazo group moves the absorption bands towards the red, except in dilute alkali, where two separate bands appear.

CONCLUSIONS

1. The absorption curves in general of polyazo dyes containing a single common auxochrome are found to be composed of the curves of the corresponding monoazo compounds in the same solvent with the exception of 2,4-bisphenylazo-1-naphthol in 95% alcohol and in glacial acetic acid. In

general the intensity of absorption of the phenylazo compounds is found to be a little less than the sum of the intensities of the monoazo dyes of which it may be considered composed.

2. Absorption bands of disazo dyes containing a single common auxochrome are broader than those of the corresponding monoazo compounds (2).

3. The similarity of the absorption bands of 2- and 4-phenylazo-1-naphthol dyes in alkali solution and the double additive band of 2,4-bisphenylazo-1-naphthol in the same solvent would indicate nearly identical resonators with similar auxochromes such as the sodium salt of a hydroxyl group.

4. The lack of similarity of the absorption bands of the 2- and 4-phenylazo-1-naphthol dyes in acetic acid and 95% alcohol and their non-additive character to produce the absorption bands of the 2,4-bisphenylazo-1-naphthol in the same solvents would indicate a different type of chromophore in the 2- and 4-phenylazo-1-naphthol dyes. Such a difference would be predicted on the known hydrogen bonding or chelated resonance ring which is possible in the 2-phenylazo-1-naphthol but not in the 4-phenylazo-1-naphthol.

5. The data provide additional evidence in favor of the theory that the equilibrium between the azoid and quinonoid forms of 2- and 4-phenylazo-1-naphthols is dependent upon the solvent in which they are placed. There is no indication that the phenylazo derivatives of the phenol series exist in a quinonoid form in appreciable quantities in any of these solvents.

COLUMBUS, OHIO.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

PREPARATION OF α,β-UNSATURATED KETONES AND THEIR REACTION WITH PHENYLHYDRAZINE

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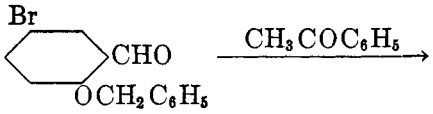
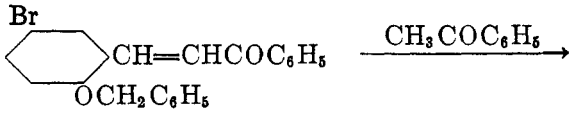
In previous work (1) it was noted that when certain aldehydes and their substitution products were condensed with acetophenone in the presence of sodium hydroxide, as indicated by Schmidt (2) and extended by Claisen and collaborators (3), both mono- and di-acetophenone derivatives were obtained. When the starting ketone contained a substituent, no diacetophenone derivative could be isolated. It was of interest to extend this work to learn if the above observations represent a general kind of behavior, and to gain insight into the possible mechanism of the change. Accordingly, a number of new ketones were prepared by condensation of salicylaldehyde derivatives with acetophenone and some of its substitution products. As before, diacetophenone derivatives were obtained only when the starting ketone was unsubstituted.

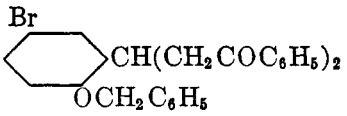
The production of the diacetophenone derivative seems to involve the formation of the α,β-unsaturated styryl ketone as a first step. This was indicated by the following facts. When a warm alcoholic solution of equimolecular proportions of 2-benzyloxy-5-bromobenzaldehyde and acetophenone was treated with 50% solution of sodium hydroxide, as indicated under the general method of condensation described below, and the product that separated was removed within three days, there was obtained an almost quantitative yield of yellow solid which, after crystallization, gave pale yellow needles that melted at 162–163°. Analysis for halogen was in good agreement with that required by 2-benzyloxy-5-bromostyryl phenyl ketone. When the experiment was repeated and the reaction mixture was allowed to remain three weeks or longer, the solid that separated first changed on standing to a nearly colorless mass that resembled sand. Purification of this material gave colorless rhombohedra that melted at 99.5–100°. Analysis of this product for halogen indicated 2-benzyloxy-5-bromobenzaldiacetophenone. In a third experiment a portion of the purified monoacetophenone derivative, m.p. 162–163°, and acetophenone were dissolved in alcohol, 50% solution of sodium hydroxide was added, and the mixture was allowed to stand. The product that

[1] Deceased April 24, 1940.

separated was crystallized from alcohol and was found to have the properties of the diacetophenone derivative. A mixture of the two melted without depression. Apparently, acetophenone can add to the ethylenic linkage of the styryl group.



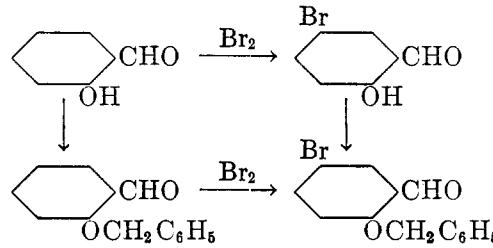




A second purpose of this study was to use the monoacetophenones obtained to test further the action of phenylhydrazine on α,β-unsaturated ketones, since in previous work (4) it was found possible in but few instances to isolate the phenylhydrazones assumed by Auwers and co-workers (5) to be the first products in this reaction. In many cases these hydrazones rearrange immediately to the isomeric pyrazolines. It was hoped that, in accordance with the suggestion of Straus (6), increase in the number of substituents in the reactants would tend to stabilize the hydrazones.

In the preparation of 2-benzyloxybenzaldehyde and its bromine substitution products, used as starting materials in many of the condensations studied here, it was found that the purity of the aldehyde and the conditions of bromination are important factors. Attempts to obtain 5-bromosalicylaldehyde by Piria's (7) method, in which bromine was added to the aldehyde in the absence of a solvent, proved to be unsatisfactory (see experimental part). It was also of interest to note the effect of a solvent. When acetic acid was used, a mixture of 5-bromo- and 3,5-dibromoaldehyde was produced, as noted by Bradley (8) when disalicylaldehyde was treated in the same way. 2-Benzyloxy-5-bromobenzaldehyde was previously obtained by Perkin (9), who reported that it was non-crystalline. He gave no further physical constants and recorded no analysis. The benzyloxybenzaldehyde used by him as starting material had been purified by distillation under ordinary pressure, and repetition of his work was found to give, as he had reported, a brownish oil that did not solidify. Distillation under a pressure of 4 mm. gave a more satisfactory product. Bromination of this in chloroform solution brought about two changes.

Halogen entered position 5 (CHO = 1) and the hydrogen bromide formed split the ether to give 5-bromosalicylaldehyde and benzyl bromide.[2] When the reaction was carried through in acetic acid solution and in the presence of anhydrous sodium acetate, splitting was avoided, and 2-benzyloxy-5-bromobenzaldehyde was obtained. The position taken by halogen was established by preparation of the same compound by benzylation of 5-bromosalicylaldehyde.



In the preparation of the α,β-unsaturated ketones, a modification of Claisen's (3) method was employed. In most cases it was found that they could be obtained by adding a saturated aqueous solution of sodium hydroxide to a warm alcoholic solution of a mixture of the required aldehyde and ketone, and allowing the mixture to stand for a day or two, as indicated by Bablich and Kostanecki (10). A longer period of standing gave, when unsubstituted acetophenone was used, a diacetophenone derivative and some tar. Formation of the latter was favored by elevated temperatures. In all cases the reaction mixture was finally diluted with several volumes of water, and acidified with hydrochloric acid to set free the new ketone. In a number of cases when low yields were obtained by this procedure the method of Glaser and Tramer (11) was tried. It did not give better results.

In the preparation of these compounds it was also of interest to try to obtain them by two routes. It might be supposed, for example, that 2-hydroxy-3,5-dibromostyryl styryl ketone could be obtained with equal ease by condensing 2-hydroxy-3,5-dibromostyryl methyl ketone with benzaldehyde or by condensing benzalacetone with the required substituted salicylaldehyde. As a matter of experiment it was shown that the first method only was satisfactory. The second, in this and other cases, gave much resinous material and low yields of the desired products.

Several of the ketones described in this report were subjected to the action of phenylhydrazine with the hope of obtaining the related phenyl-

[2] This behavior has been observed by Raiford and Howland [*J. Am. Chem. Soc.*, **53**, 1057 (1931)] in many similar cases.

hydrazones. Previous work had shown that the most suitable solvent in which to conduct this reaction is glacial acetic acid. Since the solubility of these ketones in the acid at room temperature is low, and because the hydrazones are usually rearranged by hot acid, attempts were made to bring about the condensation in some other solvent. Thus, when 3,5-dibromo-4-hydroxystyryl 4-bromophenyl ketone, dissolved in about 15 times its weight of pyridine, was mixed with slightly more than the calculated amount of phenylhydrazine along with one molecular proportion of acetic acid, and the mixture was allowed to stand at room temperature, the product isolated was identical with that obtained when the ketone and hydrazine were brought together in boiling acetic acid. The hydrazone formed in the first instance must have rearranged rapidly. In another

TABLE I

BENZALDIACETOPHENONE DERIVATIVES

SUBSTITUENTS IN BENZAL RESIDUE	YIELD %[a]	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	HALOGEN	
						Calc'd	Found
2-Benzyloxy-5-bromo-	56	Toluene-ligroin	Colorless rhombohedra	99.5–100	$C_{30}H_{25}BrO_3$	15.59	15.65
2-Benzyloxy-3,5-dibromo-	79	Acetone	Colorless prisms	147–148	$C_{30}H_{24}Br_2O_3$	27.02	26.60
2-Hydroxy-3,5-dibromo-	80	Alcohol	Colorless needles	120–121	$C_{23}H_{18}Br_2O_3$	31.87	31.77
3,5-Dibromo-4-hydroxy-	28	Alcohol	Colorless needles	154–155	$C_{23}H_{18}Br_2O_3$	31.87	31.74

[a] These values represent purified material.

case, however, conducting the condensation in boiling acetic acid for one hour failed to convert the whole of the material into pyrazoline. In this reaction a mixture of 2-hydroxy-3,5-dibromostyryl *p*-anisyl ketone with twelve times its weight of acetic acid and the requisite amount of phenylhydrazine was boiled for one hour. When the mixture was cooled and allowed to stand, it deposited pale brown crystals which melted at 167–170°, and which responded to a color test (17) for hydrazones of this group. From the mother liquor left after the separation of these crystals there was isolated a product which, after further purification, was obtained in colorless needles that melted at 193–194°, which was the pyrazoline. These products gave the same analytical data. When a purified sample of the lower-melting one was boiled for a much longer period with acetic acid it was converted into the higher-melting compound.

TABLE II

Phenyl Styryl Ketones

Substituent in phenyl	Substituent in styryl	Yield %	Solvent	Crystal form	M.P., °C.	Formula	Analyses halogen	
							Calc'd	Found
4-Methyl-	2-Hydroxy-5-bromo-	48	Toluene	Brownish needles	188 (decomp.)	$C_{16}H_{13}BrO_2$	25.23	25.15
4-Methoxy-		60	Toluene	Brownish needles	174 (decomp.)	$C_{16}H_{13}BrO_3$	24.03	23.83
4-Chloro-		21	Toluene	Yellow needles	184 (decomp.)	$C_{15}H_{10}BrClO_2$	34.22	34.35
4-Bromo-		50	Toluene	Greenish yellow needles	178–178.5 (decomp.)	$C_{15}H_{10}Br_2O_2$	41.88	41.75
4-Methyl-	2-Methoxy-5-bromo-	78[a]	Toluene-ligroin	Yellow needles	130–131	$C_{17}H_{15}BrO_2$	24.16	24.36
	2-Ethoxy-5-bromo-	nearly quant.	Alcohol-acetone	Yellow needles	144–145	$C_{18}H_{17}BrO_2$	23.18	23.23
Unsubs	2-Benzyloxy-5-bromo-	81	Alcohol-acetone	Pale yellow needles	162–163	$C_{22}H_{17}BrO_2$	20.35	20.26
4-Methyl-		71	Toluene	Yellow needles	160–161	$C_{23}H_{19}BrO_2$	19.65	19.45
4-Methoxy-		76	Alcohol-acetone	Silver needles	156–158	$C_{23}H_{19}BrO_3$	18.91	19.09
4-Chloro-		24	Dioxane[b]	Yellow needles	158–159	$C_{22}H_{16}BrClO_2$	27.01	26.81
Unsubs	2-Hydroxy-3,5-dibromo-	55	Alcohol	Long yellow needles	164–165	$C_{15}H_{10}Br_2O_2$	41.86	41.53
2-Chloro-		51	Toluene	Yellow needles	162–163	$C_{15}H_9Br_2ClO_2$	46.95	46.68
4-Chloro-		64	Toluene	Yellow needles	197–200 (decomp.)	$C_{15}H_9Br_2ClO_2$	46.95	46.72
4-Bromo-		67	Alcohol	Yellow powder	205–206 (decomp.)	$C_{15}H_9Br_3O_2$	52.06	51.90

4-Methyl-		67	Toluene	Yellow needles	178–179 (decomp.)	$C_{16}H_{12}Br_2O_2$	40.40	40.23
4-Hydroxy-		31	Alcohol	Orange needles	225–227 (decomp.)	$C_{15}H_{10}Br_2O_3$	40.20	40.30
4-Methoxy-		58	Toluene	Yellow powder	189 (decomp.)	$C_{16}H_{12}Br_2O_3$	38.83	38.63
4-Amino-		18	Alcohol	Brownish flakes	195–196 (decomp.)	$C_{15}H_{11}Br_2NO_2$	40.30	40.45
4-Methyl-	2-Ethoxy-3,5-dibromo-	45	Alcohol	Yellow plates	136–137	$C_{18}H_{16}Br_2O_2 + 0.5 C_2H_6O$	35.79	35.74
Unsubs.	2-Benzyloxy-3,5-dibromo-	8	Ligroin	Yellow needles	111–112	$C_{22}H_{16}Br_2O_2$	33.89	33.87
4-Methyl-			Acetone	Yellow needles	128–129	$C_{23}H_{18}Br_2O_2$	32.92	32.27
4-Methoxy-		88	Acetone	Pale yellow needles	137–137.5	$C_{23}H_{18}Br_2O_3$	31.87	31.94
Unsubs.	3,5-Dibromo-4-hydroxy-	54	Toluene	Pinkish needles	160–161	$C_{15}H_{10}Br_2O_2$	41.88	41.98
4-Methyl-		50	Toluene	Yellow needles	175–176	$C_{16}H_{12}Br_2O_2$	40.40	40.41
4-Amino-		41	Alcohol	Yellow powder	227–228	$C_{15}H_{11}Br_2NO_2$	40.32	40.48
2-Chloro-		7	Toluene	Gray needles	187–188	$C_{15}H_9Br_2ClO_2$	46.93	46.44

[a] This represents the crude yield. Other figures refer to purified material. The very low values indicate that many crystallizations were necessary.

[b] When this product was crystallized from alcohol it combined with one-half molecular proportion of solvent. Calc'd for $C_{22}H_{16}BrClO_2 + 0.5C_2H_5OH$: Hal., 25.63. Found: Hal., 25.42.

TABLE III

DISTYRYL KETONES

SUBSTITUENT IN FIRST STYRYL RADICAL	SUBSTITUENT IN SECOND STYRYL RADICAL	YIELD %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES HALOGEN	
							Calc'd	Found
Unsubs	2 - Hydroxy - 5 - bromo-	10	Toluene ligroin	Yellow plates	179–180 (decomp.)	$C_{17}H_{13}BrO_2$	24.31	24.42
	Methylene - 3,4 - dioxy-6-bromo-	93[a]	Toluene	Brown needles	147–148	$C_{18}H_{13}BrO_3$	22.40	22.51
	2-Hydroxy-3,5-dibromo-	15	Toluene-ligroin	Yellow leaflets	160–160.5 (decomp.)	$C_{17}H_{12}Br_2O_2$	39.21	39.14
4-Methyl-		11	Toluene	Orange powder	181–182 (decomp.)	$C_{18}H_{14}Br_2O_2$	37.91	38.04
4-Methoxy-		30	Toluene	Yellow needles	171–172 (decomp.)	$C_{18}H_{14}Br_2O_3$	36.52	36.66
4-Nitro-		81	Dioxane-water	Brown powder	216–217 (decomp.)	$C_{17}H_{11}Br_2NO_4$	35.32	35.01
4-Phenyl-		22	Toluene	Orange needles	188–189 (decomp.)	$C_{23}H_{16}Br_2O_2$	33.05	33.53
4-Bromo-		57	Toluene	Yellow needles	193 (decomp.)	$C_{17}H_{11}Br_3O_2$	49.28	49.23
Methylene-3,4-dioxy-6-bromo-		25	Toluene	Green needles	200–201 (decomp.)	$C_{18}H_{11}Br_3O_4$	45.19	45.14
3,5-Dibromo-4-hydroxy-		19	Toluene-ligroin	Greenish powder	205–206 (decomp.)	$C_{17}H_{10}Br_4O_2$	54.98	55.21
2-Benzyloxy-5-bromo-		65	Toluene	Yellow powder	186–187 (decomp.)	$C_{24}H_{17}Br_3O_2$	40.47	40.61
2-Methoxy-3,5-dibromo-		77	Toluene	Yellow needles	202–203 (decomp.)	$C_{18}H_{12}Br_4O_2$	53.69	53.73
2-Benzyloxy-3,5-dibromo-		40	Toluene	Yellow needles	200–201 (decomp.)	$C_{24}H_{16}Br_4O_2$	47.61	47.36
4-Hydroxy-3,5-dibromo-	4-Hydroxy-3,5-dibromo-		Ligroin	Yellow needles	Above 275°	$C_{17}H_{10}Br_4O_3$	54.98	54.49

[a] This represents the crude yield. Other figures refer to purified material. The very low values indicate that many crystallizations were necessary.

TABLE IV

SUBSTITUTION PRODUCTS OF 1-PHENYLPYRAZOLINE

SUBSTITUTED PHENYL OR STYRYL IN POSITION 3	SUBSTITUTED PHENYL IN POSITION 5	YIELD %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES HALOGEN	
							Calc'd	Found
4-Methoxy-	2-Benzyloxy-5-bromo-	69[a]	Toluene	Pale yellow needles	182	$C_{29}H_{25}BrN_2O_2$	15.59	15.85
4-Bromo-	2-Hydroxy-3,5-dibromo-	86	Alcohol	Yellow needles	175–177	$C_{21}H_{15}Br_3N_2O$	43.55	43.38
4-Bromo-	3,5-Dibromo-4-hydroxy-	61[a]	Toluene	Yellow needles	189–190	$C_{21}H_{15}Br_3N_2O$	43.55	43.77
4-Methyl-	2-Benzyloxy-3,5-dibromo-	79[a]	Toluene-ligroin	Yellow needles	183–184	$C_{29}H_{24}Br_2N_2O$	27.77	27.70
4-Methoxy-	2-Hydroxy-3,5-dibromo-	5[b]	Toluene	Colorless needles	193–194	$C_{22}H_{18}Br_2N_2O_2$	31.87	32.34
2-Hydroxy-3,5-dibromostyryl-	4-Bromo-	Very low[c]	Toluene-ligroin	Yellow needles	238–239	$C_{23}H_{17}Br_3N_2O$	41.59	41.95
2-Hydroxy-3,5-dibromostyryl-	2-Benzyloxy-3,5-dibromo-	47[a]	Toluene	Brown leaflets	145–155	$C_{30}H_{22}Br_4N_2O_2$	41.98	41.76

[a] These values represent purified material.

[b] Obtained from the mother liquor from which the isomeric hydrazone was crystallized.

[c] The yield of crude product was nearly quantitative, but purification required many crystallizations and involved much loss.

EXPERIMENTAL

5-Bromosalicylaldehyde was first prepared by dropping bromine into salicylaldehyde, as directed by Piria (7), but the method proved to be unsatisfactory due to the fact that the resulting solid enclosed considerable unchanged starting material. When acetic acid was used as a solvent and bromine was added slowly to avoid rise of temperature a mixture of 5-bromo- and 3,5-dibromo- salicylaldehyde was obtained. With chloroform as a solvent, only the monobromo compound was formed Crystallization from alcohol gave colorless prisms that melted at 105–106°. Danckwortt (12) reported 105°.

2-Benzyloxy-5-bromobenzaldehyde was obtained in 72% yield of purified product by benzylation of 5-bromosalicylaldehyde as directed by Perkin (9) for the unsubstituted compound. Crystallization from alcohol gave colorless, spear-pointed crystals that melted at 73–74°.

Anal. Calc'd for $C_{14}H_{11}BrO_2$: Br, 27.49. Found: Br, 27.16.

This product was further identified by its preparation in another way. 2-Benzyloxybenzaldehyde was prepared as directed by Perkin but was purified by distillation under reduced pressure as suggested by Auwers and Walker (13). It boiled at 176–177° at 4 mm. Treatment of an acetic acid solution of this ether with somewhat more than one molecular proportion of bromine, dissolved in acetic acid in the presence of sodium acetate, gave a colorless product which, after crystallization from alcohol, melted at 72.5–73.5° and did not depress the melting point of the compound described above. The yield was 80%.

3,5-Dibromosalicylaldehyde, which was used as starting material for the dibromo series, was obtained in purified form in yields of 70% or higher by following the method outlined by Lindemann and Forth (14). It separated in pale yellow needles that melted at 82–83°. Brewster (15) found 81–82°, but Lindemann and Forth reported 85°.

2-Methoxy-3,5-dibromobenzaldehyde. Twenty-four grams of the required dibromosalicylaldehyde was alkylated with dimethyl sulfate as directed by Baeyer and Villiger (16), taking care to keep the mixture alkaline. The product was collected on a filter and washed to remove possible unchanged starting material in the form of the sodium salt. Crystallization from alcohol gave long colorless needles that melted at 92–93°. The yield was 73%. Some starting material was recovered.

Anal. Calc'd for $C_8H_6Br_2O_2$: Br, 54.42. Found: Br, 54.63.

The corresponding ethyl ether was obtained by gradual addition of ethyl iodide to an alcoholic solution of potassium hydroxide and the necessary dibromosalicylaldehyde while the mixture was heated over a vigorously boiling water-bath. The liquid was then refluxed for two hours, after which volatile material was distilled off. Addition of water to the residue precipitated a yellowish solid. Crystallization from alcohol gave pale yellow tablets that melted at 86–87°. The yield of purified product was 61%. Some starting material was recovered from the mother liquor.

Anal. Calc'd for $C_9H_8Br_2O_2$: Br, 51.92. Found: Br, 51.97.

2-Benzyloxy-3,5-dibromobenzaldehyde. One molecular proportion of benzyl chloride was added to a mixture of alcoholic potash and the required dibromosalicylaldehyde, the whole was refluxed for an hour, and allowed to cool. The solid that separated was crystallized from alcohol from which it was obtained in colorless needles, m.p. 109.5–110.5°. The yield of purified product was 66%.

Anal. Calc'd for $C_{14}H_{10}Br_2O_2$: Br, 43.24. Found: Br, 43.03.

Derivatives of these compounds are indicated in tables I, II, III, and IV.

SUMMARY

1. Several derivatives of salicylaldehyde have been condensed with acetophenone and a number of its substitution products. When acetophenone contains no substituent the α,β-unsaturated ketone first formed may add a molecule of the starting ketone to give a diacetophenone derivative. This result is favored by long standing of the reaction mixture.

2. Seven of these α,β-unsaturated ketones whose structures seemed favorable to the formation of stable hydrazones were subjected to the action of phenylhydrazine. The hydrazone was isolated in only one case. In all other instances the required rearrangement product was obtained.

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[COMMUNICATION NO. 805 FROM THE KODAK RESEARCH LABORATORIES]

THE STRUCTURE OF THE SO-CALLED TOLUIDINE BLUE

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Toluidine Blue is a dye that has certain rather unique properties, in particular, its spectral absorption characteristics, which do not resemble those of ordinary blue dyes (Fig. 1). While it has long been available on the market, its structure has never been divulged. It is not listed in Schultz (1) or the Colour Index (2), presumably because it is not important in the dyeing of textiles.[1] In connection with other work on color and constitution being carried out in this laboratory, it became of interest to learn the structure of this dye.

From the results of elementary analyses of the purified, salt-free dye, it was possible to write an empirical formula, $C_{28}H_{20}N_2Na_2O_{10}S_2$. Qualitative reactions for classification indicated that it was an acid anthraquinone dye. Toluidine Blue gives a yellow vat on reduction of its aqueous solution in the presence of Raney nickel or by the use of alkaline hydrosulfite. The dye is regenerated by aerial oxidation. The anthraquinone nucleus was detected by a zinc dust distillation, using Clar's procedure (3), by which a small quantity of anthracene was secured. When the fusion mixture was acidified, considerable hydrogen sulfide was evolved, indicating the presence of a sulfonic acid group that had also been reduced in the fusion. From the residue, a purple solid was isolated; this contained carbon, hydrogen, nitrogen, and oxygen, but no sulfur or sodium. The empirical formula, $C_{28}H_{22}N_2O_4$, was arrived at from the analytical data; the dye is, thus, the disodium salt of the corresponding disulfonic acid. By subtraction of $C_{14}H_8O_2$ (anthraquinone), one is left with $C_{14}H_{14}N_2O_2$, which it seemed highly probable, comprised two toluidine residues (C_7H_7N) and two atoms of oxygen. Reconstructing a structure from these conclusions led to a ditoluidinodihydroxyanthraquinone. Of course, the hydroxyl groups might have been located in the toluene ring, but evidence secured later definitely excluded this possibility. The dye was entirely unlike the isomeric green dye, Alizarin Viridin (Schultz No. 1193), which conforms with these conclusions as to building units. Since there are 114 possible isomeric

[1] It is not the azine dye, Toluidine Blue O (No. 1041 in Schultz; No. 925 in Colour Index).

ditoluidinodihydroxyanthraquinones, without any consideration of the possibilities that the hydroxyl groups might have been in the toluene rings, or that the toluidine residues were not *para*, but *ortho* or *meta*, further degradation was essential.

The dye is sensitive to the action of nitric acid, hydrogen peroxide or ferric chloride in the presence of acid, and fuming sulfuric acid, but is unaffected by hydrochloric acid in the absence of ferric chloride or hydrogen peroxide, concentrated sulfuric acid, and bases. Although from the nature of the reagents that attack the dye one would suspect oxidation, the product appears to be the result of a hydrolysis.[2] The new substance resulting from the use of these reagents was a red solid which analyzed for $C_{14}H_8O_6$, or a tetrahydroxyanthraquinone. It formed a tetraacetate, $C_{22}H_{16}O_{10}$, from

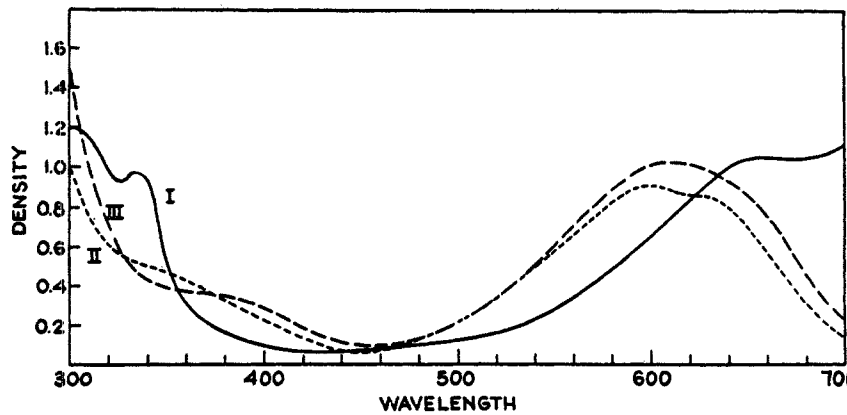


FIG. 1. I = Toluidine Blue
II = A commercial dye, Schultz No. 1199
III = A commercial dye, Schultz No. 1188

which the parent substance was regenerated on hydrolysis. The properties of the two compounds did not agree with those of any of the 14 isomers reported in the literature (there are 22 possible tetrahydroxyanthraquinones). However, the latter substances do not have sharp melting points, but tend to sublime or decompose at elevated temperatures, so that the comparisons have to be made through their color reactions or derivatives, such as the tetraacetates.

A survey of the literature on dihydroxyditoluidinoanthraquinones revealed the commercially available Alizarin Viridin, which is 7,8-dihydroxy-1,4-di-*p*-toluidinoanthraquinone, and several patents according to which other isomers may be produced. Thus, the 1,4-ditoluidino-5,8-

[2] For convenience, this type of cleavage is called oxidative hydrolysis.

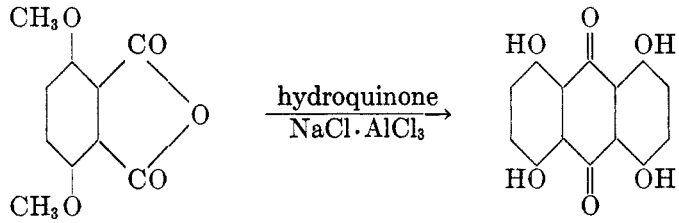
dihydroxyanthraquinone is said to result from the interaction of *p*-toluidine and 1,4,5,8,9,10-hexahydroxyanthracene (4), or 5,8-diaminoquinizarin (5), or 5,8-dichloroquinizarin (6). 1,5-Ditoluidino-4,8-dihydroxyanthraquinone is probably a product from *p*-toluidine and *p*-dinitroanthrarufin (7), or dibromoanthrarufin (8), while its disulfonic acid is probably a component of the mixture obtained when 4,8-dinitroanthrarufin-2,6-disulfonic acid is melted with *p*-toluidine (9). Further, several dyes having the sulfonic acid groups in the toluidine residue are described. These were secured by using sodium 4-aminotoluene-2-sulfonate and leuco-1,4,5,8-tetrahydroxyanthraquinone, and carrying out the reaction in a solvent (10). All of the dyes obtainable by these procedures, if attacked by the hydrolyzing (oxidizing) agents mentioned above, would be expected to yield 1,4,5,8-tetrahydroxyanthraquinone, the properties of which as given in the literature (11) were not in good agreement with those of the red solid secured by the degradation of Toluidine Blue. Hence, there seemed to be no reason to make an extensive study of such dyes.

The unknown 1,4,6,7-tetrahydroxyanthraquinone should be obtainable by a similar oxidative acid hydrolysis of 6,7-ditoluidino-1,4-dihydroxyanthraquinone (or the isomer in which the amine residues and hydroxyl groups are interchanged; neither of these has been described). The synthesis of this compound should be possible, starting with 6,7-dibromoquinizarin; the latter could be secured by a benzoylbenzoic acid synthesis, starting from 4,5-dibromophthalic anhydride (12) and hydroquinone. No particular difficulty was encountered in carrying out this series of reactions, and degradation of the dye obtained in the final step gave a tetrahydroxyanthraquinone identical with the red compound from Toluidine Blue. Thus, it seemed that the structure of the latter was established.

Because of the low yields of the 4,5-dibromophthalic anhydride, it seemed advisable to consider the possibility of substituting the corresponding dichloro derivative. Now, the only easily isolated dichloro substitution product from the chlorination of phthalic anhydride has the chlorine atoms in the 3 and 6 positions; this would be useless for our purpose. However, since the oxidative acid hydrolysis seemed a peculiar reaction, it was considered advisable to carry through a preparation and learn whether the same property would appear in the 1,4,5,8-series. When this was done, a green dye was obtained; to our surprise, this gave the *same* red tetrahydroxyanthraquinone upon degradation. If molecular rearrangements, which seemed extremely unlikely, were barred, this result implied that the position of the halogen atoms in one of the anhydrides, as reported in the literature, was incorrect.

It is possible to synthesize the 1,4,5,8-tetrahydroxyanthraquinone in an unambiguous manner, starting with 3,6-dimethoxyphthalic anhydride (13),

which, in turn, has been secured from hydroquinone by reactions which leave no doubt as to its structure.



This procedure gives a relatively pure product. Further, this product is identical in all respects (including its tetraacetate) with the red compound secured from Toluidine Blue. The following conclusions are inevitable: (a) the properties of 1,4,5,8-tetrahydroxyanthraquinone as given in the literature are incorrect, probably because a pure sample has never been available; (b) in Toluidine Blue, the groups are in the 1,4,5, and 8 positions; (c) considerable doubt is cast upon the location of the bromine atoms in the so-called 4,5-dibromophthalic anhydride. Accordingly, work in the 1,4,6,7-series was shelved, and a reinvestigation of the 1,4,5,8-series was undertaken.

A priori, 1,4-di-*p*-toluidino-5,8-dihydroxyanthraquinone would be excluded, because all the 1,4-ditoluidinoanthraquinone dyes so far reported are green. This conclusion was confirmed by the synthesis of a dye having the group arrangement in question from 5,8-dichloroquinizarin, followed by sulfonation. Not only was the product green, but its absorption spectrum proved to be identical with that of another little-used, unlisted dye, Toluidine Green. This substance would be expected to result on following the procedures in the patent given in reference (4). Repetition of those patent directions actually gave mixtures having dull shades and flat absorption curves.

4,8-Dichloroanthrarufin seemed the most likely starting material for the synthesis of 4,8-ditoluidino-1,5-dihydroxyanthraquinone, and was secured in reasonable amounts after some preliminary study. It was available from the interaction of sulfuryl chloride and anthrarufin in nitrobenzene (14). The fusion with *p*-toluidine offered no difficulty, and the product was readily purified; it was found much more convenient to start with a fairly crude dichloroanthrarufin and crystallize at this point than to prepare a pure dichloroanthrarufin.

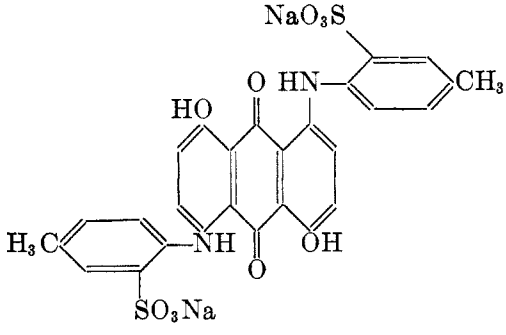
4,8-Di-*p*-toluidino-1,5-dihydroxyanthraquinone prepared from 4,8-dichloroanthrarufin is the same substance as was isolated from the zinc reduction of Toluidine Blue, and gives Toluidine Blue on sulfonation. Since oleum degrades the dye, as previously mentioned, it is essential to accom-

plish the sulfonation under milder conditions by the use of concentrated sulfuric acid at steam-bath temperature.

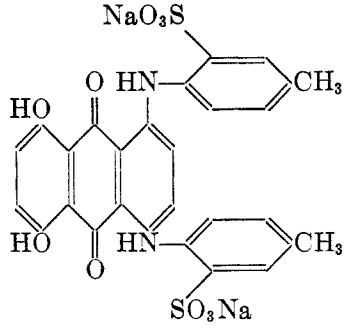
The dinitration of anthrarufin (15) is rather unsatisfactory; the yield is low and the mixtures are not readily separated. Until a carefully-purified 4,8-dinitroanthrarufin was secured, the dyes prepared by its use were unsatisfactory and the absorption curves were not identical with that of Toluidine Blue. Eventually, a pure dinitroanthrarufin was secured, and after appropriate treatment it was converted into a good specimen of Toluidine Blue. These methods of synthesis locate the toluidine and hydroxyl groups.

While the position of the sulfonic acid groups can be inferred from other dye structures given in the literature, it should be possible to locate them definitely if a reaction of cleavage of the toluidino groups were available. Toluidino groups have been split by what appears to be a simple sulfuric acid hydrolysis from 1,6,7,12-tetratoluidinopentacenequinone (16) and from some acid anthraquinone dyes *reduced* by fuming hydriodic acid (34) or by stannous chloride in the 1,4-series, but the 1,5-series was unattacked (although under the same conditions 1,5-diamino-2,4,6,8-tetrahydroxyanthraquinone was hydrolyzed) (17).

We have found that Toluidine Blue is not hydrolyzed by hydrochloric acid in the presence of stannous chloride, but if tin and hydrochloric acid are used, the cleavage[3] takes place readily, with the formation of leuco-1,4,5,8-tetrahydroxyanthraquinone and a toluidine sulfonic acid. The latter was identified as 4-aminotoluene-3-sulfonic acid by converting it to the known 4-chlorotoluene-3-sulfonamide. Degradation by reductive hydrolysis of Toluidine Green gave the same 1,4,5,8-tetrahydroxyanthraquinone and 4-aminotoluene-3-sulfonic acid. Toluidine Blue is, thus, the disodium salt of 1,5-di-(2′-sulfo-4′-toluidino)-4,8-dihydroxyanthraquinone (I), while Toluidine Green is the 1,4-isomer (II).



I

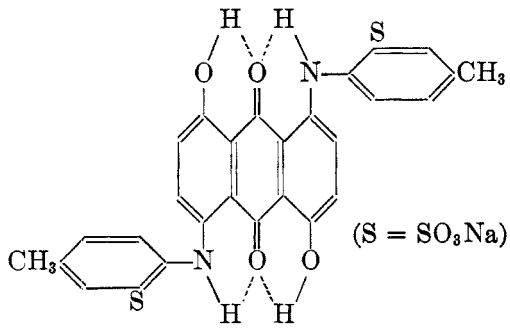


II

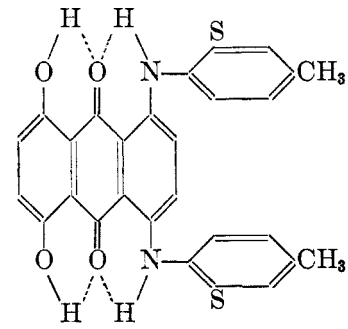
[3] For convenience this cleavage is called reductive hydrolysis.

The possibility that the blue and green dyes do not have structures of the commonly accepted types, but are 9,10-diimides, seems highly improbable, because of the method of preparation. Groups in the *alpha* positions of the anthraquinone nucleus are always replaced under milder conditions than are required to form 9,10-diimides. Further, all known 9,10-diimides are yellow to red; they are not dyes and are usually hydrolyzable by concentrated sulfuric acid (18).

Of course, it is entirely possible that Toluidine Blue is not represented by formula (I), but that it may exist to a large extent in one or more of the several possible tautomerides, each of which is a resonance hybrid. However, it may be that the unusual spectrophotometric absorption characteristics can be better accounted for by the assumption of a structure containing hydrogen bonds (III for Toluidine Blue, IV for Toluidine Green). Other properties may be reconciled with such a formulation. Since the dyes are



III



IV

not hydrolyzed except in the presence of oxidizing or reducing agents, the functions of the latter must be to destroy at least a part of the hydrogen bonding. At present the available evidence does not warrant a closer correlation between structure and absorption.

These reductive and oxidative hydrolysis procedures should be useful in reactions of degradation in the anthraquinone series. For example, Celliton Fast Blue Green B (19), which is largely 1,4-di-(β-hydroxyethylamino)-5,8-dihydroxyanthraquinone, is oxidatively hydrolyzed to give 1,4,5,8-tetrahydroxyanthraquinone. The method of reduction outlined, being applicable to the 1,5-series, is more general than that of Friedländer (17) and more useful than the use of oxidizing agents. The latter tend to destroy the amine component and may even attack the hydroxy compound; thus, quinalizarin from Alizarin Viridin is further oxidized when the procedure is applied to that dye.

A few instances of oxidative hydrolytic cleavage have been recorded in the literature. Certain aminohydroxyanthraquinones are converted to

polyhydroxyanthraquinones by the use of manganese and lead dioxides in concentrated sulfuric acid solution, or by the use of ferric salts, nitric acid, or ammonium persulfate; in some cases, additional hydroxyl groups are

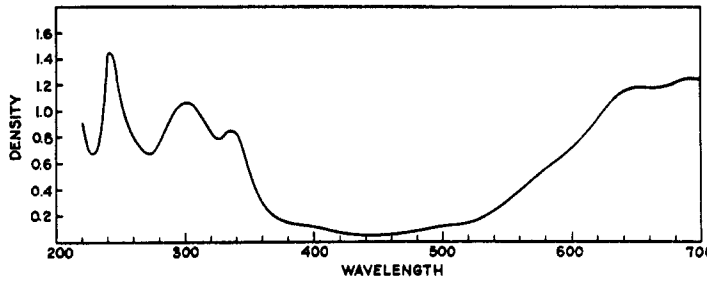


FIG. 2. TOLUIDINE BLUE

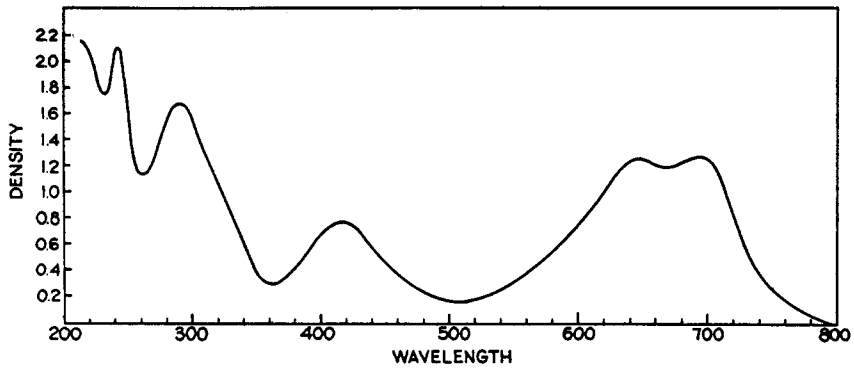


FIG. 3. TOLUIDINE GREEN

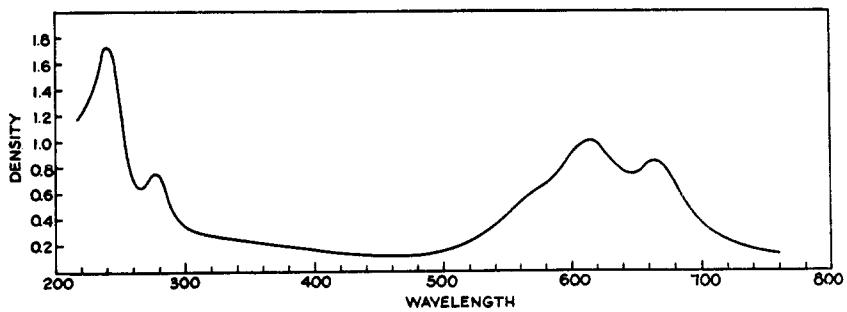


FIG. 4. SODIUM 1,4-di-β-SULFATOETHYLAMINO-5,8-DIHYDROXYANTHRAQUINONE

formed by a seeming direct oxidation of a hydrogen atom (20). According to Houben (21), it would seem that the first step is the removal of (two) hydrogen atoms to form a quinoneimide (A); this latter class of compound is known to be susceptible to acid hydrolysis, but the product is always a

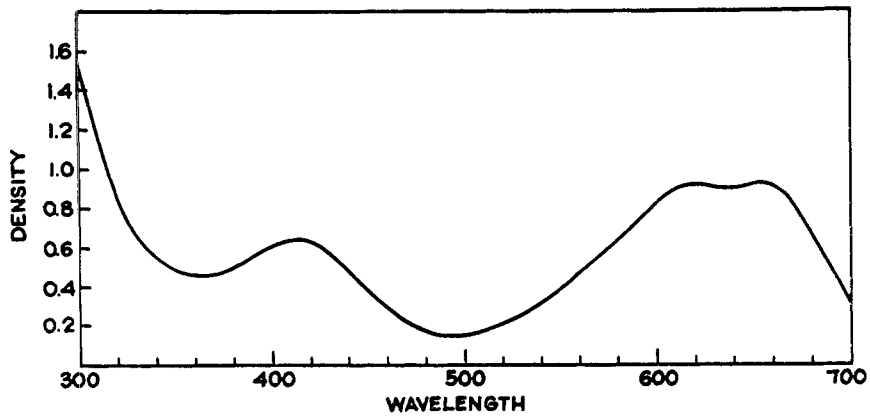


FIG. 5. ALIZARIN VIRIDIN

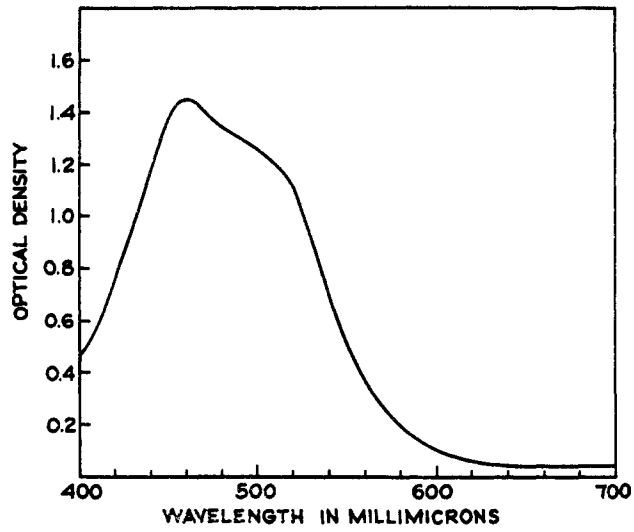
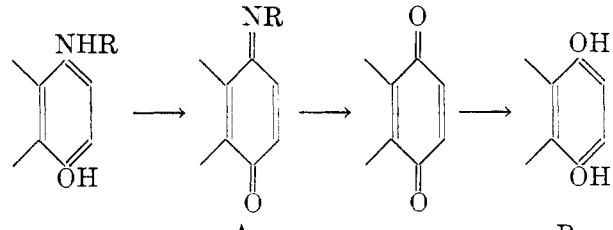


FIG. 6. VAT OF TOLUIDINE BLUE

quinone. To secure the hydroxy compound actually isolated (B) would require some sort of reduction. The high yield of 1,4,5,8-tetrahydroxyan-



A B

thraquinone obtained from Toluidine Blue contradicts such an assumption.

The principal difference between the spectral absorption characteristics of Toluidine Blue and other blue dyes (Fig. 1) is the high flat absorption in the longer wave lengths of the visible, extending over a considerable range of the spectrum; there is also evidence of two maxima in the curve of Toluidine Blue at 646, 694 (Fig. 2). An inspection of the curves of several anthraquinone dyes reveals similar instances in which there are two absorption bands of this kind in the curve; each molecule contains two hydroxyl groups (Fig. 3), Toluidine Green; Fig. 4, sodium-1,4-di-β-sulfatoethyl-

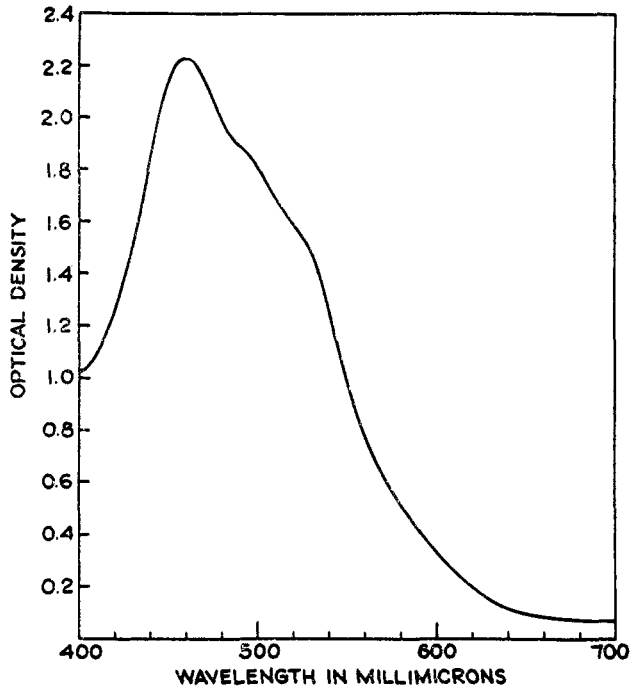


FIG. 7. VAT OF TOLUIDINE GREEN

amino-5,8-dihydroxyanthraquinone; Fig. 5, Alizarin Viridin). The inference may be drawn, then, that there is a connection between the unusual type of curve and the presence of the hydroxyl groups; it is hoped that this may be cleared up by further study.

The other curves shown are the reduced forms (vats) of Toluidine Blue (Fig. 6) and Toluidine Green (Fig. 7). In each figure, the abscissa is in millimicrons, while the ordinate is optical density; the latter is defined as $\log_{10} \frac{1}{T}$, where T = transmission. The solution is examined in a cell 1 cm. in thickness.

EXPERIMENTAL

I. TOLUIDINE BLUE SERIES

A. *Degradation*

1. *Purification and analyses.* The commercial dye appears as a dark blue powder, completely soluble in water. Qualitative classification tests indicated that the coloring matter present was a derivative of anthraquinone. It gives a yellow "vat," which appears red except in very dilute solutions, on reduction by hydrogen in the presence of Raney nickel, or by alkaline hydrosulfite (Fig. 6), or by zinc and acetic acid; this is oxidized back to the original blue by atmospheric oxygen.

After a specimen of the commercial product was extracted with absolute alcohol in a Soxhlet apparatus for twenty-one days, the dye was completely removed, leaving 35% of a residue, mainly sodium chloride, but containing an appreciable quantity of magnesium chloride. A spectroscopic examination of an ashed specimen of dye revealed the presence of sodium, magnesium, iron, aluminum, calcium, and lead, only the first being in significantly large amounts. The alcoholic solution was concentrated, the dye being collected in fractions. The first fraction (needles) was analyzed.

Anal. Calc'd for $C_{28}H_{20}N_2Na_2O_{10}S_2$: N, 4.28; S, 9.78; Na, 7.03.
Found: N, 4.33; S, 9.80, 9.82; Na, 6.82.

2. *Zinc dust distillation.* A mixture of 17 g. of the commercial dye, 85 g. of zinc chloride, 17 g. of coarse sodium chloride, and 17 g. of zinc dust (3), in a 500-cc. flask fitted with stirrer and thermometer, was heated by a metal-bath to 230°. As the mass liquefied, the temperature was raised to 260° and there was so much frothing that stirring had to be discontinued. After five minutes the melt was allowed to cool to room temperature and was treated with warm, dilute hydrochloric acid (copious evolution of hydrogen sulfide[4]). The insoluble portion was filtered and dried. When this was heated at 200–300°/2–3 mm. for ten minutes, a small amount of a pale yellow solid sublimed, which, after resublimation, was identified as anthracene, m.p. 208–210°; a mixed melting point with an authentic specimen was not depressed. The sublimation residue was further boiled with dilute hydrochloric acid to remove most of the zinc, then washed and dried. It was successively extracted with boiling alcohol and nitrobenzene, the insoluble carbonized residue being rejected. After dilution of the nitrobenzene extract with twice its volume of ethyl alcohol, and standing overnight, purplish needles with a bronzy luster had separated. These gradually decompose when heated above 300°; the solution in dioxane or nitrobenzene is a brilliant blue.

Anal. Calc'd for $C_{28}H_{22}N_2O_4$: C, 74.7; H, 4.8; N, 6.2.
Found: C, 74.8; H, 4.9; N, 6.2.

This is the 4,8-ditoluidinoanthrarufin, the synthesis of which is described below.

3. *"Oxidative hydrolysis."* During the classification tests, it was discovered that several oxidizing agents destroyed the blue color of the dye, with production of a brownish-red solution; the full list includes dilute nitric acid, or a combination of hydrochloric acid with ferric chloride or potassium periodate or persulfate or 30% hydrogen peroxide.

In illustration, to a solution of 10 g. of (purified) Toluidine Blue in 125 cc. of water, not above 85°, was added 43 cc. of concentrated nitric acid, and the whole was heated for one and one-half hours on the steam-bath. As the color changed, a dull reddish-

[4] The production of hydrogen sulfide indicated the presence of a sulfonic acid group in the dye. This was checked by similar fusions with anthraquinone-α-sulfonic acid, and 4-aminotoluene-2-sulfonic acid.

brown solid separated. After filtering and drying, this amounted to 2.6 g. (78%, based on the assumption that the dye contained 80% of coloring matter). The aqueous solution did not contain an amine (tested by diazotizing and non-coupling). The dull red solid was purified by a semimicro sublimation; it formed very fine red rods with a greenish metallic luster. The recovery was 67%. 1,4,5,8-Tetrahydroxyanthraquinone dissolves fairly readily in xylene, acetic acid, or dioxane, but is very slightly soluble in alcohol or water.

Anal. Calc'd for $C_{14}H_8O_6$: C, 61.8; H, 2.9.
Found: C, 61.5; H, 2.9.

A more dilute nitric acid used in the above hydrolysis gave a similar result.

The colors produced by the pure substance with reagents are as follows: in concentrated sulfuric acid, blue with a strong red fluorescence (pure blue if very dilute), essentially unchanged on the addition of boric acid; a blue-violet solution with sodium or potassium hydroxide, followed by separation of the colored salt in a few minutes; yellow with zinc and acetic acid, restored to red by potassium persulfate. The identity of this pure substance with the 1,4,5,8-tetrahydroxyanthraquinone described below was shown by microscopic and crystallographic examination,[5] a comparison of its behavior on sublimation, and the identity of the tetraacetates.

4. *Synthesis of 1,4,5,8-tetrahydroxyanthraquinone and its tetraacetate.* To a melt of 40 g. of anhydrous aluminum chloride and 7 g. of sodium chloride at 180° was added an intimate mixture of 6 g. of 3,6-dimethoxyphthalic anhydride (13) and 6 g. of hydroquinone, over a period of five minutes, with hand stirring. The temperature was then raised to 200–220° and maintained for a half hour at the higher figure. After cooling, the blue solid was finely pulverized, and decomposed by slow addition to hot dilute hydrochloric acid. The reddish-brown solid was collected on a filter, washed, and dried. The yield was 4 g. The product was recrystallized from xylene. It does not show a definite melting point;[6] there is visible sintering at about 350°, with some sublimation. The analysis and other properties have already been given.

The tetrahydroxy compound can also be secured by heating 5,8-dibromoquinizarin with calcium hydroxide solution in an autoclave at 240–260° for twenty-four hours.

The tetraacetate. A mixture of 0.3 g. of the tetrahydroxy compound, 20 cc. of acetic anhydride, and 1 g. of sodium acetate was refluxed for one and one-half hours. After being worked up in the usual way, the product was crystallized from hot acetic acid, from which it separates in bright yellow needles. It melts with decomposition, the temperature observed being very dependent on the rate of heating. If the bath is at 275° when the sample is immersed, the melting point is sharp at 281–282°; if the bath is heated fairly rapidly, the decomposition point is 273–275°.

Anal. Calc'd for $C_{22}H_{16}O_{10}$: C, 60.0; H, 3.6.
Found: C, 59.7, 59.9; H, 3.5, 3.5.

On carrying out a synthesis from 3,6-dimethoxyphthalic anhydride and catechol with a view to possibly obtaining a 1,4,6,7-tetrahydroxyanthraquinone, only quinalizarin (1,4,7,8) was obtained.

5. *"Reductive hydrolysis."* Twenty-five grams of the dye (approximately 80%)

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[5] For this and other work of a similar nature we are indebted to Dr. E. E. Jelley of the Kodak Research Laboratories.

[6] In the literature (11a, 22) the melting point 246° is given; the color with concentrated sulfuric acid is described as greenish-blue, which is changed to blue by boric acid. The tetraacetate is said to form bright yellow needles, decomposing at about 250° (11b).

was boiled with 2250 cc. of methanol and filtered from the undissolved salts. The solution was then transferred to a flask fitted with a reflux condenser, stirrer, and inlet tube for gas. After the addition of 40 g. of mossy tin, hydrogen chloride was passed in for two and one-half hours, while refluxing and stirring. The color became orange-brown. The solution was filtered hot from unused tin and 4.1 g. of the sparingly soluble leuco-1,4,5,8-tetrahydroxyanthraquinone. The filtrate was evaporated nearly to dryness, 300 cc. of hot water was added, and the solution was again filtered; the residual solid (3.23 g.) was leuco-1,4,5,8-tetrahydroxyanthraquinone. The total yield was 7.33 g. (86%). It was dissolved in sodium hydroxide and the solution aerated. The crude material was then further purified and identified as above.

The brown aqueous filtrate was decolorized with Darco, concentrated, and chilled in ice; 6.64 g. of 4-aminotoluene-3-sulfonic acid was obtained; a further 0.3 g. was isolated from the filtrate, making the total yield 6.94 g. (61%). For identification, the product was diazotized and converted into the 4-chloro derivative in the usual manner (23, 24). The sulfonamide was readily secured; it melted at 155–156°. An authentic specimen was prepared, which melted at 155–156°. There was no depression on admixture of the two, whereas the melting points of mixtures with the known 2-isomer (23) were depressed 15–20°.

This procedure, when applied to Alizarin Viridin, gave leuco-quinalizarin and 4-aminotoluene-3-sulfonic acid.

B. *Synthesis.*

1. *4,8-Dichloroanthrarufin.* This substance was secured by a modification of a patented procedure (14). A mixture of 2 l. of nitrobenzene and 250 g. of finely-ground anthrarufin was heated to the boiling point with vigorous stirring, and then cooled to 60° to produce a fine suspension of crystals. After the addition of 250 cc. of sulfuryl chloride, the mixture was refluxed and stirred on the steam-bath; at one-half hour intervals two 200-cc. portions of sulfuryl chloride were added, after which the heating and stirring were continued for eighteen hours. The excess sulfuryl chloride was then removed by heating to 205°. After cooling to 40–50°, the crude dichloroanthrarufin was filtered by suction and washed first with methanol and then with ether. The yield of crude product (varying with the source of the anthrarufin) is 160–170 g. The melting point varies with each lot, but always falls within the range 310–323°. If the melting point is below 310°, which will be the case if insufficient sulfuryl chloride is used, the product is not suitable for conversion to Toluidine Blue. The crude material may be recrystallized from nitrobenzene, trichlorobenzene or anisole, if desired. The pure substance melts at 336–337° with slight sublimation.

2. *4,8-Dinitroanthrarufin.*[7] A mixture of 50 g. of anthrarufin, 25 g. of boric acid, and 500 cc. of concentrated sulfuric acid was stirred at 50–60° for two hours, during which time most of the solid dissolved. The red solution was cooled to 10–15°, and 50 g. of potassium nitrate (10% excess) was added in small portions; stirring was then continued at 10–15° for three hours. The mixture was poured upon chipped ice, the crude nitration mixture was filtered through Vinyon fabric, washed with much water, and dried. This crude mixture was exhaustively extracted with three 500-cc. portions of boiling acetic acid, boiling each for five minutes, and filtering hot. The insoluble material (about 20 g.) was crude 4,8-dinitroanthrarufin. Upon recrystal-

[7] For the preparation of this substance we are indebted to Dr. Bell of these Laboratories.

lization from 1000 cc. of dioxane, 18 g. (26%) of product was recovered, in the form of yellow plates. This material is suitable for the next step.

3. *Toluidine Blue base; 4,8-di-p-toluidinoanthrarufin.* A mixture of 250 g. of dichloroanthrarufin and 3 kg. of *p*-toluidine was heated in an oil-bath at 160–175° for eighteen hours. After cooling to 60–65°, it was poured into dilute hydrochloric acid, the precipitated dye base being filtered and well washed with hot water. The dried product was digested for two hours with 2.5 l. of boiling chlorobenzene and filtered hot. The base so obtained is entirely satisfactory for conversion into the dye. The total yield (including working up filtrates) is 272 g. (75%). The other properties have already been described.

4. *Sulfonation; the dye, Toluidine Blue, I.* A solution of 270 g. of 4,8-di-*p*-toluidinoanthrarufin (Toluidine Blue base) in 2025 cc. of sulfuric acid (sp. gr. 1.84) was heated with stirring on the steam-bath (internal temperature 95–98°) for three hours. After cooling, the solution, the original green color of which had changed to blue, was poured upon about 12 l. of crushed ice and the precipitated dye was filtered. The dye acid was then dissolved in 12 l. of hot water to which had been added slightly more than the calculated amount of 40% sodium hydroxide, was filtered to remove a small amount of insoluble material, and was salted out in the usual manner. The yield was 355 g. of a product having the desired spectral absorption characteristics; it contains about 20% of sodium chloride. Fuming sulfuric acid gradually decomposed the dye, but the nature of the decomposition was not determined, other than to isolate a small amount of 1,4,5,8-tetrahydroxyanthraquinone.

C. *Isomeric ditoluidino dihydroxyanthraquinones* are obtainable from 4,8-dichloroanthrarufin and *meta*- and *ortho*-toluidines. While the *meta* isomer reacts as easily as the *para* in the procedure described above, dye base formation is incomplete with *ortho*-toluidine after twenty-four hours at 170°. The addition of boric acid to the melt in the latter case promotes the reaction so that it becomes practical. The products were recrystallized from xylene. They resemble the *para* isomer in solubilities and behavior on heating.

Anal. Calc'd for $C_{28}H_{22}N_2O_4$: C, 74.7; H, 4.9; N, 6.2.

Found: (*meta*) C, 74.7; H, 5.0; N, 6.4; (*ortho*) C, 74.9; H, 4.8; N, 6.2.

In concentrated sulfuric acid, the *para* derivative gives a yellow-green color, the *meta* a bluish-green, and the *ortho* a greenish-blue. All change to blue in a few seconds on the addition of boric acid.

II. TOLUIDINE GREEN SERIES

A. *Degradation.* This dye was secured by synthesis before it was examined otherwise. However, it is readily degraded by the processes of "reductive" and "oxidative" hydrolysis, as described above under Toluidine Blue; the products are the same and were identified in the same way. On reduction it gives an orange vat. (Fig. 7.)

B. *Synthesis.*

1. *5,8-Dibromoquinizarin.* Waldmann's procedure (25) for securing halogenated quinizarins was followed. While a melt of 535 g. of anhydrous aluminum chloride and 107 g. of sodium chloride was mechanically stirred at 200–220°, an intimate mixture of 136.5 g. of 3,6-dibromophthalic anhydride, m.p. 208–210° (section IV below) and 64 g. of hydroquinone was slowly added over a period of twenty-five minutes; after ten minutes a red color was noticed. When the addition had been completed, stirring was continued for twenty minutes. On cooling, the reddish-violet solid was pulverized, and decomposed by adding to 1500 cc. of dilute hydrochloric acid. The orange-red solid was filtered, well washed with warm water, and dried. It was then

extracted with warm alcohol. The yield of air-dried product was 149 g. (84%); it melts at 230–231° with preliminary softening at 221°. For purification it was recrystallized from acetic acid, from which it separated as red needles, m.p. 245°.

Anal. Calc'd for $C_{14}H_6Br_2O_4$: Br, 40.2. Found: Br, 39.9

2. *Formation of the dye base.* This was readily effected in three ways: heating the components in the presence of sodium acetate, or in the presence of boric acid, or refluxing the components in pyridine. Though each method gives a good product, the second is considered preferable.

A mixture of 640 g. of *p*-toluidine, 125 g. of boric acid, and 125 g. of the dibromoquinizarin was heated, with stirring, at 130–140° for three hours; a green color was noticed after a half hour. After cooling to about 75°, the melt was poured into 4 l. of dilute hydrochloric acid. The product was worked up in the usual manner. The yield was 135 g. (95%); m.p. 284–287°. The same substance, in essentially the same yield, was also secured by the use of 5,8-dichloroquinizarin (25). The product is easily recrystallized from aniline or chlorobenzene; the analytical sample melted at 311°.

Anal. Calc'd for $C_{28}H_{22}N_2O_4$: C, 74.7; H, 4.9.
Found: C, 74.9; H, 5.1.

Substances of identical appearance were equally easily secured by substituting *ortho-* and *meta*-toluidines in this procedure.

3. *Sulfonation; the dye, Toluidine Green.* To a solution of 2.7 g. of the above dye base in 27 g. of concentrated sulfuric acid, 17 g. of 60% oleum was added with cooling and stirring. After stirring for three hours at room temperature, the free acid was isolated by pouring upon ice. The sodium salt was then prepared by the same procedure as described under Toluidine Blue.

Toluidine Green could be secured equally well by the use of concentrated sulfuric acid alone, on the steam-bath, essentially as outlined under Toluidine Blue.

III. 1,4-DI-β-SULFATOETHYLAMINO-5,8-DIHYDROXYANTHRAQUINONE SERIES

A. *Degradation by oxidative hydrolysis.* When 5,8-di-β-hydroxyethylaminoquinizarin in a large volume of hot 50% acetic acid was treated with nitric acid, the solution rapidly became red. The flocculent precipitate that separated was collected and found to be 1,4,5,8-tetrahydroxyanthraquinone by a comparison of its properties (including the tetraacetate) with those of the synthetic material.

B. *Synthesis.*

1. *5,8-Di(β-hydroxyethylamino)quinizarin.* A solution of 4.5 g. of 5,8-dibromoquinizarin (m.p. 230–231°), 4.5 g. of ethanolamine, and 18 cc. of pyridine was refluxed with stirring for one hour; the solution became deep blue after a short time. After cooling to about 60°, the solution was poured into dilute hydrochloric acid. The precipitated rather gummy solid was filtered, washed with water, and dried by heating on the steam-bath. It was recrystallized from 20 cc. of boiling aniline, from which it separated in dark blue shining needles, m.p. 215–220° (with sublimation). The recrystallized material is quite soluble, with a blue-green color, in dioxane, methanol, ethanol, and acetone. 5,8-Di-(β-hydroxyethylamino)quinizarin has been made previously from leuco-1,4,5,8-tetrahydroxyanthraquinone (19).

Anal. Calc'd for $C_{18}H_{18}N_2O_6$: C 60.3; H, 5.0; N, 7.8.
Found: C, 60.6; H, 5.3; N, 8.1.

2. *Sulfation.* A solution of 10 g. of 5,8-di-(β-hydroxyethylamino)quinizarin in 10 cc. of concentrated sulfuric acid was warmed with stirring at 50–60° for thirty-five minutes. On cooling to room temperature, the viscous solution was mixed with ice

and was diluted to 300 cc. with cold water. Then, quite slowly, a solution of 14.1 g. of sodium hydroxide in 100 cc. of water was added to neutralize the sulfuric acid. The solution was evaporated to dryness on the steam-bath. The dye was then extracted in a Soxhlet apparatus with methyl alcohol for a hundred and forty-two hours. The yield was 6.2 g. (52.3%).

IV. DIBROMINATION OF PHTHALIC ANHYDRIDE

The treatment of phthalic anhydride with two equivalents of bromine leads to a mixture, as would be anticipated (12, 26, 27, 28, 29, 30). The principal product is said to be the 4,5-dibromophthalic anhydride (26, 27, 28, 29, 32), which is isolated by recrystallizing the reaction product from water. In one instance (30) it is recorded that, *once only*, 3,4-dibromophthalic acid was secured. The 3,6-isomer has never been so obtained, but only by oxidation of a ring compound (31).

When an attempt was made to prepare 4,5-dibromophthalic anhydride according to the literature, the product did not crystallize from water. A solid anhydride was readily secured, however, by the use of acetic acid; this proved to be the 3,6-isomer, never before isolated from the bromination mixture. Confirmatory evidence that the compound was 3,6-dibromophthalic anhydride was secured by the synthesis of Toluidine Green, described above, and by finding that the compound would not condense with hydroquinone in the presence of concentrated sulfuric acid. According to the patent literature (33), the last reaction is characteristic of phthalic anhydrides substituted in the 3 and 6 positions; all others condense readily. Since the anhydride has been obtained many times and by five different operators by the use of acetic acid, this result is not an accident.

After the isolation of the 3,6-anhydride, the acetic acid filtrate was concentrated nearly to dryness, and a portion dissolved in hot water. A considerable amount of 3,4-dibromophthalic acid separated from the cold solution. Another portion was taken up in acetic anhydride; some of the 4,5-anhydride crystallized.

Since this work was completed, it was reported (32) that a similar inability to isolate the 4,5-dibromophthalic acid had been encountered. These authors devised a procedure in which the desired acid was separated as a double salt, after partial neutralization, and isolated as the ester. On following their procedure, it was found that a mixture of 3,4- and 4,5-esters was secured; they were not readily separated, although some of the latter isomer crystallized out first.

The method of bromination outlined in the patent literature (12) was followed. The quantitative separation of the isomers has not been worked out, and the yields given only represent the amount of products readily isolated.

A. *3,6-Dibromophthalic anhydride series.* Starting with 400 g. of phthalic anhydride, 1200 g. of 60% oleum, 520 g. of bromine, and 2 g. of iodine, at about 60°, the

yield of 3,6-dibromophthalic anhydride, after recrystallizing three times from acetic acid, was 130–150 g. (m.p. 208–210°). Since the 4,5-isomer has a melting point in the same range, mixed melting points are essential for distinguishing between the two. The analytical sample was recrystallized to constant melting point (212–214°) from acetic acid.

Anal. Calc'd for $C_8H_2Br_2O_3$: Br, 52.3. Found: Br, 52.3.

This anhydride was also isolated during the various fractional crystallizations of mixtures.

B. *3,4-Dibromophthalic acid series.* When water was used, as suggested in the patent, sixteen days elapsed before the first solid (17 g.) crude 3,4-dibromophthalic acid separated. After four recrystallizations from water, it melted at 197° with decomposition.

Anal. Calc'd for $C_8H_4Br_2O_4$: Br, 49.4. Found: Br, 49.1.

It was more readily secured, (50 g.) from the filtrate obtained in A, by removing as much of the acetic acid as possible on the steam-bath and dissolving the residue in the minimum of hot water.

The acid was condensed with hydroquinone in a sodium-aluminum chloride melt to give 5,6-dibromoquinizarin. The new substance separated from chlorobenzene in reddish-brown needles, m.p. 227°.

Anal. Calc'd for $C_{14}H_6Br_2O_4$: Br, 40.2. Found: Br, 40.1.

The methyl ester was secured by the customary procedure. It separated from methanol in short rods, m.p. 79°. A mixed melting point with the isomeric 4,5-dibromo ester (m.p. 81°) was 55–65°.

Anal. Calc'd for $C_{10}H_8Br_2O_4$: C, 34.1; H, 2.3.
Found: C, 34.0; H, 2.2.

The acid is regenerated without difficulty on hydrolysis.

C. *4,5-Dibromophthalic acid series.* When the acetic acid filtrate from A was concentrated nearly to dryness on the steam-bath, and the residue dissolved in 500 cc. of hot acetic anhydride, a brown solution resulted. On cooling, the anhydride separated; after one recrystallization from acetic acid, it amounted to 40 g. The melting point was 212–214°; a mixture of this and the 3,6-isomer melted over the range 175–190°.

When the acid double salt procedure (32) was followed, the yield of methyl 4,5-dibromophthalate was 27 g. from 400 g. of phthalic anhydride. The double salt is a mixture, containing both the 4,5- and 3,4-dibromophthalic acids for, on esterification, both the esters result. The mixture is not readily separated, though some of the 4,5-ester crystallizes first. The residue of mixed crystals (m.p. 55–60°) is unaffected by repeated recrystallizations from methanol or petroleum ether.

6,7-Dibromoquinizarin was prepared in the same way as the other homologs. It also separated as red needles from xylene, m.p. 296–298°.

Anal. Calc'd for $C_{14}H_6Br_2O_4$: Br, 40.2. Found: Br, 40.0

We are pleased to acknowledge the technical assistance of our associates in the Kodak Research Laboratories.

SUMMARY

1. The structures of the isomeric dyes Toluidine Blue and Toluidine Green have been determined by degradation and synthesis. Toluidine Blue is the disodium salt of the 2′-disulfonic acid of 1,5-di-4′-toluidino-

4,8-dihydroxyanthraquinone, while in Toluidine Green the groups are in the 1,4 and 5,8 positions, respectively.

2. The usefulness of oxidative and reductive hydrolysis has been pointed out.

3. A new, unambiguous method of synthesis of 1,4,5,8-tetrahydroxyanthraquinone has been given.

4. The dibromination of phthalic anhydride has been described. Three of the four possible isomeric dibromophthalic acids have been secured.

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(7) German Patent 89,090, *Frdl.*, **4**, 314 (1894–1897), describes a blue substance without orienting the groups; German Patent 136,778, *Frdl.*, **6**, 381 (1900–1902), uses a 1,5-di-*p*-toluidino-4,8-dihydroxyanthraquinone which, they say, is obtainable from German Patent 89,090.
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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

ORIENTATION IN THE FRIES REARRANGEMENT OF PHENYL CAPRYLATE

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Any explanation of the mechanism of the Fries rearrangement should be based upon the fact that metallic complexes and not the original components are the reacting substances. Some of these complexes have been isolated and identified while others still have a hypothetical existence. Phenoxyaluminum dichloride was shown to be a reacting component by Sandulesco and Girard (1) and the formation of an acid chloride-aluminum chloride complex was demonstrated by Perrier (2), Böeseken (3) and Kohler (4). A ketone-aluminum chloride complex was isolated by Olivier (5), and it was stated by this author and also by Groggins (6) that this complex could not promote further acylations. Recently Ralston, McCorkle, and Bauer (7) have shown that the products resulting from a Fries rearrangement are dependent upon the molecular ratio of aluminum chloride employed and have suggested that there is a relation between the amount of aluminum chloride and the reacting complexes present.

Previous knowledge of the Fries mechanism has been obtained from the completed reactions rather than a study of the reaction at intermediate points. Some knowledge of the mechanism of the rearrangement should be obtained by a study of the reaction products present at intermediate points. We have, therefore, made a study of the rearrangement of phenyl caprylate with the purpose of determining the products which are present at a number of intermediate stages in the reaction. One series of runs has been made in which the amount of aluminum chloride used was approximately molecularly equivalent to the ester, another series in which decidedly less aluminum chloride was used, and another in which the amount of aluminum chloride was materially in excess of an equal molecular ratio. In attempting to correlate these data we have also studied the rearrangement of phenyl caprylate by various aluminum chloride complexes rather than aluminum chloride itself.

Table I shows the products obtained at various time intervals when phenyl caprylate is rearranged in the presence of a 1.1 mole ratio of aluminum chloride in tetrachloroethane at 100°.

The increase in the value for p/o as the reaction progresses is extremely

significant. It can readily be seen that any comparison of the effect of reaction conditions upon orientation when equal molecular proportions of ester and aluminum chloride are used must take into consideration the percentage of ester rearranged.

Another run under similar conditions using equal molecular proportions of ester and aluminum chloride gave, after fifteen minutes, 64% phenyl caprylate, 5.4% *p*-hydroxycaprylophenone, and 23.6% *o*-hydroxycaprylophenone or a *p/o* value of 0.23. After six hours the ester decreased to 7.3% and the para and ortho hydroxy ketones increased to 29.1% and 58.5% respectively giving a value of 0.50 for *p/o*.

In our previous work (7) upon the rearrangement of phenyl caprylate by aluminum chloride and also upon the acylation of phenol by caprylyl chloride, we have shown that an increase in the amount of aluminum chloride employed increased the value for the ratio *p/o*. It was shown that when there was only sufficient aluminum chloride present to form the

TABLE I

REARRANGEMENT OF PHENYL CAPRYLATE BY 1.1 MOLES OF ALUMINUM CHLORIDE AT 100°. SOLVENT: TETRACHLOROETHANE

RUN NO.	TIME (MIN.)	% PARA	% ORTHO	% ESTER	*p/o*
1	15	8.6	18.2	66.0	0.47
2	30	18.5	29.5	46.5	.63
3	60	30.8	32.2	30.8	.95
4	120	35.5	41.0	18.2	.87
5	240	40.5	43.1	10.5	.94

complex $C_6H_5OAlCl_2$ a preferential ortho orientation was obtained, but if the complex $C_7H_{15}COCl \cdot AlCl_3$ is present the orientation is preferentially para. If the mechanism of the rearrangement of phenyl caprylate is a splitting followed by an acylation and removal of the aluminum chloride as a ketone complex, the ratio of aluminum chloride to reacting products should be highest at the initial stages of the reaction, and the orientation should be preferentially para during this period. Since this is not the case, it appears that the aluminum chloride must be rather firmly held by the ester. The addition of one-tenth mole of aluminum chloride to one-tenth mole of phenyl caprylate dissolved in 50 cc. of tetrachloroethane produced a temperature rise of 20.5°. Since no hydrogen chloride was evolved and since an addition of the same amount of aluminum chloride to 50 cc. of tetrachloroethane produced no temperature rise, it appears that the ester itself forms a complex with aluminum chloride. This ester-aluminum chloride complex is probably also present in the Friedel-Crafts

acylation of phenol, since partially completed reactions show substantial amounts of ester.

The mechanism of the rearrangement as postulated by Rosenmund and Schnurr (8), Skraup and Poller (9), and also Cox (10) assumes that the ester splits into phenoxyaluminum dichloride and acid chloride, followed by a reaction of acylation. The rearrangement of the phenyl caprylate-aluminum chloride complex would be as follows:

$$C_6H_5OCC_7H_{15} \rightarrow C_6H_5OAlCl_2 + C_7H_{15}COCl \rightarrow Cl_2AlOC_6H_4COC_7H_{15} + HCl$$

$$\begin{matrix} \| \\ O \\ | \\ AlCl_3 \end{matrix}$$

In the acylation of phenoxyaluminum dichloride by caprylyl chloride, it has been shown that the acyl group replaces an ortho hydrogen preferentially, and it appears that ortho substitution predominates at the initial stage of the reaction. If this is the only reaction which takes place, however, it is difficult to explain why the value for p/o changes as the reaction proceeds. Since $AlCl_2OC_6H_4CC_7H_{15}$ contains the group $AlCl_2O$—, previ-

$$\begin{matrix} \| \\ O \end{matrix}$$

ously shown to be reactive, and also the keto group, which could possibly remove aluminum chloride from the ester complex, it is probable that this product becomes a reacting component.

In order better to evaluate the action of the various reacting complexes a series of runs was made in which materially less than a molecular equivalent of aluminum chloride was present.

Table II shows the products obtained when phenyl caprylate is rearranged with 0.5 mole ratio of aluminum chloride in tetrachloroethane at 100°.

Since the over-all yield of ketone has materially exceeded the molecular amount of aluminum chloride added, the later stages of the rearrangement must be brought about by aluminum chloride complexes of the ketones. The decided increase in the value for p/o is significant. The data presented in Table II show that the *o*-hydroxy ketone forms much faster than the *p*-hydroxy ketone in the early stages of the reaction, but the rearrangement produces almost entirely *p*-hydroxy ketone after fifty per cent of the ester has been rearranged. Since this point corresponds molecularly to the amount of aluminum chloride added, it appears that rearrangement brought about by aluminum chloride complexes produces essentially para ketone. It appears that after the rearrangement has progressed to any appreciable extent we are dealing with at least two separate reactions, one of which orients essentially ortho and predominates in the early stages, and the

second of which orients para and is the dominant reaction as the rearrangement proceeds towards completion.

A rearrangement of phenyl caprylate conducted for six hours at 100° in the presence of 0.25 mole per cent of aluminum chloride gave 20.0% *p*-hydroxycaprylophenone, 16.0% of *o*-hydroxycaprylophenone, and 46.5% of phenyl caprylate. These values are in substantial agreement with those of the previous runs.

When phenyl caprylate was allowed to react with an equal molecular amount of phenoxyaluminum dichloride in tetrachloroethane for six hours at 100°, the product consisted of 52.0% *p*-hydroxycaprylophenone, 38.2% *o*-hydroxycaprylophenone, 5.0% phenyl caprylate, and a trace of caprylic acid. The value for *p/o* is 1.36. This demonstrates that phenoxyaluminum dichloride is capable of rearranging phenyl caprylate and that it gives a higher value for *p/o* than when aluminum chloride is used in equal molecular amounts under similar conditions, and that the value for *p/o*

TABLE II

REARRANGEMENT OF PHENYL CAPRYLATE BY 0.5 MOLE OF ALUMINUM CHLORIDE AT 100°. SOLVENT: TETRACHLOROETHANE

RUN NO.	TIME (MIN.)	% PARA	% ORTHO	% ESTER	*p/o*
6	30	10.9	19.1	62.3	0.57
7	60	19.1	22.3	53.0	0.86
8	120	31.0	25.4	34.5	1.22
9	360	41.0	25.4	24.5	1.62

corresponds to that obtained when a deficient amount of aluminum chloride is employed.

Phenyl caprylate was treated with an equal molecular proportion of the previously formed aluminum chloride salt of *o*-hydroxycaprylophenone in tetrachloroethane for six hours at 100°. The recovery of *o*-hydroxycaprylophenone was 96.4%; 58.2% of the original ester was recovered unchanged, and 19.1% formed *p*-hydroxycaprylophenone. Ten and eight-tenths per cent of the ester was recovered as caprylic acid, the formation of which is of interest and will be discussed later. It is apparent that the aluminum chloride salt of *o*-hydroxycaprylophenone is capable of rearranging phenyl caprylate, although it is in no wise as effective as phenoxyaluminum dichloride or aluminum chloride. The orientation is predominantly para.

When phenyl caprylate reacted with an equal molecular equivalent of the aluminum chloride salt of *p*-hydroxycaprylophenone under similar conditions, considerable decomposition was observed. Only 70.5% of the original *p*-hydroxycaprylophenone was recovered. Twenty-one and

eight-tenths per cent of the original ester was recovered and 7.7% isolated as *o*-hydroxycaprylophenone. The reaction product also contained 27.3% of caprylic acid. It is evident that considerable rearrangement of the phenyl caprylate was encountered under these conditions, but because of the decomposition no definite conclusion can be drawn as to the orientation.

It is apparent that the aluminum chloride salts of hydroxy ketones are capable of rearranging phenyl esters, and this accounts for yields of ketones molecularly greater than the amount of aluminum chloride employed. In order to determine the influence of the keto group alone upon this rearrangement, we treated phenyl caprylate with an equal molecular amount of a previously formed aluminum chloride complex of caprylophenone. The reaction was conducted under the same conditions as those described with the hydroxy ketones. Only 10.9% of the phenyl caprylate was recovered unchanged. Thirty-one and eight-tenths per cent was rearranged to *p*-hydroxycaprylophenone, 29.5% appeared as *o*-hydroxycaprylophenone, and 27.6% of the ester appeared as caprylic acid. The formation of this acid is characteristic of runs in which phenyl caprylate was rearranged with 0.25 mole and 0.50 mole of aluminum chloride as well as rearrangements brought about by the aluminum chloride complex of caprylophenone and aluminum chloride salts of *o*- and *p*-hydroxycaprylophenone. It appears that there is a direct correlation between rearrangements as brought about by ketone or hydroxy ketone complexes, and rearrangements in the presence of deficient amounts of aluminum chloride.

The study of the rearrangement as brought about by the use of a molecular equivalent of aluminum chloride or less indicates that under these conditions reactions other than a splitting of an ester complex followed by an acylation must be considered.

The first reaction in the rearrangement is evidently the formation of an ester-aluminum chloride complex followed by a splitting of this complex to phenoxyaluminum dichloride and acid chloride as follows:

$$C_6H_5O\underset{\underset{O\cdot AlCl_3}{\|}}{C}C_7H_{15} \rightarrow C_6H_5OAlCl_2 + C_7H_{15}\underset{\underset{O}{\|}}{C}Cl \rightarrow AlCl_2OC_6H_4COC_7H_{15} + HCl$$

This splitting does not take place instantaneously, and at intermediate points we have present ester-aluminum chloride complex, phenoxyaluminum dichloride, acid chloride, and aluminum salts of the isomeric hydroxycaprylophenones. It seems probable that the acid chloride does not form an aluminum chloride complex by removing the aluminum chloride from the ester complex under these conditions, since *o*-hydroxy ketones are preferentially formed at the beginning of the Fries rearrangement. We

have previously shown (7) that high values for p/o are obtained when an acid chloride-aluminum chloride complex is present during an acylation. The statement that the acid chloride complex is not present under these conditions is in conformity with the findings of Norris and Sturgis (11) who showed that by rearranging phenyl acetate with a molecular equivalent of aluminum chloride, using benzene as a solvent, no acetophenone was formed, but when two molecular equivalents of aluminum chloride were employed the formation of acetophenone was the predominant reaction. The formation of acetophenone would probably require the presence of an acid chloride-aluminum chloride complex.

If splitting followed by acylation is the only reaction which occurs, we should obtain a constant value for p/o which is independent of the percentage of ester rearranged. The formation of any appreciable amount of aluminum chloride salts of hydroxy ketones will cause a competition between the ester and the ketonic group for the aluminum chloride. The formation of an irreversible ketone complex in certain acylations has been conclusively shown by many workers. If this holds for the rearrangement of phenyl esters with a molecular equivalent of aluminum chloride, it is evident that when the reaction has proceeded half way, the only aluminum chloride available to bring about further rearrangement is that attached to the hydroxyl group of the hydroxy ketone. A similar condition is encountered when less than a molecular equivalent of aluminum chloride is employed to bring about the rearrangement.

We have shown that $C_6H_5OAlCl_2$ is capable of rearranging phenyl caprylate. The following mechanism is proposed:

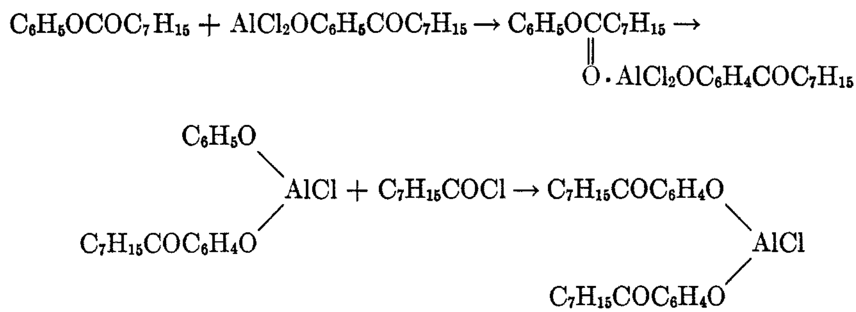
$$C_6H_5OCOC_7H_{15} + C_6H_5OAlCl_2 \rightarrow C_6H_5O\underset{\substack{\| \\ O\cdot AlCl_2OC_6H_5}}{C}C_7H_{15} \rightarrow$$

$$\begin{array}{l} C_6H_5O \diagdown \\ \qquad AlCl \\ C_6H_5O \diagup \end{array} + C_7H_{15}\underset{\substack{\| \\ O}}{C}Cl \rightarrow \begin{array}{l} C_7H_{15}COC_6H_5O \diagdown \\ \qquad\qquad\qquad AlCl \\ \qquad\quad C_6H_5O \diagup \end{array} + HCl$$

The aluminum chloride complex hydrolyzes to hydroxycaprylophenones and phenol.

Since it has been further shown that the aluminum chloride salts of hydroxycaprylophenones are capable of rearranging phenyl caprylate, it

may be assumed that these rearrangements follow a similar course, thus:



The formation of caprylic acid in the runs previously described is possibly due to the slow rate of acylation of the intermediate complex.

This reaction forms mostly para ketone and is encountered under conditions where there is a competition for the aluminum chloride, such as runs in which a molecular equivalent or less of aluminum chloride is employed, or when an aluminum chloride complex is used to effect the rearrangement. It also accounts for the observations that the amount of hydroxy ketones formed is greater than the molecular amount of aluminum chloride employed.

When more than an equal molecular proportion of aluminum chloride is used in the rearrangement of phenyl caprylate, we have free aluminum chloride present in addition to the ester-aluminum chloride complex during the first part of the reaction. This permits the formation of the complex $C_7H_{15}\underset{\underset{O}{\|}}{C}Cl \cdot AlCl_3$, the presence of which materially changes the reaction mechanism.

Table III shows the products obtained at various time intervals when phenyl caprylate is rearranged in the presence of 1.3 mole ratio of aluminum chloride in tetrachloroethane at 100°.

In addition to the compounds shown in Table III, substantial amounts of *p*-caprylylphenyl caprylate were isolated and identified in the first three runs. The amount of this compound present was 9.1% in the forty second run, 10.9% in the five minute, and 6.8% in the fifteen minute run. It was not present in the one and two hour runs. Its isolation, as an intermediate in this rearrangement, throws considerable light upon the reaction mechanism.

Table IV shows the products formed when the amount of aluminum chloride is increased to two moles.

It will be noted that increase in the amount of aluminum chloride greatly

increases the reaction rate. In the two mole run, the rate is so rapid that it is impossible to follow the course of the reaction. When an excess of aluminum chloride is employed, we do not observe a shift in the value of *p/o* as the rearrangement progresses, and it appears that the reaction mechanism differs from runs where a deficient amount of aluminum chloride is used.

It is believed that when substantially more than one molecular equivalent of aluminum chloride is employed the mechanism of the rearrangement of phenyl caprylate is as follows:

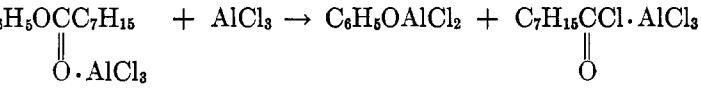


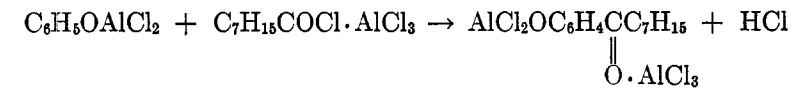
TABLE III

REARRANGEMENT OF PHENYL CAPRYLATE BY 1.3 MOLES OF ALUMINUM CHLORIDE AT 100°. SOLVENT: TETRACHLOROETHANE

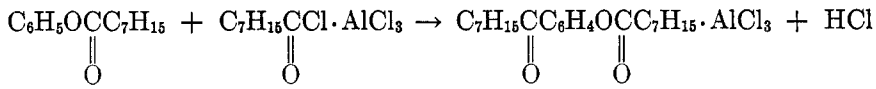
RUN NO.	TIME (MIN.)	% PARA	% ORTHO	% ESTER	*p/o*
10	40 sec.	3.64	0.0	81.5	
11	5	23.2	12.3	52.3	1.88
12	15	33.2	16.8	39.5	1.97
13	60	49.5	28.9	19.3	1.71
14	120	54.5	30.1	12.6	1.81

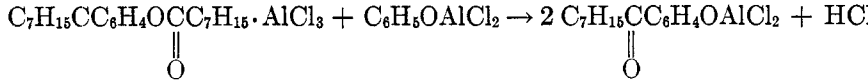
The reaction then follows one of two courses:

1. The phenoxyaluminum dichloride may be acylated, thus:



2. The ester may be acylated and this product reacts with phenoxyaluminum dichloride, thus:





The more ester present, the greater the probability of the second mechanism, which means that it is the dominant reaction in the early stages of the rearrangement.

In order to study further this second mechanism, 0.05 mole of *p*-caprylylphenyl caprylate was reacted with 0.05 mole of phenol and 0.13 mole of aluminum chloride for six hours at 100° in tetrachloroethane. This resulted in the formation of 83.6% *p*-hydroxycaprylophenone and 15.9% *o*-hydroxycaprylophenone. The theoretical yield of para isomers which could be formed by scission of the *p*-caprylylphenyl caprylate is 50%. The acylation of the phenol, therefore, under these conditions resulted in 33.6% of *p*- and 15.9% of *o*-hydroxy ketones and the value for *p/o* is 2.1 which indicates that there is a preference for the formation of the para isomer.

That *p*-caprylylphenyl caprylate is an intermediate in the rearrangement of phenyl caprylate where excess aluminum chloride is employed is shown by a run in which phenyl caprylate was brought into reaction with two moles of aluminum chloride for 30 minutes at 50°. The products consisted of 17.7% *p*-hydroxycaprylophenone, 17.0% *o*-hydroxycaprylophenone, 39.1% phenyl caprylate, and 18.6% *p*-caprylylphenyl caprylate. No *o*-caprylylphenyl caprylate was isolated in any of the runs.

TABLE IV

REARRANGEMENT OF PHENYL CAPRYLATE BY 2.0 MOLES OF ALUMINUM CHLORIDE AT 100°. SOLVENT: TETRACHLOROETHANE

RUN NO.	TIME (MIN.)	% PARA	% ORTHO	% ESTER	*p/o*
15	5	55.5	38.6	2.3	1.44
16	15	56.0	40.0	0.9	1.40

In another run 0.1 mole of phenyl caprylate was added to 0.1 mole of aluminum chloride in tetrachloroethane and to this was added 0.1 mole of caprylyl chloride and 0.1 mole of aluminum chloride. We thus have present an ester-aluminum chloride complex and a caprylyl chloride-aluminum chloride complex. The product consisted of 10.1% *o*-hydroxycaprylophenone, 12.1% *p*-hydroxycaprylophenone, 7.2% caprylic acid, 2.3% phenyl caprylate, and 52.0% *p*-caprylophenyl caprylate.

In a previous paper we stated that *o*-hydroxycaprylophenone did not rearrange to *p*-hydroxycaprylophenone when heated for six hours with two moles of aluminum chloride at 100° in the presence of tetrachloroethane, and that the para isomer does not rearrange to the ortho isomer under similar conditions. The work of Eykmann (12), Rosenmund and Schnurr (8), and Stoughton (13) shows that high temperatures favor the formation of para isomers. Rosenmund and Schnurr rearranged *p*-acetylcresol to *o*-acetylcresol by heating the former for 30 minutes at 170° and Stoughton showed that 4-acetylnaphthol rearranged to 2-acetylnaphthol when heated with an equal weight of aluminum chloride for three hours

at 100–120°. It seems probable that the value for *p/o* is dependent to some extent on the temperature, since in the rearrangement of phenyl caprylate there have been shown to be at least two simultaneous reactions, the products of which do not have similar values for the ratio *p/o*. We have, therefore, investigated the effect of temperature upon the rearrangement of phenyl caprylate in the presence of aluminum chloride.

Table V shows the effect of temperature upon the rearrangement of phenyl caprylate in the presence of an equal molecular proportion of aluminum chloride.

Although it has been observed that data concerning the effect of a reaction condition upon orientation must be compared at substantially the same percentage conversion of the ester, it is apparent that the value for *p/o* is higher at the lower temperature than at 100°. It appears, therefore, that low temperatures favor the formation of *p*-hydroxy ketones in the rearrangement of phenyl caprylate. That this is not due to a rearrangement of *p*-hydroxycaprylophenone to *o*-hydroxycaprylophenone is shown by the fact when 0.1 mole of *p*-hydroxycaprylophenone was refluxed with 0.13 mole of aluminum chloride in tetrachloroethane for two hours at 146° the recovery of *p*-hydroxycaprylophenone was 99.6%.

TABLE V

EFFECT OF TEMPERATURE UPON THE REARRANGEMENT OF PHENYL CAPRYLATE WITH ONE MOLE RATIO OF ALUMINUM CHLORIDE. SOLVENT: TETRACHLOROETHANE

RUN NO.	TEMP., °C.	TIME	% PARA	% ORTHO	% ESTER	*p/o*
17	25	7 days	5.9	7.7	81.4	0.76
18	50	8 hrs.	4.5	8.2	77.8	.55
19	50	30 hrs.	17.7	20.0	51.0	.88
1	100	15 min.	8.6	18.2	66.0	.47

When 0.1 mole of *p*-hydroxycaprylophenone was heated with 0.13 mole of aluminum chloride at 180° for three hours, the product consisted of 59% *o*- and 10.5% *p*-hydroxycaprylophenone and 21.7% residue. Rearrangement of *p*-hydroxycaprylophenone to the ortho isomer, therefore, takes place at temperatures above 146°. It appears that tetrachloroethane does not influence orientation, since when 0.1 mole of phenylcaprylate was rearranged with 0.13 mole of aluminum chloride at 100° for six hours in the absence of a solvent we obtained 64% para- and 34.6% ortho-hydroxycaprylophenone, which gives a value for *p/o* of 1.85. This value is in agreement with the value of 1.81 obtained when this ester was rearranged in the presence of tetrachloroethane under similar conditions (Run 14). When phenyl caprylate was rearranged in the presence of 0.1 mole of alumi-

num chloride in the absence of a solvent, the product consisted of 24.0% of *p*-hydroxycaprylophenone and 63.5% of the ortho isomer. The increase in temperature from 100° to 190° greatly increased the percentage of ortho isomer.

EXPERIMENTAL

The following procedures are typical examples of runs reported in this article.

Fries rearrangement of phenyl caprylate. Phenyl caprylate (22 g., 0.1 mole) prepared as previously described (7) was dissolved in 60 cc. of tetrachloroethane and the mixture placed in a three-necked flask, equipped with a mechanical stirrer and thermometer. The solution was heated to 80° and aluminum chloride (13.3 g., 0.1 mole) added. The reaction mixture was heated for six hours at 100° after which it was hydrolyzed, steam distilled and the isomers separated and analyzed as previously described (7).

In those runs in which *p*-caprylylphenyl caprylate appeared, it was separated from the ortho ester fraction by fractional distillation. The compound was identified by mixed melting point with an authentic sample.

Reaction of phenyl caprylate with phenoxyaluminum dichloride. Phenol (9.4 g., 0.1 mole) was dissolved in 50 cc. of tetrachloroethane and aluminum chloride (13.3 g., 0.1 mole) was added. The mixture was heated at 100° until hydrogen chloride ceased to be evolved. Phenyl caprylate (22 g., 0.1 mole) was added and the mixture heated for six hours at 100°. The product was hydrolyzed, steam distilled, and the isomers separated as previously described. The excess phenol was removed during the steam distillation. The product consisted of 11.5 g. (52%) of *p*-hydroxycaprylophenone, 8.4 g. (38.2%) of *o*-hydroxycaprylophenone, 1.1 g. (5.0%) of phenyl caprylate, and a trace of caprylic acid which was separated from the para fraction. The caprylic acid was separated from *p*-hydroxycaprylophenone by fractional distillation and was identified as the diamide of 4,4′-diaminodiphenylmethane, m.p. and mixed m.p. 182–183° (14).

Reaction of phenyl caprylate with the aluminum chloride salt of o-hydroxycaprylophenone. *o*-Hydroxycaprylophenone (22 g., 0.1 mole) was dissolved in 50 cc. of tetrachloroethane and aluminum chloride (13.3 g., 0.1 mole) added. There was a considerable evolution of hydrogen chloride during the addition of aluminum chloride. After heating to 100° for a short time to complete the reaction, phenyl caprylate (22.0 g., 0.1 mole) was added and the mixture heated for six hours at 100°. The product was treated in the usual manner. Ninety-six and four-tenths per cent of the *o*-hydroxycaprylophenone was recovered unchanged and also 58.2% of the phenyl caprylate. The yield of *p*-hydroxycaprylophenone was 19.1%. An additional 10.8% of phenyl caprylate was recovered as caprylic acid.

Reaction of phenyl caprylate with the aluminum chloride salt of p-hydroxycaprylophenone. The same procedure was used in this experiment as in the preceding example except that the *o*-hydroxycaprylophenone was replaced by *p*-hydroxycaprylophenone. Seventy and five-tenths per cent of the *p*-hydroxycaprylophenone was recovered unchanged together with 21.8% of the original ester. The yield of *o*-hydroxycaprylophenone was 77%. Caprylic acid (27.3%) was also recovered.

Reaction of phenyl caprylate with aluminum chloride-caprylophenone complex. Caprylophenone (20.3 g., 0.1 mole) was dissolved in 50 cc. of tetrachloroethane and aluminum chloride (13.3 g., 0.1 mole) added. After heating to 100°, phenyl caprylate

(22.0 g., 0.1 mole) was added and the heating continued for 6 hours. The product was treated in the customary manner. The mixture of phenyl caprylate, *o*-hydroxycaprylophenone and caprylophenone obtained after removing the para ketone and caprylic acid with sodium hydroxide was distilled. The residue (10 g., 49.5%) was assumed to be a decomposition product of the complex, aluminum chloride-caprylophenone. Ten and nine-tenths per cent of the ester was recovered unchanged and 27.6% appeared as caprylic acid. The yield of *p*-hydroxycaprylophenone was 31.8% and that of *o*-hydroxycaprylophenone 29.5%.

Preparation of p-*caprylylphenyl caprylate.* *p*-Hydroxycaprylophenone (22.0 g., 0.1 mole) was heated with caprylyl chloride (18 g., 0.11 mole) to approximately the boiling point of caprylyl chloride for one hour. The product was distilled; a small amount of caprylyl chloride came over followed by 33 g. (95%) of the ester, b.p. 215–225°/1 mm., which solidified upon standing. Upon crystallization from either ethanol or petroleum ether (b.p. 60–68°) the m.p. was 56.5–57.5°.

Anal. Calc'd for $C_{22}H_{34}O_3$: C, 76.9; H, 10.2.

Found: C, 77.0; H, 10.4.

Reaction of p-*caprylylphenyl caprylate with phenoxyaluminum dichloride.* *p*-Caprylylphenyl caprylate (17.3, 0.05 mole) was dissolved in 50 cc. of tetrachloroethane together with phenol (4.7 g., 0.05 mole), and aluminum chloride (13.3 g., 0.1 mole) was added. The reaction was heated for six hours at 100° and the products isolated as previously described. The following yields of products were obtained: *p*-hydroxycaprylophenone 18.4 g. (83.6%) and *o*-hydroxycaprylophenone 3.5 g. (15.9%).

Reaction of caprylyl chloride with phenyl caprylate. Phenyl caprylate (22.0 g., 0.1 mole) was dissolved in 50 cc. of tetrachloroethane and aluminum chloride (13.3 g., 0.1 mole) added. During the addition of the aluminum chloride there was a continuous temperature rise from 27° to 55°. Caprylyl chloride (16.2 g., 0.1 mole) was added rapidly. No temperature rise was observed during this addition. An additional 13.3 g. (0.1 mole) of aluminum chloride was now added and the reaction heated for 3 hours at 90–95°. The product was hydrolyzed and the isomers separated in the manner previously described. The yields were as follows: *p*-caprylylphenyl caprylate 18.0 g. (52.0%), *o*-hydroxycaprylophenone 3.0 g., (13.6%), phenyl caprylate 0.8 g. (3.6%), caprylic acid 2.5 g. (8.7%), and *p*-hydroxycaprylophenone 4.2 g. (19.1%). From the alkali-soluble fraction there was isolated in addition to caprylic acid and *p*-hydroxycaprylophenone a material (3.1 g., 8.9%), b.p. 205–220°/1 mm., which was considered to be a hydroxy diketone.

Attempted rearrangement of p-*hydroxycaprylophenone.* *p*-Hydroxycaprylophenone (22.0 g., 0.1 mole) was dissolved in 50 cc. of tetrachloroethane, and aluminum chloride (17.5 g., 0.13 mole) added. The reaction was refluxed for 2 hours, hydrolyzed, and steam distilled to remove the tetrachloroethane. From the residue by alkali extraction was isolated 21.9 g. (99.0%) of *p*-hydroxycaprylophenone.

Under similar conditions *o*-hydroxycaprylophenone was recovered unchanged, (20.5 g., 93.0%).

Rearrangement of p-*hydroxycaprylophenone.* *p*-Hydroxycaprylophenone (22.0 g., 0.1 mole) was heated with aluminum chloride (18.3 g., 0.1 mole) for 1 hour at 170–190°. The reaction product was treated in the usual manner. From the product was isolated 2.3 g. (10.5%) of *p*-hydroxycaprylophenone, and 13 g. (59.0%) of *o*-hydroxycaprylophenone. The 2,4-dinitrophenylhydrazone of the ortho ketone melted at 143–144° alone or mixed with an authentic sample (15).

Rearrangement of phenyl caprylate without solvent (170–190°). Phenyl caprylate

(22.0 g., 0.1 mole) was heated with aluminum chloride (17.3 g., 0.13 mole) for 1 hour at 170–190°. The reaction mixture was then cooled, hydrolyzed, and the isomers separated as previously described. *p*-Hydroxycaprylophenone (5.3 g., 24%) and *o*-hydroxycaprylophenone (14.0 g., 63.5%) were isolated.

Rearrangement of phenyl caprylate without solvent (90–100°). The above reaction was conducted at 90–100° for 4 hours. The yield of products was, *p*-hydroxycaprylophenone 14.1 g., (64.0%) and *o*-hydroxycaprylophenone 7.6 g., (34.6%).

SUMMARY

1. A study of the partially completed and completed rearrangements of phenyl caprylate in the presence of varying molecular proportions of aluminum chloride has been made. Phenyl caprylate was rearranged by means of the various aluminum chloride complexes which were considered likely to be present in the rearrangement of phenyl caprylate.

2. When approximately equal molecular proportions or less of aluminum chloride are used to effect the rearrangement, the value of *p/o* increases as the reaction progresses.

3. The molecular amount of ester rearranged is greater than the molecular equivalent of aluminum chloride employed if the amount of aluminum chloride is less than a molecular proportion.

4. Phenoxyaluminum dichloride, the aluminum chloride salts of *o*- and *p*-hydroxycaprylophenone, and the aluminum chloride complex of caprylophenone bring about the rearrangement of phenyl caprylate.

5. When substantially more than molecular proportions of aluminum chloride are employed, the ratio of isomers is essentially independent of the amount of ester rearranged. *p*-Caprylylphenyl caprylate has been identified as an intermediate when sufficient aluminum chloride is present to form the caprylyl chloride-aluminum chloride complex.

6. Temperatures above 140° favor the formation of *o*-hydroxycaprylophenone. *p*-Hydroxycaprylophenone rearranges to *o*-hydroxycaprylophenone at 180°.

7. Some suggestions as to the various mechanisms involved have been proposed.

CHICAGO, ILL.

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MERCAPTOTHIAZOLES: OXIDATION AND ALKYLATION STUDIES

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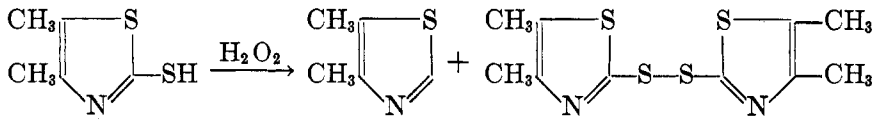
Since the discovery (1) of the presence of the thiazole nucleus in vitamin B_1, there has been a revival of interest in chemistry pertaining to the thiazole ring (2). We have investigated the feasibility of preparation of thiazoles unsubstituted in the 2 position from the readily obtainable 2-mercapto compounds, since the problem has a bearing on possible vitamin syntheses.[1] The oxidative replacement by hydrogen of the mercapto group in compounds containing the grouping —N=C(—SH)—N= in which the mercapto group is joined to a heterocyclic ring is easily accomplished (3), and it was to be expected that analogous methods would be successful with mercaptothiazoles which correspond to the type —N=C(—SH)—S—.

In fact, the oxidation of 2-mercapto-4-methylthiazole by hydrogen peroxide in both neutral and alkaline solution has already been reported by Ochiai and Nagasawa (2b); 4-methylthiazole is formed in the former case, 4-methylthiazole-2-sulfonic acid in the latter. The oxidation of 2-mercaptothiazoles by peroxide has also been the subject of several patents (4). The reaction is carried out in strongly acid medium, and high yields of the corresponding unsubstituted thiazoles are claimed. Apparently other oxidizing agents have not previously been employed in this connection.

The present paper deals with a study of the oxidation of 2-mercapto-4,5-dimethylthiazole, using as oxidizing agents hydrogen peroxide and nitric acid (3), both of which reagents have been used to remove SH groups from analogous ring structures. Hydrogen peroxide was employed in neutral solution and in conjunction with varying amounts of acid, with the results which are summarized in the accompanying table. It is evident that, while some of the desired thiazole is produced by neutral peroxide, it is advisable to work at moderately high acid concentrations. When the reaction is carried out in neutral or slightly acid solutions 4,5-dimethylthiazole-2 disulfide forms the bulk of the reaction product,

[1] The possibility of effecting this reaction by use of either hydrogen peroxide or nitric acid was first pointed out by one of us (E. R. B.) in French Patent 803495 (1936) issued to the Research Corporation.



while at high acid concentrations this oxidation product is not detected. Dilute nitric acid was found also to be an efficient agent for removal of the mercapto group. The yield of unsubstituted thiazole is about the same as when strongly acid peroxide is used; no by-products were isolated.

The 2-mercaptothiazoles are easily prepared from ammonium dithiocarbamate plus the proper α-halogeno ketone. The analogous reaction with dithiocarbamic esters should lead to thiazole-2 thioethers. This was confirmed by experiment: methyl dithiocarbamate gave with chloroacetone

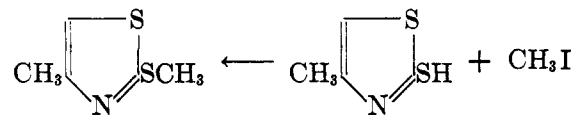
TABLE I

HYDROGEN PEROXIDE OXIDATION OF 2-MERCAPTO-4,5-DIMETHYLTHIAZOLE. INFLUENCE OF ACID CONCENTRATION

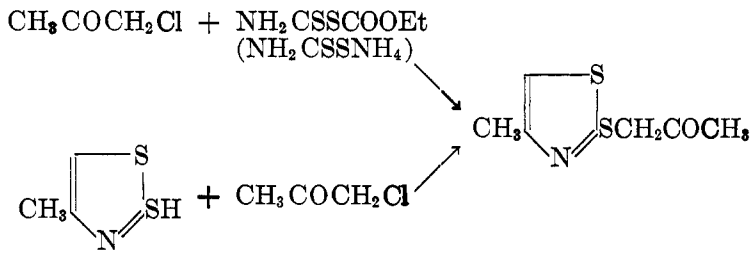
PARTS BY WEIGHT OF:				YIELD OF 4,5-DIMETHYLTHIAZOLE
Mercaptothiazole	Hydrochloric acid Sp. gr. 1.19	Water	Hydrogen Peroxide 30%	
58	—	275–300	136	10–11%
58	20	220	136	34%
58	40	200	136	52–60%
58	240	—	136	60%

2-methylthio-4-methylthiazole, which was conveniently obtained also by methylation (5) of 2-mercapto-4-methylthiazole with methyl iodide.

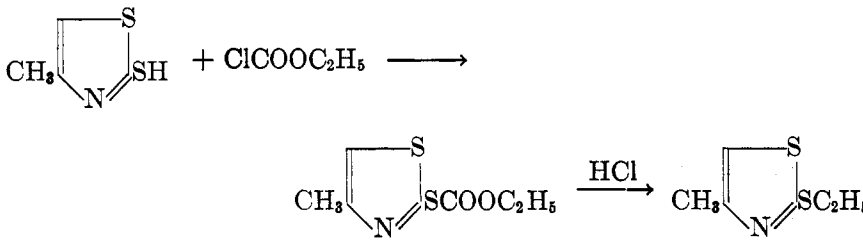
$$CH_3COCH_2Cl + NH_2CSSCH_3 \longrightarrow$$



Chloroacetone reacted with S-carbethoxy dithiocarbamate but the product was not the expected S-carbethoxythiazole; instead it was shown to be 2-acetonylthio-4-methylthiazole (the amphoteric nature of which is noteworthy), best obtained by the action of chloroacetone upon 2-mercapto-4-methylthiazole (no bicyclic thiazolium salt is formed), and which was further detected among the products of the reaction between chloroacetone and ammonium dithiocarbamate.



The action of ethyl chlorocarbonate upon 2-mercapto-4-methylthiazole was found also to proceed in a somewhat anomalous fashion. At room temperature 2-carbethoxythio-4-methylthiazole was formed in good yields but, if the reaction mixture was heated at 100°, carbon dioxide was eliminated with consequent formation of 2-ethylthio-4-methylthiazole. A



parallel to this reaction is the production of S-ethylisothiourea chloride from ethyl chlorocarbonate and thiourea (6).

Mention should also be made of a curious decomposition which thiazole-2 disulfides appear to undergo, especially when in a not highly purified state. 4,5-Dimethylthiazole-2 disulfide, on standing at room temperature for several months in a loosely stoppered flask, was found to have decomposed. In addition to a small amount of unchanged disulfide, 2-mercapto-4,5-dimethylthiazole, 4,5-dimethylthiazole-2-monosulfide[2] and sulfuric acid were shown to be present. The mechanism of this internal oxidation-reduction (15) is not clear; tentatively it may be looked upon as hydrolytic cleavage (5) under mild conditions yielding an unstable intermediate (8), which then acts as an oxidizing agent upon other constituents present. The amounts of decomposition products which were isolated are roughly in agreement with the equation:

$$4RSSR + 4H_2O \rightarrow RSR + 6RSH + H_2SO_4$$

[2] The same thiazole monosulfide was also obtained in small amounts in one of the peroxide oxidation experiments; compare the formation of thiazoline-2 monosulfide by treatment of 2-mercaptothiazoline with nitrous acid (7).

EXPERIMENTAL PART

Preparation of Mercaptothiazoles

The ammonium dithiocarbamate was made by the interaction of alcoholic ammonia and carbon disulfide (9) and was used without purification. The chloroacetone was Eastman's practical grade containing some asym-dichloroacetone which, however, did not interfere in the reactions studied. 3-Chlorobutanone-2 was prepared by the action of sulfuryl chloride on methyl ethyl ketone (10) and separated from the simultaneously formed isomer by fractional distillation. 3-Bromobutanone-2 was prepared by bromination of methyl ethyl ketone in the presence of water at room temperature (11); 1-bromobutanone-2 was present in the higher-boiling fraction obtained on distillation of the reaction product.

Chloroacetone and the isomeric bromobutanones were found to react rapidly with ammonium dithiocarbamate. In preparing mercaptothiazoles from such reactive halides, it was found necessary to avoid an excess of α-halogeno ketone during the reaction, since otherwise extensive amounts of by-product were formed. The procedure adopted was to add the theoretical amount of halogen ketone slowly through a dropping-funnel to a suspension of the dithiocarbamate in absolute alcohol, meanwhile agitating the mixture constantly in an ice-bath. The reactants were allowed to stand at room temperature for 12 hours, heated for 1 hour on a water-bath, and the product worked up in a suitable manner.

2-Mercapto-4-methylthiazole (5, 12). The reaction mixture from 60 g. of chloroacetone and 71.5 g. of ammonium dithiocarbamate in 140 cc. of absolute alcohol was filtered and the solid washed with absolute alcohol. Evaporation of the filtrate gave an oil, which on seeding and shaking with water was transformed into a crystalline cake. This was pressed on tile, yielding 51.5 g. (85%) of substantially pure material, m.p. 88.0–88.5° from isopropyl ether-alcohol. Small amounts could be distilled; b.p. at 3 mm. *ca.* 188°.

2-Mercapto-4,5-dimethylthiazole. (a) *Preparation from 3-chlorobutanone-2.* To 10 g. of ammonium dithiocarbamate suspended in 20 cc. of absolute alcohol was added 11.7 g. of chloro ketone. The mixture was heated for one-half hour on a water-bath, after which the solvent was evaporated and the residue treated with water. Filtration yielded 6.4 g., m.p. 163°.

(b) *Preparation from 3-bromobutanone-2.* The condensation of 29.4 g. of bromo ketone with 21.4 g. of ammonium dithiocarbamate in 45 cc. of absolute alcohol was effected, and the solvent removed by evaporation. To the residue water was added, the solution filtered, and the material thus obtained pressed on tile; yield 21.5 g. (75%), m.p. 163° from alcohol. For analysis a portion was recrystallized from ethyl acetate, m.p. 163.5–163.8°.

Anal. Calc'd for $C_5H_7NS_2$: C, 41.35; H, 4.86; N, 9.64.
Found: C, 41.55; H, 4.73; N, 9.71.

2-Mercapto-4-ethylthiazole. Thirty-three grams of brominated methyl ethyl ketone, b.p. at 23 mm. 58-68°, and 24 g. of ammonium dithiocarbamate in 50 cc. of absolute alcohol were allowed to react in the usual manner. After removal of the solvent and treatment with water, the solid mass remaining was well washed with ether. The 12 g. of ether-insoluble material thus obtained was identified as 2-mercapto-4,5-dimethylthiazole. The ether solution, on evaporation, yielded 18 g. of impure crystalline material which was pressed on tile and recrystallized from ethyl

alcohol, giving 2-mercapto-4-ethylthiazole, m.p. 87.0–87.1°, stable, white, silvery needles (crude material easily oxidized by air).

Anal. Calc'd for $C_5H_7NS_2$: C, 41.35; H, 4.86; N, 9.64.
Found: C, 41.21; H, 4.78; N, 9.96.

Oxidation of Mercaptothiazoles

Oxidation of 2-mercapto-4-methylthiazole. To a continuously agitated suspension of 10 g. of the mercaptothiazole in 45 cc. of water, 26 g. of commercial 30% hydrogen peroxide was added slowly from a dropping-funnel, keeping the temperature at 65–70°. The reaction proceeded with evolution of heat. After the addition, the mixture was heated at 80° for 15 minutes and was then cooled to 0°. The light brown oil which had formed solidified to a crystalline cake. This was separated from the aqueous portion (see below) and pressed on tile, yielding 6 g. of substantially pure disulfide, nearly white crystals from alcohol, m.p. 61.0–61.5°.

Anal. Calc'd for $C_8H_8N_2S_4$: C, 36.90; H, 3.10; N, 10.76.
Found: C, 36.79; H, 2.99; N, 10.64.

The purified disulfide decomposed on standing over a period of months; the decomposition products were not investigated. An attempt was made to prepare this same disulfide by condensing together chloroacetone with thiuram disulfide (13) in the presence of alcohol; no disulfide was obtained.

The aqueous portion (see above) was washed with ether, then made strongly alkaline with sodium hydroxide, and the liberated base taken up in ether. After drying over sodium sulfate and distilling, 0.5 g. of 4-methylthiazole boiling at 70–71° at 59 mm. was obtained and identified by its characteristic picrate, m.p. 181° (2b).

4,5-Dimethylthiazole. Ten grams of 3-chlorobutanone-2 dissolved in 10 cc. of absolute alcohol was treated at 0° with 8.5 g. of crude thioformamide and the mixture kept at 0–4° for 4 days and then for 3 days at room temperature. 6 *N* Hydrochloric acid was added, the solution washed with ether, and excess solid potassium hydroxide carefully added. The liberated base was taken up in ether and fractionated, yield 2.3 g., b.p. (59 mm.) 81–83°.

Anal. Calc'd for C_5H_7NS: C, 53.06; H, 6.23; N, 12.38.
Found: C, 53.22; H, 6.26; N, 12.63.

The picrate, obtained with ethereal picric acid, precipitated immediately, m.p. 186–187° from ethanol; the methiodide formed slowly on mixing the components, m.p. 223–223.5° (decomp.) from ethanol.

Oxidation of 2-mercapto-4,5-dimethylthiazole with hydrogen peroxide. (a) *Oxidation in neutral solution.* Thirty-four grams of commercial hydrogen peroxide was neutralized by titrating with 18.4 cc. of standard sodium hydroxide solution, using phenolphthalein as indicator. The neutral solution was added slowly (15 minutes) through a dropping-funnel to the continuously agitated suspension of 14.5 g. of mercaptothiazole in 50 cc. of water, keeping the temperature between 65–70°; a yellow oil precipitated out. When the addition was completed, the mixture was heated to 80° for 15 minutes and then allowed to cool. On standing, the oil crystallized to a solid cake, which was separated from the aqueous portion and pressed on tile. The yield was 11 g. (76%), m.p. 51.6–52.0° after recrystallization from ethyl alcohol.

Anal. Calc'd for $C_{10}H_{12}N_2S_4$: C, 41.63; H, 4.19; N, 9.71.
Found: C, 41.49; H, 4.40; N, 10.04.

The disulfide is weakly basic in nature, dissolving readily in 6 *N* hydrochloric acid

and precipitating unchanged on dilution of the resulting solution; it does not form a stable picrate.

The aqueous solution from the above reaction was extracted with ether and evaporated on the water-bath to a small volume. The thiazole base was liberated with excess potassium hydroxide, taken up in ether and distilled. One and one-tenth grams of pure 4,5-dimethylthiazole was obtained, b.p. (59 mm.) 82°. The picrate and methiodide were prepared and did not depress the melting point when mixed with authentic samples.

In a similar experiment, 2.9 g. of mercaptothiazole suspended in 12 cc. of water was oxidized by addition of 6.8 g. of neutralized 30% hydrogen peroxide; 0.25 g. of 4,5-dimethylthiazole was obtained.

(b) *Oxidation in moderately acid solution.* To a suspension of 2.9 g. of mercaptothiazole in 11 cc. of water and 1 g. of C.P. hydrochloric acid (sp. gr. 1.19), 6.8 g. of commercial 30% hydrogen peroxide was added slowly at 70–75° as in (a). The reaction mixture was worked up as above, giving 1.25 g. (44%) of the disulfide and 0.75 g. (34%) of 4,5-dimethylthiazole.

The same amount (2.9 g.) of mercaptothiazole, suspended in 10 cc. of water and 2 g. of C.P. hydrochloric acid, was oxidized by 6.8 g. of 30% hydrogen peroxide giving 1.15 g. (52%) of 4,5-dimethylthiazole. In this experiment [and also in (c) below] an evolution of heat was noted on the addition of hydrogen peroxide, and it was necessary to cool externally to keep the temperature at about 70°; no disulfide was obtained.

(c) *Oxidation in strongly acid solution.* As in the above experiments, 13.6 g. of 30% hydrogen peroxide was added to 5.8 g. of mercaptothiazole in 24 g. of C.P. hydrochloric acid. No disulfide was isolated; 2.7 g. (60%) of 4,5-dimethylthiazole was obtained. In another experiment carried out with these relative proportions of reactants, a slightly lower yield of 4,5-dimethylthiazole was obtained, and from the residue remaining after distillation of the volatile base, a small amount of low-melting crystalline material was isolated. After recrystallization from alcohol it melted at 41.0–41.2° [b.p. (2 mm.) *ca.* 190–200°], and gave analytical figures agreeing with those calculated for the thiazole monosulfide.

Anal. Calc'd for $C_{10}H_{12}N_2S_3$: C, 46.84; H, 4.72; N, 10.93.
Found: C, 47.28; H, 4.85; N, 11.21.

With ethereal picric acid it formed a monopicrate, bars or tufts from ethanol, m.p. 111.0–111.2°.

Anal. Calc'd for $C_{16}H_{15}N_5O_7S_3$: N, 14.43. Found: N, 14.20.

Oxidation of 2-mercapto-4,5-dimethylthiazole with nitric acid. It was found that dilute nitric acid (1 volume of nitric acid, sp. gr. 1.42, plus 3 volumes of water) reacted vigorously with the mercaptothiazole when heated to about 80°. Because of the rapid gas evolution accompanying the reaction, no attempt was made to carry out the oxidation on larger than 1 g. portions of the mercaptothiazole, each such portion being heated with 25 cc. of dilute acid until the reaction had ceased, and then afterwards to boiling for a few minutes. Ten such reaction mixtures were combined, evaporated to a small volume, and the free base isolated and characterized as before. Distillation gave 5.0 g. (65%) of pure product.

Thiazole Thioethers

Treatment of mercaptothiazoles with excess of an appropriate reagent containing a reactive halogen, was found the most convenient method (5) for preparing this class of substances. In the cases studied the reaction took place readily to give almost

quantitative yields of the crystalline hydro-halogen salts, easily purified by washing with ether, from which the free bases could be obtained simply and easily. This was accomplished by dissolving in water, adding excess of alkali carbonate, and extracting with ether. From the ether solution after drying over sodium sulfate, the base was usually isolated by distillation *in vacuo* (in the case of a solid thioether by evaporation of solvent and recrystallization). The simple alkylthiothiazoles are stable liquids possessing a characteristic odor, and are not very readily soluble in ether; the picrates, formed when ethereal solutions of the components are mixed, crystallize out on standing.

2-Methylthio-4-methylthiazole. (a) *From 2-mercapto-4-methylthiazole.* When the mercaptothiazole was mixed with methyl iodide at room temperature, either alone or in the presence of ether, a spontaneous reaction took place with evolution of heat. The free base, b.p. (3 mm.) 65–68° was obtained in good yield.

Anal. Calc'd for $C_5H_7NS_2$: C, 41.35; H, 4.86; N, 9.64.
Found: C, 41.12; H, 4.88; N, 9.62.

The picrate was recrystallized from ethyl acetate, m.p. 123.5–123.7°.

(b) *From methyl dithiocarbamate.* A mixture of 6 g. of methyl dithiocarbamate (14), 5.2 g. of chloroacetone, and 6 cc. of absolute alcohol was refluxed for 12 hours on a water-bath. The product was taken up in water, washed with ether, and the base isolated in the usual manner, yield 3 g., b.p. (3 mm.) 65–68°, picrate, m.p. and mixed m.p., 123.5–124.0°.

2-Methylthio-4,5-dimethylthiazole. (a) *From 2-mercapto-4,5-dimethylthiazole.* Three grams of mercaptothiazole was mixed with methyl iodide and the resulting paste allowed to stand for 48 hours. The yield of base was 3 g. (91%) b.p. (2 mm.) 87°.

Anal. Calc'd for $C_6H_9NS_2$: C, 45.25; H, 5.70; N, 8.80.
Found: C, 45.23; H, 5.85; N, 9.14.

The picrate was recrystallized from ethanol, m.p. 134.5–135.5°.

(b) *From methyl dithiocarbamate.* Ten grams of chlorobutanone, 10 g. of methyl dithiocarbamate, and 10 cc. of absolute alcohol were allowed to stand at room temperature for 4 days. After working up, 0.5 g. of 2-methylthio-4,5-dimethylthiazole (low yield evidently due to incomplete reaction) was obtained, having the same properties as the base obtained by method (a).

2-Ethylthio-4-methylthiazole. A methanol solution of 2 g. of 2-mercapto-4-methylthiazole was treated with ethyl bromide. After standing at room temperature for several hours, a second liquid phase made its appearance, and after 24 hours a crystalline cake of 2-ethylthio-4-methylthiazole hydrobromide had formed. The yield of base was 2.4 g., b.p. 83–85° at 4 mm.

Anal. Calc'd for $C_6H_9NS_2$: C, 45.25; H, 5.70; N, 8.80.
Found: C, 44.82; H, 5.62; N, 8.56.

The picrate melted at 114.0–114.5° (from ethanol).

2-Carbethoxythio-4-methylthiazole. 2-Mercapto-4-methylthiazole (2.5 g.) and ethyl chlorocarbonate (2.25 g.) were placed in a stoppered flask equipped with a calcium chloride tube and the mixture allowed to stand at room temperature for 5 days. The reaction took place for the most part during the first hour, the mercaptothiazole going into solution and the carbethoxythiomethylthiazole hydrochloride crystallizing out. After washing with ether, water was added, which led to the formation of two phases [evidently the hydrochloride is largely dissociated in solution (5)]. Sodium carbonate was added and the base isolated in the usual manner, yield 2.65 g., b.p. 123–125° at 4 mm.

Anal. Calc'd for $C_7H_9NO_2S_2$: C, 41.36; H, 4.46; N, 6.89.
Found: C, 41.39; H, 4.54; N, 7.01.

The thiazole thioether does not form a stable picrate.

When the above reaction was carried out on a water-bath instead of at room temperature, there was a noticeable evolution of carbon dioxide, which was complete after 3 hours. No carbethoxythiomethylthiazole could be detected among the reaction products. Instead there were formed considerable amounts of 2-ethylthio-4-methylthiazole, which was isolated and identified (picrate, m.p. and mixed m.p. 114.0–114.5°); 2-mercapto-4-methylthiazole was also isolated and identified by mixed m.p. with an authentic sample. Another experiment, in which 2-mercapto-4-methylhiazole had been allowed to remain in contact with chlorocarbonic ester for four months at room temperature, gave approximately equal amounts of carbethoxythiothiazole and ethylthiothiazole. 2-Carbethoxythio-4-methylthiazole free base, when treated with gaseous hydrochloric acid and heated at 100° for 45 minutes (after which time carbon dioxide evolution had stopped), was found to have been converted to 2-ethylthio-4-methylthiazole.

S-Carbethoxy dithiocarbamate. Thirty-three grams of ethyl chlorocarbonate was added slowly with shaking to a suspension of 33 g. of ammonium dithiocarbamate in 60 cc. of absolute alcohol kept at 0°. Reaction took place with formation of a white solid. The mixture was allowed to stand for one-half hour at room temperature, after which the solvent was evaporated and the residue washed well with water and pressed on tile. The product, yield 37 g. (75%) was substantially pure, m.p. 98.9–99.4° from ethyl acetate, easily soluble in ether.

Anal. Calc'd for $C_4H_7NO_2S_2$: C, 29.08; H, 4.27; N, 8.48.
Found: C, 29.22; H, 4.40; N, 8.73.

In another experiment the reaction was carried out with less strong cooling (acetone as reaction medium). A spontaneous evolution of heat was noted and, in addition to the ether-soluble fraction, there was obtained a small amount of material insoluble in both ether and water. It consisted of a yellow powder which melted above 200°. This material was extracted with hot alcohol, giving a solution which on cooling yielded needles having no definite melting point. Recrystallization from alcohol gave an apparently homogeneous product.

Anal. Calc'd for $C_6H_7N_3O_2S_3$: C, 28.90; H, 2.83; N, 16.85.
Found: C, 29.24; H, 3.32; N, 16.82, 16.95.

On the basis of the analysis and method of formation the substance may be formulated as S-carbethoxy trithiocyanurate. The alcoholic mother liquors on evaporation yielded crystalline material of non-homogeneous appearance; possibly di- and tri-S-carbethoxy trithiocyanurates were present.

2-Acetonylthio-4-methylthiazole. (a) *From 2-mercapto-4-methylthiazole.* A mixture of mercaptothiazole, chloroacetone, and ether or methanol was allowed to stand for 12 hours and the resulting hydrochloride recrystallized from alcohol, m.p. 158.5–159.0°.

Anal. Calc'd for $C_7H_{10}ClNOS_2$: C, 37.57; H, 4.51; N, 6.26.
Found: C, 37.52; H, 4.77; N, 6.03.

The addition of base to the aqueous solution of the hydrochloride caused an oil to precipitate which dissolved again in excess 6 *N* sodium hydroxide, could be precipitated from basic solution by addition of hydrochloric acid; and redissolved in excess of either acid or base. The organic base had the m.p. 45.5–46.0° from alcohol, b.p. *ca.* 112–115° at 3 mm., easily soluble in ether.

Anal. Calc'd for $C_7H_9NOS_2$: C, 44.89; H, 4.84; N, 7.48.
Found: C, 44.88; H, 4.70; N, 7.52.

(b) *From chloroacetone.* Eleven grams each of ammonium dithiocarbamate and chloroacetone were heated with anhydrous ether for 1 hour on the water-bath. Fil-

tration of the reaction products and evaporation of the filtrate yielded 3.5 g. of material which was identified as 2-acetonylthio-4-methylthiazole hydrochloride. Evidently the ether solution contained an intermediate (5) which during evaporation reacted with chloroacetone to give the ether-insoluble product isolated.

The same hydrochloride was obtained from the reaction between 3.3 g. of S-carbethoxy dithiocarbamate and 1.85 g. of chloroacetone in 4 cc. of absolute alcohol, either on refluxing for 4 hours on a water-bath, or after standing at room temperature for one month.

Spontaneous Decomposition of Thiazole Disulfide

Decomposition of 4,5-dimethylthiazole-2 disulfide. Pure disulfide, m.p. 51.5°, was substantially unaltered after standing loosely stoppered for three months. Crude disulfide, m.p. 48°, after standing the same length of time, was found to be converted largely into decomposition products (strong qualitative test for sulfate ion). Seven and two-tenths grams of such material was treated with 60 cc. of concentrated hydrochloric acid, giving a clear yellow solution. Two hundred cubic centimeters of water was added, which caused an immediate crystalline precipitate. By cooling and filtering, it was possible to separate 3.6 g. of 2-mercapto-4,5-dimethylthiazole (mixed m.p.); no disulfide separated at this point. Making the filtrate alkaline, extracting the precipitated oil with ether, and removing the solvent yielded about 2.5 cc. of oil. Treatment of this with ethereal picric acid and separation of the picrate formed gave 1.0 g. of 4,5-dimethylthiazole-2 monosulfide picrate (mixed m.p. and analysis) corresponding to 0.5 g. of monosulfide. The residual oil which did not form a picrate was taken up in 6 *N* hydrochloric acid, washed with ethyl acetate, and the base liberated with alkali. The oil obtained in this manner crystallized on cooling, giving 1.2 g. of unchanged disulfide (mixed m.p.).

SUMMARY

1. The oxidative replacement by hydrogen of the 2-mercapto group in thiazoles may conveniently be effected either by hydrogen peroxide in acid solution or by dilute nitric acid.

2. Thiazole-2 thioethers are best prepared by direct etherification of the corresponding mercaptothiazole. In some cases they may be obtained by interaction of the appropriate ester of dithiocarbamic acid with an α-halogeno ketone. A thiazole-2 carbethoxythioether, in the presence of dry hydrogen chloride, was rendered unstable, yielding S-ethylmercaptothiazole and carbon dioxide.

3. A thiazole-2 disulfide was shown to decompose spontaneously in contact with the atmosphere, giving thiazole-2 monosulfide, 2-mercaptothiazole and sulfuric acid.

PASADENA, CALIF.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

CONDENSATION OF HETEROCYCLIC AMINES WITH DICARBOXYLIC ACID ANHYDRIDES

DAVID SHAPIRO AND FELIX BERGMANN

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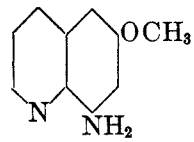
Heterocyclic chemotherapeuticals which bear amino groups are commonly introduced into the body as cations. However, as the p_H of the blood and of the majority of living cells lies between 7.0 and 7.5, it is to be anticipated that the free bases are circulating in the body fluids. It is, therefore, of interest to convert such amines into derivatives, which under "natural" circumstances appear as anions. It is known (1), *e.g.*, that cationic detergents are powerful inhibitors of bacterial growth, whereas anionic detergents show only a weak action in some exceptional cases.

As model experiments, we studied the condensation of 6-methoxy-8-aminoquinoline (I) and sulfapyridine (II) with succinic, maleic, and phthalic anhydrides, in order to see if the presence of the tertiary nitrogen atom in the hetero nucleus would interfere with the condensation reactions of the aromatic amino group and change the rules which are usually accepted for these condensations. Maleic anhydride especially has the ability to form acid salts with the tertiary nitrogen of the quinoline system (2). Two main factors generally determine the trend of the reaction between amines and anhydrides: temperature, and relative amounts of the components, whereas the reaction time is of minor importance. For example, phthalic anhydride and aniline in equimolar mixture yield below 100° the acid amide, whereas above this point the anil is formed. However, when the amount of amine is increased, the diamide prevails more and more (3). These results, however, change from one compound to another; Morgan and Walton (4) have shown that a mixture of one mole of atoxyl with two moles of succinic anhydride give at 180° exclusively the succinamidoarsanilic acid; only at 240° does cyclization to the imide derivative occur. From an equimolar mixture of the two reactants, appreciable amounts of the diamide can be isolated. On the other hand, it was reported by Sanna (5) that *p*-iodoaniline in boiling benzene yields the succinanilic acid after short reaction times, and the anil by prolonged heating.

In the experiments to be described here, the following observations have been made. An equimolar mixture of I with succinic anhydride below 100° yields the acid amide (III) quantitatively. Above 100°, with or with-

out solvent, a mixture of the diamide (IV) and the anil (V) is obtained; increasing the amount of the anhydride to five moles gives only V. With maleic anhydride, only low temperature condensation is possible, leading to VI, whose structure is proved by the fact that diazomethane methylates the free carboxyl and adds to the double bond (VII). If the acid were linked to the tertiary nitrogen, dimethyl pyrazolinedicarboxylate would have resulted (2). On the other hand, we obtained with phthalic anhydride under all conditions, even at room temperature, exclusively the imide (VIII). The acid amide (IX), which is formed from VIII by alkaline hydrolysis, reverts to the imide at the melting point (70°), or by boiling in dilute alcohol.

With sulfapyridine the following behavior has been observed. In the condensation with succinic anhydride, 100° again appears to be the limit between formation of the acid amide (X) or the anil (XI); the molar relation of the two components, however, exerts no influence, because the diamide was never obtained. It is somewhat surprising that XI is even hydrolyzed by soda. With maleic anhydride, the acid XII is the sole reaction product, even at 190°. It may be recalled that Miller and co-workers (6) found a similar behavior of sulfanilamide towards these two anhydrides. In the



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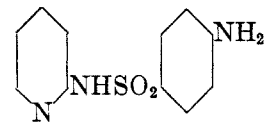

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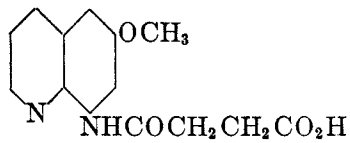

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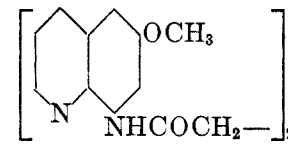

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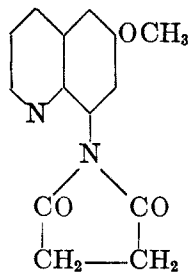

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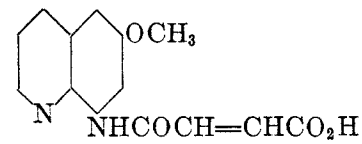

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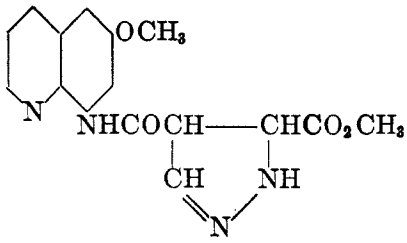

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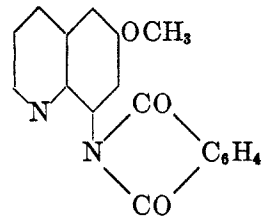

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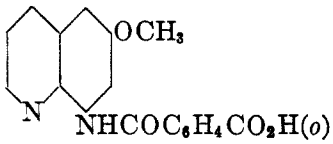

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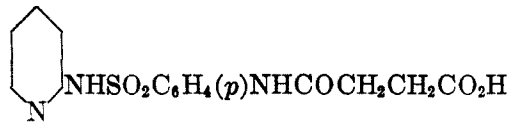

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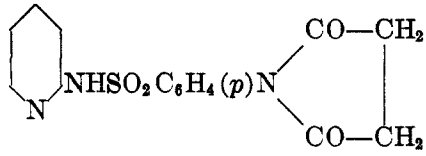
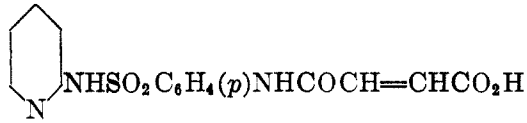


XI



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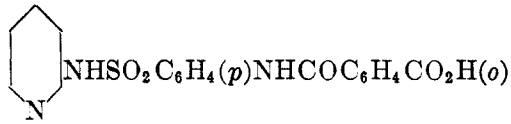

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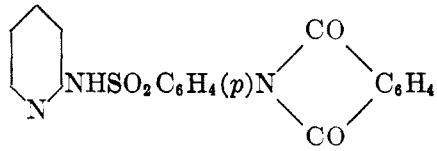

XIV

reaction with II, phthalic anhydride behaves like succinic anhydride; the acid XIII, however, shows the same melting point as the imide XIV. Apparently conversion of XIII into XIV occurs below the melting point of the former.

The results of this investigation are summarized in Table I. The solubility of the various new compounds in hydrochloric acid or acetic acid shows no regularity, as can be seen from Table II.

TABLE I

	SUCCINIC ANHYDRIDE	MALEIC ANHYDRIDE	PHTHALIC ANHYDRIDE
Base I			
Below 100°	Acid amide	Acid amide	Imide
Above 100°	Imide (and diamide)	No result	Imide
Base II			
Below 100°	Acid amide	Acid amide	Acid amide
Above 100°	Imide	Acid amide	Imide

TABLE II

SOLUBILITIES OF THE CONDENSATION PRODUCTS IN HYDROCHLORIC ACID AND ACETIC ACID

FORMULA NO.	CONC'D HCl	DIL. HC	GLACIAL ACETIC ACID	DIL. ACETIC ACID
III	insoluble	insoluble	soluble	insoluble
V	insoluble	insoluble	insoluble	soluble
VI	soluble on heating	(suspension ?)	soluble	soluble
IX	dissolves in the first moment and precipitates immediately		soluble	insoluble
VIII	soluble	insoluble	insoluble	insoluble
X	insoluble	insoluble	soluble	(soluble ?)
XI	soluble	insoluble	insoluble	insoluble
XII	soluble	(insoluble ?)	insoluble	insoluble
XIII	soluble	insoluble	insoluble	insoluble
XIV	insoluble	insoluble	insoluble	insoluble
IV	insoluble	insoluble		

EXPERIMENTAL

I. *Condensation reactions of 6-methoxy-8-aminoquinoline* (I)

(a) The amine did not react with succinic acid (2 moles) in boiling dioxane.

(b) I (1.75 g.) and succinic anhydride (1 g., 1 equiv.) were boiled for 3 hours in benzene (50 cc.). While still hot, the solution deposited a brown precipitate, which was soluble in cold soda. From ethanol, short yellow needles, m.p. 151° (decomp.) were obtained. The substance (III) is also soluble in much water and crystallizes from it unchanged; yield, 2.6 g.

Anal. Calc'd for $C_{14}H_{14}N_2O_4$: C, 61.3; H, 5.1.
Found: C, 60.7; H, 5.3.

The *methyl ester* was prepared with diazomethane; m.p. 127–128° (from benzene).

Anal. Calc'd for $C_{15}H_{16}N_2O_4$: N, 9.7. Found: N, 9.9.

(c) I (1.75 g.) and succinic anhydride (1 g.) were thoroughly mixed and heated to 120° for 2 hours. The mixture was washed with hot water, and the residue boiled with butyl acetate. From this solvent, the imide V crystallized in quadrangular, nearly colorless blocks, m.p. 178°; yield, 1 g.

Anal. Calc'd for $C_{14}H_{12}N_2O_3$: C, 65.6; H, 4.7; N, 10.9.
Found: C, 65.3; H, 5.1; N, 11.2.

The second substance, which is insoluble in butyl acetate, was recrystallized from pyridine; m.p. 258°, yield 1.2 g. (IV).

Anal. Calc'd for $C_{24}H_{22}N_4O_4$: C, 67.0; H, 5.1; N, 13.0.
Found: C, 67.0; H, 5.1; N, 13.0.

At 180°, the reaction gave the same results. When 5 equivalents of succinic anhydride was used at 120°, only the imide V could be isolated; yield, 1.5 g.

The imide was hydrolyzed by 5% sodium hydroxide on the steam-bath within 15 minutes. On acidifying with acetic acid, the product III of m.p. 150° was precipitated.

(d) I and maleic anhydride yielded only tarry products, when heated to 120° or boiled in xylene solution.

(e) I (1.75 g.) and maleic anhydride (1 g.) were gently heated on the water-bath in benzene solution (50 cc.). After a few minutes, a yellow mass crystallized; this substance (VI) crystallized from alcohol in brick-red needles; m.p. 225° (decomp.), yield, 2.6 g.

Anal. Calc'd for $C_{14}H_{12}N_2O_4 + H_2O$: N, 9.7. Found: N, 9.5.

The reaction product of the acid VI with diazomethane was recrystallized from methanol, m.p. 160–162° (VII).

Anal. Calc'd for $C_{16}H_{16}N_4O_4$: N, 17.1. Found: N, 17.2.

(f) I (1.75 g.) and phthalic anhydride (1.5 g., 1 equiv.) were dissolved at room temperature in 10 cc. of dioxane. After some hours, the reaction product (VIII) settled out; the same result was obtained in boiling dioxane; yield, quantitative. After recrystallization from dioxane, the m.p. was 261°.

Anal. Calc'd for $C_{18}H_{12}N_2O_3$: N, 9.2. Found: N, 9.1.

The imide VIII is insoluble in soda; in 10% sodium hydroxide, however, it dissolves in a few minutes. From this solution, the free acid IX can be precipitated at 0° by dilute acetic acid; yield, nearly quantitative. When dissolved in hot dilute alcohol, it regenerated the imide. The acid IX melts at about 70°, but immediately solidifies and shows then the m.p. 260° of the imide.

Anal. Calc'd for $C_{18}H_{14}N_2O_4$: C, 67.1; H, 4.3; N, 8.7.
Found: C, 67.4; H, 4.2; N, 8.7.

II. *Condensation reactions of sulfapyridine* (II)

(a) II (1.25 g.) and succinic anhydride (0.5 g., 1 equiv.) in dioxane (30 cc.) were heated on a water-bath for 3 hours. The solvent was evaporated *in vacuo*, the residue dissolved in cold soda, and precipitated with dilute hydrochloric acid. After recrystallization from ethanol, it showed the m.p. 145° (X); yield, 1.4 g.

Anal. Calc'd for $C_{15}H_{15}N_3O_5S$: N, 12.0. Found: N, 11.8.

(b) II (2.5 g.) and succinic anhydride (1 g.) were heated for 2 hours at 140°. The mixture was extracted with boiling water and the residue recrystallized from 40% acetic acid or pyridine; yield, 3.1 g., needles, m.p. 288–290° (XI). The imide is hydrolyzed immediately by cold sodium hydroxide or by warm soda solution to the acid X.

Anal. Calc'd for $C_{15}H_{13}N_3O_4S$: N, 12.7. Found: N, 12.5.

(c) II (2.5 g.) and maleic anhydride (1 g.) were heated on a steam-bath in dioxane (60 cc.). After half an hour, a yellow precipitate appeared (XII); yield, 3 g. From nitrobenzene, a brown powder was obtained, m.p. 208°.

Anal. Calc'd for $C_{15}H_{13}N_3O_5S$: N, 12.1. Found: N, 12.1.

When a mixture of the two reactants was melted at 120° or at 190°, the acid XII was also the sole reaction product. The acid is stable even at 205°.

(d) II (2.5 g.) and phthalic anhydride (1.5 g.) were boiled in dioxane (50 cc.) for one-half hour, after which the reaction product (XIII) settled out. The acid was purified by dissolving in cold soda and precipitating with dilute acetic acid at 0°. The m.p., 276°, is identical with that of the imide (XIV). For analysis, the substance was dried at room temperature; yield, quantitative.

Anal. Calc'd for $C_{19}H_{15}N_3O_5S + H_2O$: C, 54.9; H, 4.1; N, 10.1.
Found: C, 55.1; H, 4.2; N, 10.1, 10.2.

(e) II (1.25 g.) and phthalic anhydride (0.75 g.) were heated to 190° for 2 hours. The gray mass was then triturated with cold soda and recrystallized from pyridine; m.p. 276°, yield, 1.7 g.

Anal. Calc'd for $C_{19}H_{13}N_3O_4S$: N, 11.1. Found: N, 10.8.

Hydrolysis of the imide is easily effected by cold sodium hydroxide.

We wish to thank Dr. L. Haskelberg of this Institute for a gift of the quinoline base used in these experiments.

REHOVOTH, PALESTINE.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE SYNTHESIS OF SOME *dl*-PELLETIERINE DERIVATIVES

M. A. SPIELMAN,[1] SAMUEL SWADESH, AND C. W. MORTENSON

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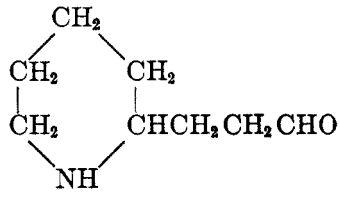
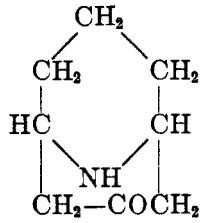
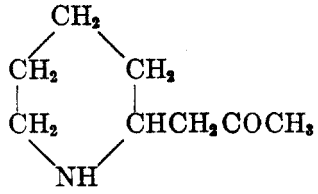
The bark of the pomegranate tree (*Punica granatum*) contains a number of alkaloids among which pelletierine (I), pseudopelletierine (II), and iso-



I.



II.



III.

pelletierine (III) predominate. N-Methyl derivatives are present in lesser amounts. The structures of pseudo- and iso-pelletierine have been worked out by degradative methods and made secure by synthesis. Hess and Eichel (1) have established the structure of pelletierine by an indirect oxidation to β-(2-piperidyl)propionic acid. No synthesis has, however, been published, although the alkaloid is of simple constitution and possesses considerable interest as an anthelminthic agent.

We have been engaged for some time in an attempt to synthesize pelletierine, and the recent communication of Wibaut and Beets (2) prompts us to publish our results to date. The European authors projected the following scheme: α-Picoline was condensed with bromacetal through the aid of phenyllithium to give β-(2-pyridyl)propionacetal (IV) which was hydrogenated to a crude *dl*-β-(2-piperidyl)propionacetal (V). The approach

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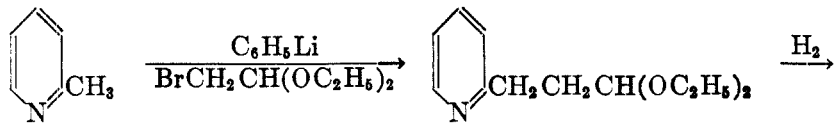
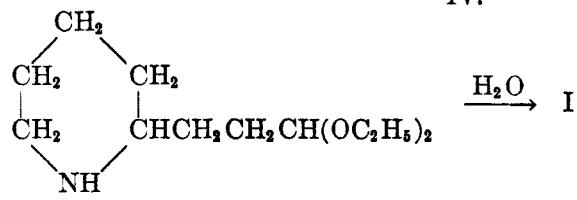


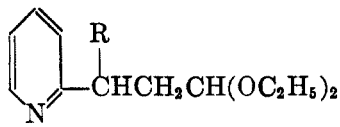
IV.



V.

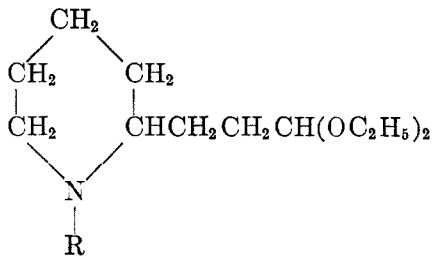
failed beyond this point. We have carried the problem somewhat further, and those parts of our work which do not duplicate the efforts of Wibaut and Beets are the subject of this report.

We have prepared IV by the published phenyllithium method, and also by the use of butyllithium and propyllithium. The phenyllithium method is preferable, because with the use of the latter two reagents, β-(2-pyridyl)-heptacetal (VI) and β-(2-pyridyl)hexacetal (VII) respectively, appear in small amounts as by-products. At the time, we attributed their formation to alkylation by unchanged alkyl halides, which are difficult to avoid in the formation of alkyllithium compounds; however, they may well be traceable to the interesting lithium-halogen interchange described in numerous papers by Gilman and associates (3).

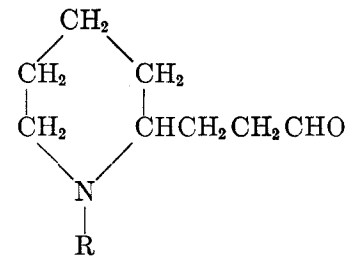


VI. R = *n*-C_4H_9
VII. R = *n*-C_3H_7

Hydrogenation of β-(2-pyridyl)propionacetal in the presence of Raney nickel gave a nearly quantitative yield of pure *dl*-β-(2-piperidyl)propionacetal (V), referred to hereafter as pelletierine acetal, with optical inactivity implied. By appropriate reactions, beginning with pelletierine acetal, we were able to make several pelletierine derivatives which in every case correspond in properties to those described by Hess (1,4,5) in his characterization of the natural alkaloid. Thus, pelletierine acetal was benzoylated to N-benzoylpelletierine acetal (VIII) which was hydrolyzed to N-benzoylpelletierine (XII), a solid. Similarly, N-acetylpelletierine acetal (IX) gave N-acetylpelletierine (XIII). Treatment of pelletierine acetal with ethyl



VIII R = C_6H_5CO
IX R = CH_3CO
X R = $COOC_2H_5$
XI R = $C_{10}H_7NHCO$

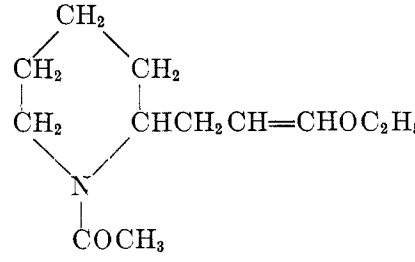


XII R = C_6H_5CO
XIII R = CH_3CO
XIV R = $COOC_2H_5$

chlorocarbonate produced the corresponding urethane (X) which was split by acetic acid to the known pelletierine urethane (XIV). A characteristic derivative of pelletierine acetal is the urea (XI) formed by reaction with α-naphthyl isocyanate.

We were unable to prepare free pelletierine from any of the above derivatives. Like Wibaut and Beets, we anticipated no trouble in hydrolyzing pelletierine acetal, but every set of conditions which led to hydrolysis also gave resinification. Strong acids were as unavailing as weak acids, mineral or organic, concentrated or dilute. An atmosphere of hydrogen was of no help nor were reducing conditions as, for example, in a sodium bisulfite solution. The various N-acyl derivatives of pelletierine were equally intractable; even the urethane (XIV) was destroyed by hydrolysis, as already reported by Hess.

An interesting reaction was discovered in the attempt to split pelletierine acetal with acetic anhydride. The result was an excellent yield of the N-acetyl enol ether (XV). The opening of the acetal linkage in this fashion is comparable to the fission of the spiro-acetal side chain in the sapogenin series (6).

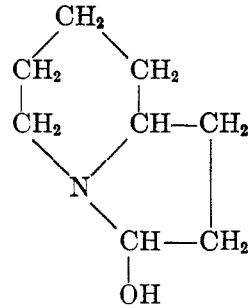


XV.

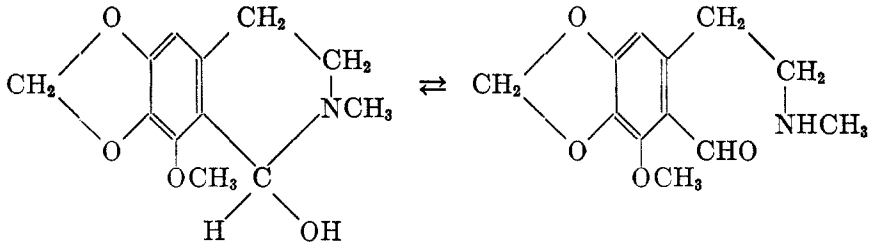
DISCUSSION

The principle object in the way of a pelletierine synthesis is the marked instability of the free alkaloid. It can be distilled only with decomposition

in a hydrogen atmosphere, and when exposed to air, even at room temperature, it resinifies within a few hours. Because it is both a strong secondary amine and a primary aldehyde, conditions are almost ideal for autocatalyzed aldol condensation. Furthermore, pelletierine can assume a carbinol amine structure (XVI) which recalls the tautomerism between the



XVI.



XVII. XVIII.

carbinol amine (XVII) and amino aldehyde (XVIII) forms of cotarnine (7). Cotarnine condenses instantly in the cold with compounds containing the active methylene group, *e.g.*, nitromethane, and since pelletierine can assume such a pseudo-base or carbinol amine form and also contains an active methylene group, a pronounced tendency to self-condensation is not surprising. Etherification and dehydration, which are common among pseudo-bases, probably also play a part.

We believe that the synthesis of a number of products corresponding to derivatives of the natural alkaloid gives ample proof of the gross structure assigned to pelletierine by Hess. The amount, if any, which exists in the carbinol amine form (XVI) can be determined only by physical means.

The work is not being continued.

EXPERIMENTAL

β-(2-Pyridyl)propionacetal (IV) by the alkyllithium method. To a well-stirred mixture of 700 cc. of absolute ether and 14 g. of finely cut lithium was added during

forty-five minutes 137 g. of *n*-butyl bromide. After one hour of refluxing, the yield of butyllithium was 70% as determined by titration. Then 65.1 g. of α-picoline was added, followed as rapidly as possible (8) by 137.9 g. of bromacetal. The mixture was cautiously decomposed by water, and the product isolated by extraction with ether. The ether extracts were dried over Drierite and then distilled. After removing unchanged α-picoline and bromacetal, there was obtained 51 g. or 24.4% (based on lithium) of β-(2-pyridyl)propionacetal; b.p. 128° at 8 mm.; n_D^{25} 1.5070.

Anal. Calc'd for $C_{12}H_{19}NO_2$: N, 6.69; C_2H_5O, 43.1.
Found: N, 6.80, 6.67; C_2H_5O, 42.1.

The structure of the acetal was established by permanganate oxidation to β-(2-pyridyl)propionic acid; m.p. and mixed m.p. 139–140°; m.p. of gold double salt, 162–163° (9).

β-(2-Pyridyl)heptacetal (VI) was isolated in 5.7% yield by working over the residues from the above synthesis; b.p. 156–159° at 8 mm.

Anal. Calc'd for $C_{16}H_{27}NO_2$: N, 5.26; C_2H_5O, 33.95.
Found: N, 5.35, 5.26; C_2H_5O, 34.0, 33.6.

β-(2-Pyridyl)hexacetal (VII). One run was made using *n*-propyllithium as the condensing agent. Results were the same, except that the by-product (6.8%) contained the *n*-propyl group. It boiled at 145–148° at 8 mm.

Anal. Calc'd for $C_{15}H_{25}NO_2$: N, 5.57; C_2H_5O, 35.8.
Found: N, 5.42, 5.46; C_2H_5O, 35.4, 35.8.

Pelletierine acetal (V). Nineteen grams of β-(2-pyridyl)propionacetal in 100 cc. of alcohol was boiled with 5 g. of Raney nickel for one hour. After centrifugation, the solution was made up to 120 cc. and hydrogenated in the presence of 15 g. of fresh catalyst. At 150° and 2500 pounds per square inch pressure (170 atmos.), the theoretical drop occurred in thirty minutes, and no further drop occurred after one hour. Distillation gave 16 g. or 82% of pelletierine acetal as a water-white liquid; b.p. 101–106° at 3 mm. Refractionated, it boiled at 91–92° at 1 mm.; n_D^{25} 1.4568.

Anal. Calc'd for $C_{12}H_{25}NO_2$: N, 6.5; OC_2H_5, 41.7.
Found: N, 6.5, 6.6; OC_2H_5, 41.2.

N-Benzoylpelletierine acetal (VIII). Benzoylation was achieved with benzoyl chloride and aqueous alkali to give 95% of a thick oil; b.p. 177–178° at 1 mm.; n_D^{25} 1.5229.

Anal. Calc'd for $C_{19}H_{29}NO_3$: N, 4.4. Found: N, 4.6.

N-Benzoylpelletierine (XII). One gram of the above acetal was heated to 90° for three hours with 20 cc. of 95% acetic acid. The hot solution was poured into ice-water and neutralized. A white solid separated; m.p. crude, 70–75°. It was crystallized with difficulty from petroleum ether to raise the melting point to 74–76°. Hess (4) reports 75°.

Anal. Calc'd for $C_{15}H_{19}NO_2$: N, 5.72. Found: N, 5.70, 5.79.

N-Acetylpelletierine acetal (IX). To a mixture of 65 cc. of cold 30% sodium hydroxide solution and 7 g. of pelletierine acetal, 15 g. of acetyl chloride was added during thirty minutes with violent agitation. The mixture was extracted with ether and the extract dried over anhydrous sodium sulfate. On distillation a 5.0 g. fraction (60% yield) was collected at 147–149° at 2 mm.; n_D^{25} 1.4712.

Anal. Calc'd for $C_{14}H_{27}NO_3$: N, 5.44. Found: N, 5.58.

N-Acetylpelletierine (XIII). Four grams of N-acetylpelletierine acetal was heated to 90° for three hours with 20 cc. of 95% acetic acid. Fractionation gave 1.5 g. or a 54% yield of a colorless oil which reduced Tollens' reagent instantly. It boiled at 139–141° at 2 mm.; 174° at 18 mm.; n_D^{26} 1.4908. Hess (4) gives 173–174° at 18 mm.

Anal. Calc'd for $C_{10}H_{17}NO_2$: N, 7.64. Found: N, 7.90.

The gold chloride double salt prepared as described by Hess (4) melted at 94°; the literature reports 95–96°.

Anal. Calc'd for $C_{10}H_{18}AuCl_4NO_2$: Au, 37.7. Found: Au, 37.1, 37.3.

Pelletierine acetal ethyl urethane (X). Seven grams of ethyl chlorocarbonate was added dropwise to 30 cc. of cold 30% sodium hydroxide solution containing 5.0 g. of pelletierine acetal. After shaking thirty minutes, the mass was extracted with ether and the extract distilled. The yield was 88%; b.p. 146–147° at 2 mm.; n_D^{25} 1.4580.

Anal. Calc'd for $C_{15}H_{29}NO_4$: N, 4.88. Found: N, 4.70.

Pelletierine ethyl urethane (XIV). Two grams of the acetal urethane (X) was hydrolyzed in 95% acetic acid at 90° during four hours to give 1.1 g. (74.5% yield) of a colorless oil having an ester-like odor and boiling at 119–121° at 1 mm.; n_D^{25} 1.4771. The literature value (5) is 173–174° at 20–21 mm.

Anal. Calc'd for $C_{11}H_{19}NO_3$: N, 6.6. Found: N, 6.8, 6.9.

N-(α-Naphthylcarbamyl)pelletierine acetal (XI). The derivative was formed from equal amounts of α-naphthyl isocyanate and pelletierine acetal in petroleum ether. Recrystallized from acetone-petroleum ether, it melted at 109°.

Anal. Calc'd for $C_{23}H_{32}N_2O_3$: N, 7.29; C_2H_5O, 23.4.
Found: N, 7.30, 7.44; C_2H_5O, 22.7, 22.7.

N-Acetylpelletierine enol ethyl ether (XV). Three grams of pelletierine acetal was refluxed in 50 cc. of acetic anhydride for six hours. Distillation of the reddish-brown reaction mixture gave 2.7 g. (92%) of a colorless oil; b.p. 155–157° at 6 mm.; 121–122° at 1 mm.; n_D^{25} 1.4872. It decomposed potassium permanganate rapidly in the cold and also decolorized bromine in carbon tetrachloride.

Anal. Calc'd for $C_{12}H_{21}NO_2$: N, 6.64; C_2H_5O, 21.3.
Found: N, 6.60, 6.65; C_2H_5O, 21.5, 21.1

SUMMARY

The diethyl acetal of *dl*-pelletierine has been synthesized and characterized. It has been used as starting material in the preparation of a number of *dl*-pelletierine derivatives.

A comparison of the synthetic substances with those derived from natural pelletierine indicate the correctness of the structure assigned to pelletierine by Hess.

MADISON, WIS.

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[CONTRIBUTION FROM THE ESSO LABORATORIES OF THE STANDARD OIL DEVELOPMENT CO.]

HIGH-MOLECULAR-WEIGHT HYDROCARBONS AND HYDROCARBON INTERMEDIATES. II

L. A. MIKESKA AND C. A. COHEN

Received November 30, 1940

Previous publications (1, 2) from this Laboratory have described the preparation of several series of synthetic hydrocarbons of high molecular weight and certain physical properties of interest to petroleum technologists such as viscosity, viscosity index, and aniline point. In the latter paper (2), the methods employed in the preparation of some of the hydrocarbons and corresponding intermediates were described in detail and covered only the preparation of monosubstituted derivatives of benzene, naphthalene, and diphenyl in which the alkyl substituent contained not more than eighteen carbon atoms in a continuous chain. Some compounds having an additional side chain of four carbon atoms were included due to the close structural relationship.

Recently some doubt has been expressed (3) with respect to the degree of purity of some of the hydrocarbons described in the original paper. In order to provide a basis for evaluation of the purity of the hydrocarbons in question, it was considered desirable to publish the experimental data obtained and the details of the methods employed in the preparation of the remainder of the hydrocarbons originally described.

This paper covers the preparation of monosubstituted derivatives of benzene, naphthalene, and diphenyl, together with the corresponding hydroaromatic hydrocarbons and intermediates in which the alkyl substituent contains twenty or more carbon atoms in a continuous chain. The numbers in brackets appearing before the names of the hydrocarbons described in this paper refer to the numbers connoting individual hydrocarbons in Table I of the original article (1).

As may be seen from the analytical data recorded below, the ketones which served as intermediates in the preparation of the hydrocarbons were of a high order of purity. The mild conditions employed in the reduction of the carbonyl groups to methylene groups, or conversion of the former by means of Grignard reagents and subsequent dehydration into alkylidene groups, make it improbable that any deep-seated changes in the structure of the molecules occur in these steps. No attempt was made to determine the position of the double bonds in the olefinic derivatives. For purposes

of convenience, it was assumed that the dehydration of tertiary alcohols took place through the main chain instead of the side chain of the isoparaffin, although both parts of the chain were, in all probability, involved. Where there are slight differences between the theoretical and observed indices of refraction on the one hand, and dispersions on the other, it is felt that these are likely due to errors involved in extrapolation from one temperature to another, or possibly to some inadequacy of the instrument used. As relatively large amounts of the hydrocarbons were required in order to determine their physical constants, including their viscosities at various temperatures, no attempt was made to purify them to the point at which they had a constant index of refraction. The small amounts of impurities, too small to be detected by analysis, which were assumed to be present, were considered to be too insignificant to exert any measurable effect on the viscosities and viscosity indices of the hydrocarbons, the determination of which constituted the primary objective of the investigation.

EXPERIMENTAL

General method of procedure. All of the alkyl aromatics described in this paper were prepared by the reduction of the appropriate ketones, or else by the action of Grignard reagents on the latter, with subsequent dehydration of the resulting tertiary carbinols. The ketones were prepared by condensing acid chlorides of the required structure and molecular weight with aromatics in the presence of aluminum chloride.

The ketones were reduced to hydrocarbons by means of amalgamated zinc and hydrochloric acid according to a modification of Clemmensen's method. Relatively pure compounds were thus obtained in good yield.

The alkyl hydroaromatics were prepared by hydrogenation of the corresponding alkyl aromatics in the presence of platinum oxide (4).

Inasmuch as the method of preparing the ketones was essentially the same in all cases, the preparation of only one ketone, heneicosyl phenyl ketone, is given in detail. For the other ketones, only the deviations from the standard procedure are recorded. The boiling points reported in this article are somewhat high due to superheating, since no fractionating column was used.

n-*Heneicosyl phenyl ketone.* $C_6H_5CO(CH_2)_{20}CH_3$. To obtain the behenic chloride used in the preparation of the ketone, 34.2 g. of pure behenic acid was added slowly to 10 g. of phosphorus trichloride. The mixture was then heated for 30 minutes at 70° in a water-bath, whereupon the phosphorous acid which was formed during the reaction, settled to the bottom of the flask as a viscous, colorless oil. The behenyl chloride was then carefully decanted into 100 cc. of pure dry benzene and 25 g. of aluminum chloride was added in small portions with occasional shaking over a period of about 0.5 hour while maintaining the temperature near 0° by cooling in an ice-bath. The mixture was then stoppered with a calcium chloride tube and allowed to stand overnight at room temperature.

The following day, the reaction mixture was poured into a mixture of ice and 100 cc. of concentrated hydrochloric acid. The ketone was extracted with ether, the ether extract washed free of hydrochloric acid, and finally dried over anhydrous sodium sulfate. The solution was then saturated with dry ammonia in order to precipitate any unchanged behenic acid as ammonium behenate, whwich as then removed by filtration. The residue obtained on removal of the ether from the fil-

trate was recrystallized from acetone. A snow-white, crystalline product was obtained which melted at 73–76°.

Anal. Calc'd for $C_{28}H_{48}O$: C, 83.92; H, 12.08.
Found: C, 83.97; H, 12.19.

[2] n-*Docosylbenzene.* $C_6H_5(CH_2)_{21}CH_3$. The *n*-heneicosyl phenyl ketone was reduced to the corresponding hydrocarbon by Clemmensen's (5) method which was modified somewhat so as to speed up the reaction and improve the yield.

About a 7.5 cm. (3 inches) layer of mossy zinc, amalgamated according to Clemmensen's directions with a 5% aqueous solution of mercuric chloride, was placed into a one-liter Erlenmeyer flask which was equipped with a reflux condenser and an inlet tube for hydrogen chloride. Fifty grams of *n*-heneicosyl phenyl ketone dissolved in 300 cc. of xylene was then added, followed with just enough concentrated hydrochloric acid to form a lower layer covering only about half of the zinc. The contents of the flask were then heated to boiling and hydrogen chloride continuously passed into the refluxing mixture in order to replace the hydrochloric acid consumed. After a contact time of seven hours, the reaction mixture was poured into water, the hydrocarbons extracted with ether, the extract washed free of hydrochloric acid and finally dried over anhydrous sodium sulfate. The residue obtained after removal of the solvents was distilled under 4 mm. pressure. Most of the product (38 g.) distilled between 245° and 247°. On recrystallization of this distillate from ether, a snow-white crystalline product was obtained melting at 42–44°.

Anal. Calc'd for $C_{28}H_{50}$: C, 86.96; H, 13.04.
Found: C, 86.94; H, 13.02.

[6] *5-Phenyl*-n-*hexacosene-5.* $CH_3(CH_2)_3C(C_6H_5):CH(CH_2)_{19}CH_3$. Eight and two-tenths grams of magnesium, which had been activated by warming with a small crystal of iodine, was suspended in 200 cc. of dry ether. To this suspension was slowly added 33 g. of *n*-butyl chloride with occasional shaking. When the reaction had gone to completion the resulting Grignard reagent was slowly added to a solution of 55 g. of phenyl *n*-heneicosyl ketone in 300 cc. of dry ether. After all of the *n*-butylmagnesium chloride had been added, the mixture was refluxed for 2 hours, cooled, and poured into a mixture of ice and hydrochloric acid. The ether extract was washed free of acid, dried over sodium sulfate, and the ether removed, whereupon 62 g. of a semi-solid residue was obtained. No attempt was made to isolate and purify the carbinol.

This residue was treated with 25 g. of oxalic acid and the mixture heated for 3 hours at 180–200° in an atmosphere of carbon dioxide. The reaction mixture was then poured into water, extracted with ether, the ether extract washed free of acid, and finally dried over sodium sulfate. The residue obtained on removal of the ether was distilled under 3 mm. pressure. The entire product distilled at 245–260°.

As analytical data showed that the material still contained oxygen, it was retreated with a quantity of *n*-butylmagnesium chloride and the resulting carbinol subsequently dehydrated with oxalic acid. On distillation of the resulting product, 57 g. of a distillate boiling at 255–265° at 6 mm. was obtained. The latter was an almost colorless, viscous oil.

Anal. Calc'd for $C_{32}H_{56}$: C, 87.19; H, 12.81.
Found: C, 87.08; H, 12.75.

[4][1] *5-Phenyl*-n-*hexacosane.* $CH_3(CH_2)_3CH(C_6H_5)(CH_2)_{20}CH_3$. A pressure bottle was charged with 25 g. of 5-phenyl-*n*-hexacosene-5, 100 cc. of glacial acetic acid, and 0.3 g. of platinum oxide catalyst and arranged for hydrogenation. Absorption of

[1] The product labeled [4] in *J. Org. Chem.*, **2**, 502 (1938) should have been labeled [3].

hydrogen began immediately, and was interrupted when the calculated amount of hydrogen had been absorbed.

After the removal of the suspended catalyst the solution was poured into water, extracted with ether and the ether extract washed free of acetic acid and dried over sodium sulfate. On removal of the solvent, 23.5 g. of an almost colorless, viscous oil boiling at 245–255° at 4 mm. was obtained. The oil solidified on cooling.

No attempt was made to separate the major product of the reaction from the small amount of cyclohexane derivative which was probably formed during the hydrogenation. The product melted at 32–33°.

Anal. Calc'd for $C_{32}H_{58}$: C, 86.78; H, 13.22.
Found: C, 86.79; H, 13.16.

[14] *5-Cyclohexyl-*n*-hexacosane.* $CH_3(CH_2)_8CH(C_6H_{11})(CH_2)_{20}CH_3$. To obtain this hydroaromatic derivative, 18 g. of 5-phenyl-*n*-hexacosane dissolved in 100 cc. of glacial acetic acid was treated with hydrogen at room temperature in the presence of platinum oxide catalyst until the calculated volume of hydrogen had been absorbed. The catalyst was then removed by filtration, the filtrate was dissolved in ether, and the solution washed free of acetic acid and dried over sodium sulfate. The residue obtained on removal of the ether was distilled under 2 mm. pressure. The entire product distilled at 245–250°, leaving no residue. The distillate consisted of 18 g. of a colorless oil which solidified on standing. The solid melted at 30–31°.

Anal. Calc'd for $C_{32}H_{64}$: C, 85.62; H, 14.38.
Found: C, 85.75; H, 14.32.

[13] n-*Docosylcyclohexane.* $C_6H_{11}(CH_2)_{21}CH_3$. Fifteen grams of *n*-docosylbenzene in 100 cc. of glacial acetic acid with 0.3 g. of platinum oxide was hydrogenated until the calculated amount of hydrogen had been absorbed. After the removal of the catalyst the filtrate was poured into water, extracted with ether, and the ether extract washed free of acetic acid and dried over sodium sulfate. On removal of a part of the ether and cooling of the solution, the product precipitated as a white crystalline mass. On recrystallization of this solid from ether, a product melting at 49–50° was obtained.

Anal. Calc'd for $C_{28}H_{56}$: C, 85.62; H, 14.38.
Found: C, 85.77; H, 14.24.

n-*Heneicosyl naphthyl ketone.* $C_{10}H_7CO(CH_2)_{20}CH_3$. One hundred and fifty grams of behenic acid (m.p. 79–81°) was added to 56 g. of phosphorus trichloride and the mixture heated at 70° in a water-bath for 20 min. When the mixture had cooled and stood at room temperature, the phosphorous acid which had formed settled to the bottom of the flask. The acid chloride was then decanted into a flask containing 34 g. of naphthalene dissolved in 250 cc. of carbon disulfide. The solution was cooled to 0°, and a total of 60 g. of aluminum chloride was added in small amounts with cooling and occasional shaking. When all of the aluminum chloride had been added, the mixture was allowed to stand overnight at room temperature.

The mixture was refluxed for 2.5 hours on the steam-bath and decomposed with ice and hydrochloric acid. It was extracted with ether, the extract was washed free of hydrochloric acid and dried over sodium sulfate. On removal of the solvents, a crystalline residue was obtained. This was redissolved in ether and the solution was saturated with ammonia in order to precipitate any unchanged behenic acid. The ammonium behenate was removed by filtration. The residue obtained on removal of the ether from the filtrate was recrystallized from acetone and then from petroleum ether (b.p. 65–95°). In this state of purity the product melted at 67–69°; yield over 80%.

Anal. Calc'd for $C_{32}H_{50}O$: C, 85.24; H, 11.19.
Found: C, 85.42; H, 11.29.

[16] n-*Docosylnaphthalene.* $C_{10}H_7(CH_2)_{21}CH_3$. Sixty-eight grams of *n*-heneicosyl naphthyl ketone was reduced with zinc amalgam, the reduction being carried out by the same method as in the preparation of *n*-docosylbenzene [2]. After three recrystallizations from ether, the reduction product, in the form of snow-white crystals, melted at 56–58°.

Anal. Calc'd for $C_{32}H_{52}$: C, 87.99; H, 12.01.
Found: C, 88.04; H, 11.94.

[20] *5-Naphthyl*-n-*hexacosene-5.* $CH_3(CH_2)_3C(C_{10}H_7):CH(CH_2)_{19}CH_3$. *n*-Butylmagnesium chloride solution was prepared in the usual manner from 9.4 g. of activated magnesium, 38 g. of *n*-butyl chloride and 200 cc. of dry ether. This was gradually added to a solution of 73 g. of *n*-heneicosyl naphthyl ketone in 300 cc. of dry ether, and the mixture was refluxed for 5 hours. The reaction product was recovered in the usual manner, and was heated with 30 g. of oxalic acid at 180–200° for 3 hours under carbon dioxide. The product was isolated in the usual way, and was distilled at 2 mm. Eighty-two grams of distillate boiling between 250° and 290° was obtained. The distillate was then re-treated successively with the Grignard reagent and oxalic acid, as described under the preparation of 5-phenyl-*n*-hexacosene-5. Sixty-three grams of a colorless, viscous oil distilling at 245–265° at 3 mm. was finally obtained.

Anal. Calc'd for $C_{36}H_{58}$: C, 88.07; H, 11.93.
Found: C, 87.75; H, 12.22.

[19] *5-Naphthyl*-n-*hexacosane.* $CH_3(CH_2)_3CH(C_{10}H_7)(CH_2)_{10}CH_3$. The reduction of 5-naphthyl-*n*-hexacosene-5 was carried out similarly to the reduction of 5-phenyl-*n*-hexacosene-5. From 21 g. of the alkene, 18 g. of a colorless oil distilling between 240° and 250° was obtained. The product, which solidified on standing, melted at 39–40°.

Anal. Calc'd for $C_{36}H_{60}$: C, 87.72; H, 12.28.
Found: C, 87.38; H, 12.37.

α-n-*Butyl*-n-*nonadecyl naphthyl ketone.* $C_{10}H_7COCH(C_4H_9)(CH_2)_{17}CH_3$. This ketone was prepared by the action of *α*-*n*-butylarachidyl chloride on naphthalene in carbon disulfide solution in the presence of aluminum chloride. The details of the preparation were the same as those of the preparation of heneicosyl phenyl ketone. *α*-*n*-Butylarachidic acid was prepared by successive condensation of malonic ester with *n*-octadecyl iodide and *n*-butyl chloride, with subsequent hydrolysis and decarboxylation.

Fifty-six grams of *α*-*n*-butyl-*n*-nonadecyl naphthyl ketone was obtained from 55 g. of *α*-*n*-butylarachidic acid and 19 g. of naphthalene. The ketone distilled between 280° and 300° at 4 mm.

Anal. Calc'd for $C_{34}H_{54}O$: C, 85.27; H, 11.39.
Found: C, 84.96; H, 11.47.

[21] (2-n-*Butyl*-n-*eicosyl*)*naphthalene.* $C_{10}H_7CH_2CH(C_4H_9)(CH_2)_{17}CH_3$. One hundred three grams of *α*-*n*-butyl-*n*-nonadecyl naphthyl ketone was reduced with zinc amalgam, according to the method used in the preparation of docosylbenzene. After the reaction had been completed, the product was isolated and was distilled at 5 mm. Eighty-six grams of product distilling between 270° and 290° was obtained. As it was found that the product still contained oxygen, the reduction with zinc amalgam was repeated. The product was again isolated and distilled at 5 mm.

Sixty-nine grams of a distillate boiling between 270° and 290° was obtained. This material was a light-colored viscous oil.

Anal. Calc'd for $C_{34}H_{56}$: C, 87.85; H, 12.15.
Found: C, 87.62; H, 11.96.

n-*Heneicosyl tetrahydronaphthyl ketone.* $C_{10}H_{11}CO(CH_2)_{20}CH_3$. This ketone was prepared by the action of behenyl chloride on an equimolecular proportion of tetrahydronaphthalene in carbon disulfide solution in the presence of aluminum chloride, like the preparation of *n*-heneicosyl naphthyl ketone. After removal of the unreacted behenic acid, the product was distilled at 3 mm. The distillate, when recrystallized from acetone, melted at 61–62°.

A large amount of a lower-melting product was isolated from the acetone mother liquors. It is probable that this product was an isomeric ketone (position isomer), but no attempt was made to establish its composition.

Anal. Calc'd for $C_{32}H_{54}O$: C, 84.51; H, 11.97.
Found: C, 84.57; H, 11.97.

[32] n-*Docosyltetrahydronaphthalene.* $C_{10}H_{11}(CH_2)_{21}CH_3$. Eighty grams of *n*-heneicosyl tetrahydronaphthyl ketone was reduced with zinc amalgam and hydrochloric acid as in the preparation of *n*-docosylbenzene. After a second treatment with zinc amalgam and hydrochloric acid the product was isolated in the usual manner, and was distilled at 2 mm. The product distilled between 265° and 275°. The distillate solidified on cooling, and, without any further purification, melted at 43–45°.

Anal. Calc'd for $C_{32}H_{56}$: C, 87.18; H, 12.82.
Found: C, 87.34; H, 12.99.

[35] *5-Tetrahydronaphthyl*-n-*hexacosene-5.* $CH_3(CH_2)_3C(C_{10}H_{11}):CH(CH_2)_{19}CH_3$. One hundred twenty-nine grams of *n*-heneicosyl tetrahydronaphthyl ketone was condensed with *n*-butylmagnesium chloride in ether solution, as for the naphthalene derivative. After the first treatment with oxalic acid, the product was distilled at 4 mm. The fraction boiling between 270° and 280° was treated successively with *n*-butylmagnesium chloride and oxalic acid. The product was recovered in the usual manner and was distilled at 3 mm. One hundred and twenty-one grams of an almost colorless, viscous distillate boiling between 290° and 300° was obtained.

Anal. Calc'd for $C_{36}H_{62}$: C, 87.33; H, 12.67.
Found: C, 87.24; H, 12.51.

[36] *5-Tetrahydronaphthyl*-n-*hexacosane.* $CH_3(CH_2)_3CH(C_{10}H_{11})(CH_2)_{20}CH_3$. The reduction of 5-tetrahydronaphthylhexacosene-5 was carried out in every respect like the reduction of 5-phenylhexacosene-5. After the calculated amount of hydrogen had been absorbed, the reaction product was isolated as in the experiment mentioned above. From 56 g. of the olefin, 46 g. of an almost colorless oil, boiling between 275° and 285° at 3 mm. was obtained.

Anal. Calc'd for $C_{36}H_{64}$: C, 87.00; H, 13.00.
Found: C, 87.17; H, 12.93.

[38] n-*Docosyldecahydronaphthalene.* $C_{10}H_{17}(CH_2)_{21}CH_3$. The reduction of docosylnaphthalene to docosyldecahydronaphthalene was like that of 5-phenyl-*n*-hexacosane to 5-cyclohexyl-*n*-hexacosane. When the required amount of hydrogen had been absorbed, the catalyst was removed and the filtrate was successively diluted with water and extracted with ether. The extract was washed, dried over sodium sulfate, partially concentrated, and cooled to 0°. The hydrocarbon readily crystal-

lized from the solution. On a second recrystallization from ether, it was obtained in the form of snow-white crystals which melted at 53–54°.

Anal. Calc'd for $C_{32}H_{62}$: C, 86.00; H, 14.00.
Found: C, 86.04; H, 14.02.

n-*Heneicosyl biphenyl ketone.* $C_{12}H_9CO(CH_2)_{20}CH_3$. Two hundred grams of behenic acid chloride was condensed with 76 g. of biphenyl in carbon disulfide solution, as in the preparation of *n*-heneicosyl naphthyl ketone. On decomposition of the aluminum chloride complex with ice and hydrochloric acid, the ketone separated from the reaction mixture as a voluminous, crystalline mass. The mixture was filtered, and the precipitate washed several times with cold acetone in order to remove any unreacted behenic acid. The ketone was then recrystallized successively from methyl ethyl ketone and from chloroform. An almost snow-white product melting at 109–110° was obtained.

Anal. Calc'd for $C_{34}H_{52}O$: C, 85.46; H, 11.02.
Found: C, 85.47; H, 11.10.

[43] n-*Docosylbiphenyl.* $C_{12}H_9(CH_2)_{21}CH_3$. Ninety grams of heneicosyl biphenyl ketone was reduced with amalgamated zinc and hydrochloric acid, like the other ketones. On completion of the reduction, the xylene solution was washed free of hydrochloric acid and was dried over sodium sulfate. The residue obtained on removal of the xylene was recrystallized twice from ether. Forty-five grams of snow-white crystalline material, melting at 82–84.5° was obtained.

Anal. Calc'd for $C_{34}H_{54}$: C, 88.23; H, 11.77.
Found: C, 88.17; H, 11.71.

[44] *5-Biphenyl*-n-*hexacosene-5.* $CH_3(CH_2)_3C(C_{12}H_9):CH(CH_2)_{19}CH_3$. Ninety-eight grams of *n*-heneicosyl biphenyl ketone was brought into reaction with a Grignard reagent prepared from 12.3 g. of activated magnesium and 50 g. of *n*-butyl chloride as in the preparation of 5-naphthyl-*n*-hexacosene-5. After the first treatment with oxalic acid, the residue, which was insoluble in ether, was crystallized from acetone, yielding 92 g. As the product still contained oxygen, it was treated successively with *n*-butylmagnesium chloride and oxalic acid. The reaction product was washed with water and was distilled at 4 mm. Sixty-four grams of distillate boiling between 290° and 310° was obtained. The product melted at 37–39°.

Anal. Calc'd for $C_{38}H_{60}$: C, 88.29; H, 11.71.
Found: C, 88.19; H, 11.65.

[45] *5-Biphenyl*-n-*hexacosane.* $CH_3(CH_2)_3CH(C_{12}H_9)(CH_2)_{20}CH_3$. The reduction of 5-biphenyl-*n*-hexacosene-5 was carried out as in the preparation of 5-phenyl-*n*-hexacosane. When the required amount of hydrogen had been absorbed, the product was isolated and distilled at 2 mm. The entire product distilled between 290° and 300°. It solidified on cooling. Without any further purification, it melted at 44–45°.

Anal. Calc'd for $C_{38}H_{62}$: C, 87.95; H, 12.05.
Found: C, 87.99; H, 12.05.

SUMMARY

The preparation of sixteen hydrocarbons of high molecular weight, and of their intermediates is described. Inasmuch as the physical properties usually given for hydrocarbons have been reported in a previous publication (1), they are not included in this paper. The melting points of

products melting above room temperature as well as the approximate boiling points of most of the compounds are given.

ELIZABETH, N. J.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE ROSENMUND-VON BRAUN NITRILE SYNTHESIS[1]

C. F. KOELSCH AND A. G. WHITNEY

Received April 19, 1941

The general value of the reaction between cuprous cyanide and aryl halides as a preparative method for nitriles is demonstrated by the number of recent investigations in which it has been used. But nothing is known of the mechanism of the transformation involved, and no systematic study has been made to determine the optimum conditions for carrying out the reaction. Usually a mixture of an aryl halide with cuprous cyanide is heated at 250° for six hours or more, sometimes with no added substance and sometimes with pyridine added as a promoter or solvent.

Since this synthesis is one involving replacement of an aromatically bound halogen, it was felt that a quantitative study of it might lead to useful data regarding the relative reactivities of aryl halides and in addition might lead to the development of a rational procedure for carrying out the reaction. This paper reports the results of such a study.

It was expected that a reaction taking place between two phases, solid and liquid, would not be as free from complications as the equation Ar—X + CuCN → Ar—CN + CuX would indicate. This was soon found to be the case. The reaction between *p*-bromotoluene and cuprous cyanide at 250° was only 15% completed after the first hour, but after the next thirty minutes the reaction was nearly 75% completed. Similar behavior was found to be characteristic of the reactions of all the aromatic halides studied (Figs. 1 to 9). In each case[2] there was an induction period during which little reaction took place, and this was followed by a period of rapid reaction.

Such behavior made it impossible to obtain reaction constants for use in comparing the reactivities of the various halides. But for practical purposes a comparison was made by considering the reactivity of an aryl halide to be inversely proportional to the length of time, including the

[1] Abstracted from a thesis submitted to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Ph.D. degree, August, 1940.

[2] Points corresponding to extent of reaction during probable induction periods were not determined for all the aryl halides. However when such points were established, the induction period was clearly shown, and therefore it was assumed in all the curves.

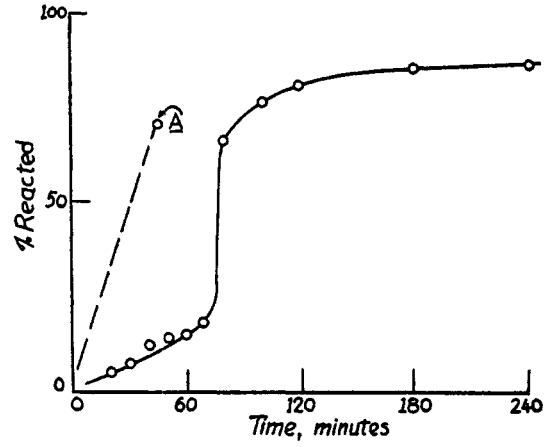

FIG. 1. p-C_7H_7Br
A, with p-C_7H_7CN

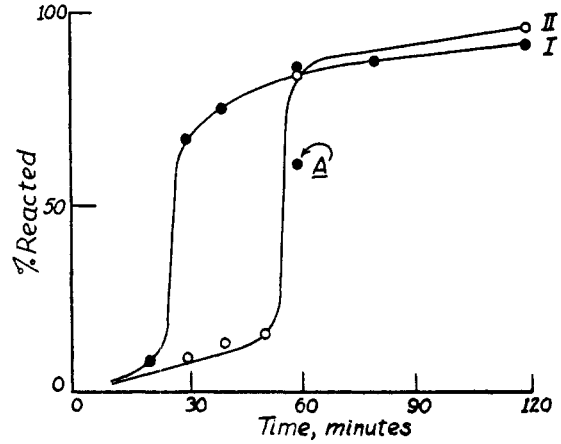

FIG. 2. I, C_6H_5Br; A, under CO_2. II, $C_6H_5Br + C_6H_4(OH)_2$

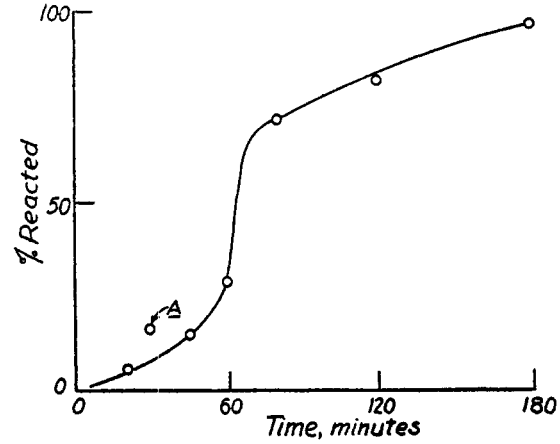

FIG. 3. m-C_7H_7Br
A, with 0.05 g. $CuSO_4$

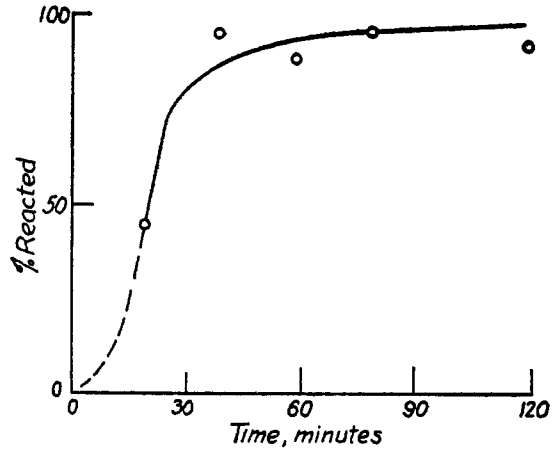

FIG. 4. s-$(CH_3)_3C_6H_2Br$

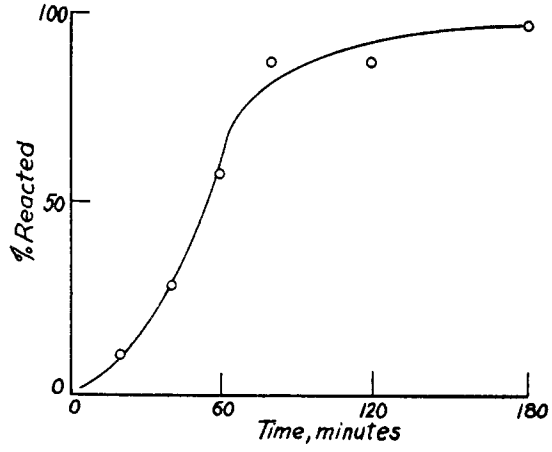

FIG. 5. p-$C_6H_5COC_6H_4Br$

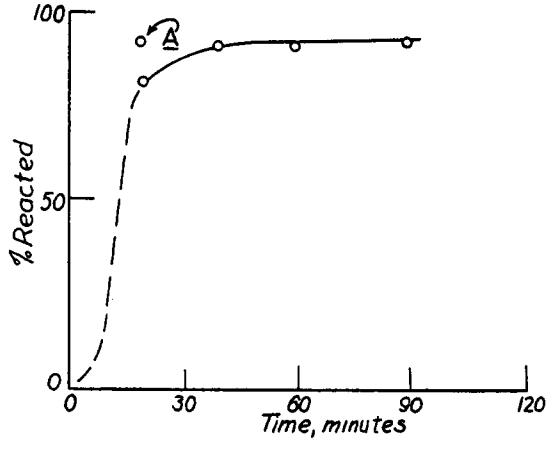

FIG. 6. α-$C_{10}H_7Br$
A, with 0.3 g. C_5H_5N

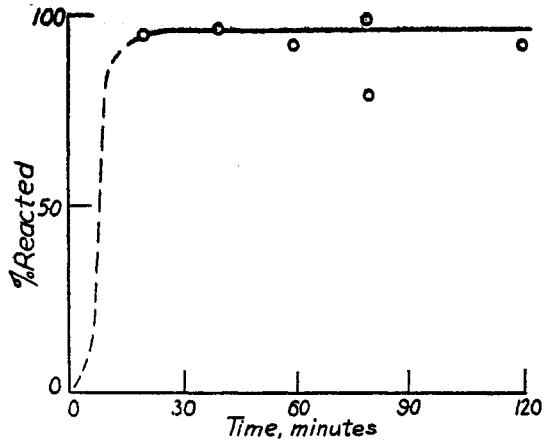

FIG. 7. p-BrC_6H_4COOH

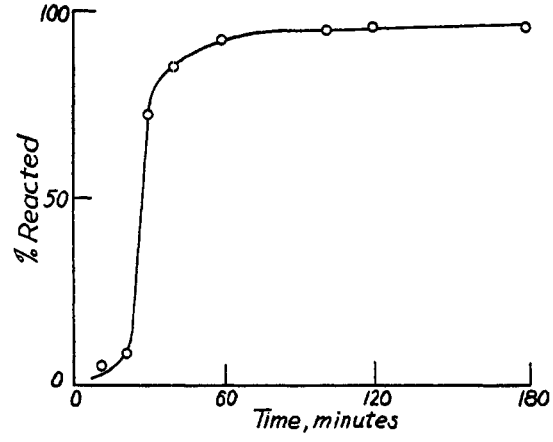

FIG. 8. o-C_7H_7Br

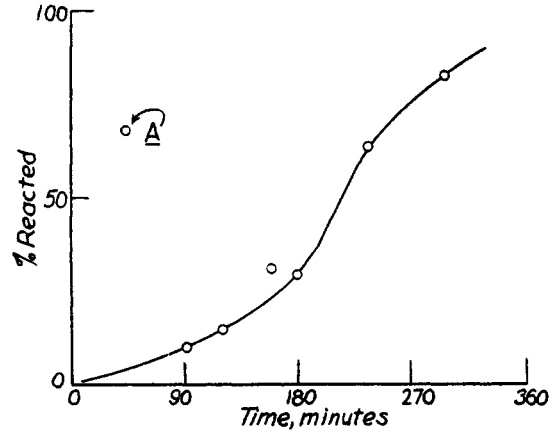

FIG. 9. p-$(C_6H_5)_2CHC_6H_4Br$
A, with p-C_7H_7CN

induction period, which was required for the substance to react with cuprous cyanide to the extent of 50%. On this basis the compounds studied were arranged in the following series of increasing reactivities: *p*-bromotriphenylmethane < *m*-bromotoluene < *p*-bromobenzophenone < *o*-bromotoluene < bromobenzene < bromomesitylene < α-bromonaphthalene < *p*-bromobenzoic acid. The curves describing the reactions indicate that the customary six hour heating period is usually too long, for with most aryl halides reaction is nearly complete after two hours.

An induction period indicated an autocatalytic reaction, and in the present case it was thought that the catalyst formed was probably the aromatic nitrile. This substance, through its ability to form a complex with cuprous cyanide, might dissolve the inorganic compound and thus accelerate the reaction by tending to make the mixture homogeneous. In agreement with this concept, it was found that when a small amount of *p*-tolunitrile was added to a mixture of *p*-bromotriphenylmethane and cuprous cyanide, the extent to which the reaction proceeded in a given time was greatly increased (Fig. 10, Curve I). When the amount of added nitrile was made larger, the extent of reaction fell off again, showing that the diluting effect of the nitrile finally outweighed its catalytic effect. Point A in Fig. 9, taken from Fig. 10, shows that the time required for 65% reaction between *p*-bromotriphenylmethane and cuprous cyanide was reduced by a factor of nearly six by the addition of the optimum amount of *p*-tolunitrile. The time for 71% completion of the comparatively fast reaction between *p*-bromotoluene and cuprous cyanide was almost halved (Fig. 1, point A) when *p*-tolunitrile was added to the reaction mixture.

But the line connecting point A (Fig. 1) with the origin had a slope representing a slower over-all reaction rate than the maximum rate of the uncatalyzed reaction. Since the uncatalyzed reaction curve had only begun to flatten out at 71% completion, this meant that not all of the induction period was eliminated by the addition of *p*-tolunitrile. Inhomogeneity of the reaction mixture at the start of the reaction therefore was not the only factor responsible for the induction period.

On the theory that peroxides, present originally and destroyed during the course of the reaction, might be acting as anticatalytic agents, the course of the reaction between bromobenzene and cuprous cyanide (Fig. 2, Curve I) was re-investigated using a series of reaction mixtures each containing 10–12 mg. of hydroquinone (Fig. 2, Curve II). The length of the induction period was almost doubled by the antioxidant; this indicated that an oxidizing agent might promote the reaction. Accordingly, the effect of adding varying amounts of cupric sulfate to reaction mixtures of *p*-bromotriphenylmethane and cuprous cyanide was investigated. The

cupric salt was found to exert a marked promoting effect[3] (Fig. 10, Curve 2); so part of the induction period in the usual reaction mixtures can be ascribed to the necessity for some of the cuprous salt to become oxidized.

The following equations represent a mechanism which may account for the catalytic power specific to copper salts, and for the apparent necessity for the presence of both cuprous and cupric forms of these salts in reactions involving replacement of aromatically bound halogen.

$$\mathrm{Ar{-}X + Cu^{++} \rightleftarrows [Ar{-}X \rightarrow Cu]^{++} \xrightarrow{Cu^{+}} Cu^{++} + [Ar{-}X \rightarrow Cu]^{+}}$$

$$\mathrm{[Ar{-}X \rightarrow Cu]^{+} \rightarrow CuX + Ar^{+}}$$

It is assumed that only Cu^{++} can form a stable complex with a halide through interaction with the halogen. In the absence of reducing agent

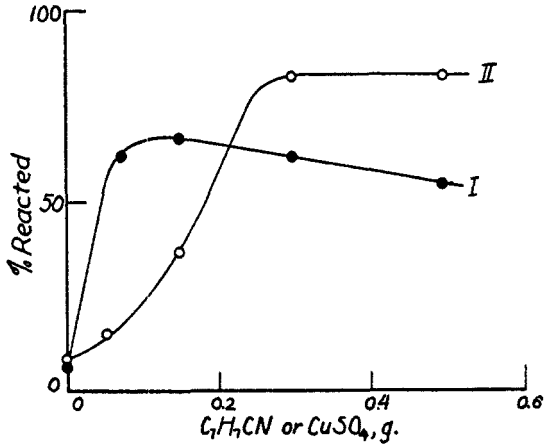

FIG. 10. 0.5 g. p-$(C_6H_5)_2CHC_6H_4Br$
With: I, p-C_7H_7CN, 45 min.; II, $CuSO_4$, 60 min.

(Cu^{+}) this complex can only revert to the substances from which it was formed. But a cuprous salt converts it into a new complex which can decompose to an aryl ion, which will then combine with any anion present.

The observations made in the present research have been of practical utility in a number of syntheses carried out in this laboratory. To a mixture of an aryl halide with cuprous cyanide is added a few drops of tolunitrile and a small spatulaful of cupric sulfate. The whole is then placed in a bath heated by boiling biphenyl (250°). Completion of reac-

[3] Weston and Adkins [*J. Am. Chem. Soc.*, **50**, 859 (1928)] observed that the formation of a catalyst from copper for the reactions between bromobenzene and potassium phenoxide or bromotoluene and acet-toluidide took place only when air was present.

tion, indicated by a marked diminution in volume of the solid copper salts and the formation of a dark liquid phase, follows rapidly (10 to 30 minutes).

EXPERIMENTAL

A weighed amount of an aromatic bromide together with two equivalents of cuprous cyanide was sealed in a 10 x 80 mm. soft glass tube. The reaction mixture was then heated for the required length of time in a bath of diethyl phthalate kept at 250° by contact with the vapor of boiling biphenyl in an appropriately designed apparatus. After being heated, the tube was removed and broken in a 250 ml. round bottomed analytical flask, where its contents were crushed. Organic substances were extracted by boiling with two successive 100-ml. portions of acetone. The acetone was removed after each extraction by decantation through a Hirsch filter, any copper salts caught on the filter being returned to the analytical flask. The adhering acetone was evaporated on a steam-bath and an excess of potassium dichromate was added, followed by 10–15 ml. of water.

The flask was then attached by means of a ground glass joint to a still-head bearing a dropping-funnel and a condenser pointing downwards. The lower end of the condenser dipped into a mixture of 8 ml. of 4% sodium hydroxide and 5 to 8 drops of 30% hydrogen peroxide contained in a 250 ml. Erlenmeyer flask. Through the dropping-funnel was then added 15 ml. of 40% (wt.) sulfuric acid to the analytical flask containing the copper salts and dichromate. The mixture was heated until fumes of sulfur trioxide were given off (20 to 30 minutes), bromine, hydrogen cyanide, and cyanogen bromide being taken up by the sodium peroxide solution. This solution was then boiled for five minutes, cooled, acidified with sulfuric acid, and again boiled for five minutes in order to convert all bromine and cyanogen bromide to bromide (1) and to expel hydrogen cyanide. The solution was cooled, made slightly alkaline with sodium hydroxide, and finally neutralized (litmus) with acetic acid. Potassium chromate was added as an indicator and the bromide was titrated with 0.1 *N* silver nitrate.

Numerous control experiments, in which the bromine contents of synthetic mixtures of cuprous bromide and cuprous cyanide were determined, showed that the analytical method was never in error by more than 1% and that the usual error was less than 0.3%.

The data from which Fig. 1 was constructed, given in Table I, are typical of the data representing the behaviors of the other aryl halides. It will be noted that the few duplicate determinations check each other well and that most of the points lie close to the curve. Accordingly it was not considered necessary to run duplicate determinations for every point.

Miscellaneous experiments. Since some of the curves did not approach 100% reaction, a loss of bromine was indicated. Experiments in which *p*-tolunitrile was heated (250°) for five hours in a sealed tube filled with carbon dioxide or for thirty-six hours in a sealed tube filled with air showed that this loss was not caused by bromination of the nitrile.

C_7H_7CN, g.	Cu_2Br_2, g.	% Br
0.3435	0.4310	49.3 (air)
.3626	.4434	51.7 (air)
.3478	.3293	52.9 (CO_2)
.3085	.4525	52.9 (CO_2)
	Calcd.,	55.7

Increasing the concentration of cuprous bromide in a reaction mixture caused a greater loss; a mixture of 0.4968 g. of *p*-bromotoluene, 0.4484 g. of cuprous bromide, and two equivalents of cuprous cyanide was heated for three hours at 250°. The analytical titration required 54.37 ml. of 0.1 *N* silver nitrate but the cuprous bromide added would require 31.25 ml. The difference, 23.12 ml. representing cuprous bromide formed, corresponded to 79.5% reaction, while under the usual conditions (Fig. 1) 84.8% reaction would have taken place.

This pointed to the loss of cuprous bromide through the formation of a complex slightly soluble in acetone. It was then found that a complex of cuprous bromide and *p*-tolunitrile could be prepared. Cuprous bromide was dissolved by heating

TABLE I

REACTIONS OF *p*-BROMOTOLUENE WITH CUPROUS CYANIDE

Ar—Br, g.	ml. 0.1 *N* $AgNO_3$	time, mins.	% reacted
0.4417	1.65	20	6.4
.5090	2.35	30	7.9
.4829	3.38	40	12.0
.5272	4.30	50	13.9
.5128	4.42	60	14.7
.5316	4.52	60	14.5
.5182	5.32	70	17.6
.4764	18.28	80	65.6
.5058	22.68	100	76.6
.5090	23.87	120	80.2
.5125	25.42	180	84.8
.5164	25.17	180	83.3
.5051	25.40	240	86.0
.4928 (a)	24.47	180	84.9
.4976 (b)	21.42	60	73.6
.5050 (c)	2.57	300	8.7
.5030 (c)	2.98	420	10.1
.5599 (d)	23.42	45	71.5
.5077 (e)	21.22	45	71.5

(a) Contained 3 eq. of Cu_2Cy_2, (b) Plus 0.3 g. of $CuSO_4$, (c) at 210°, (d) Plus 0.4977 g. of C_7H_7CN, (e) Plus 0.5356 g. of C_7H_7CN.

with an excess of the nitrile; on being cooled, the solution deposited a colorless crystalline substance which was then air dried on a suction filter.

Anal. Calc'd for $C_7H_7CN + Cu_2Br_2$, Br, 39.5. Found: Br, 39.2, 39.8.

The complex was at least partially dissociated into its components when it was dissolved in acetone, but it is possible that some of it escaped dissociation in the analytical method, and that its formation accounted for the failure of the analysis ever to show 100% reaction.

SUMMARY

It is shown that the reaction between aromatic bromides and cuprous cyanide is autocatalytic and that the time required for the reaction to

reach practical completion can be shortened materially if small amounts of cupric salts and of nitriles are included in the reaction mixtures. A mechanism is proposed to account for the catalytic effect of copper salts on reactions involving aromatic halogen compounds.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

THE REACTION OF β-BENZIL MONOXIME WITH BENZENESULFONYL CHLORIDE IN THE PRESENCE OF ALKALI

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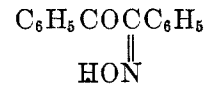
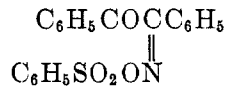
In 1904 Werner and Piguet (1) reported that β-benzil monoxime (I) reacts with benzenesulfonyl chloride in the presence of aqueous sodium hydroxide to give a sulfur-containing derivative to which they assigned structure (III) because phenylisocyanide was detected among its decomposition products.



(I)



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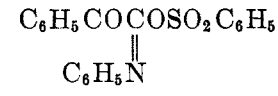

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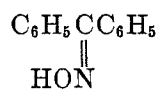

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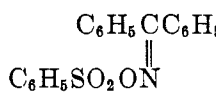
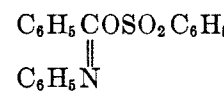


(V)



(VI)

Since benzophenone oxime (IV) with benzenesulfonyl chloride gives the benzenesulfonyl derivative (V), which on heating undergoes the Beckmann rearrangement to form (VI) (2), it seemed entirely possible that the derivative obtained by Werner and Piguet from β-benzil monoxime and benzenesulfonyl chloride has structure (II) and that its Beckmann rearrangement to (III) does not require the presence of alkali. Evidence supporting these ideas is presented in the present paper.

The earlier workers (1) reported that on treating β-benzil monoxime with benzenesulfonyl chloride and aqueous sodium hydroxide, a strong odor of phenylisocyanide was observed and that the sulfur-containing derivative (melting at 114°) was obtained. We also have observed the strong odor of phenylisocyanide in this preparation, but when the reaction is carried out in an ice-bath an excellent yield (89%) of practically pure derivative (melting at 120–121°) is obtained.

Werner and Piguet (1) reported that on treatment with hot dilute sulfuric acid, the derivative gives phenylisocyanide, benzonitrile, benzoic acid,

and benzenesulfonic acid; also, with hot alcoholic potassium hydroxide, the derivative gives phenylisocyanide. They assumed that the phenylisocyanide, as well as the benzoic and benzenesulfonic acids, were formed by the direct decomposition of the derivative and that the benzonitrile was produced by a molecular rearrangement of a portion of the phenylisocyanide; hence, the derivative was assigned structure (III). We wish to point out that although phenylisocyanide on heating for several hours at high temperatures (200–300°) undergoes rearrangement to form benzonitrile (3), it seems very unlikely that this change would take place in the presence of sulfuric acid, since, in the presence of acid, phenylisocyanide is readily hydrolyzed to form aniline.

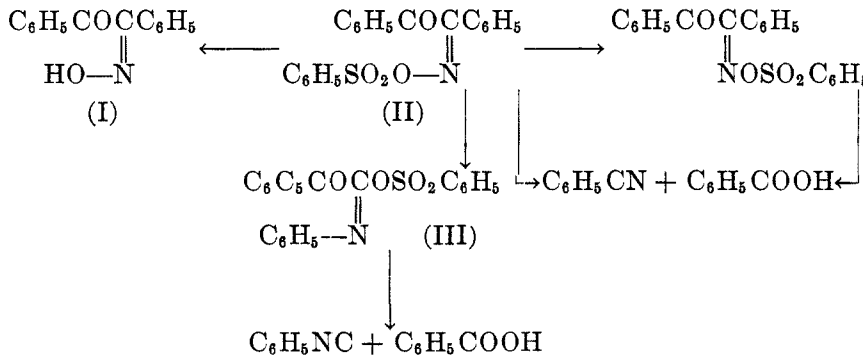
The pertinent results of our investigation may be summarized as follows: When dropped upon a red hot platinum foil, the derivative decomposes vigorously giving a strong odor of phenylisocyanide; however, when a few crystals of the derivative are heated to 120–130° (just above the melting point) no odor of phenylisocyanide is detected, the only odor being that of benzonitrile. A good yield (45%) of benzonitrile has been obtained by decomposing the derivative in this manner.

When an alcoholic solution of the derivative is allowed to stand at room temperature in the presence of potassium hydroxide, the odor of phenylisocyanide soon becomes pronounced, but on working up the reaction mixture it is found that more benzonitrile than phenylisocyanide is formed. On hydrolyzing the benzonitrile to benzoic acid and the phenylisocyanide to aniline, we obtained 81% of the two moles of benzoic acid that are theoretically possible (cleavage of the derivative giving one mole of benzoic acid and one mole of benzonitrile), and only 10% of the one mole of aniline that is theoretically possible. Since the excess (31%) above one mole (50%) of the acid obtained must have come from the benzonitrile, the yield of the latter was at least 62% of the theoretical amount, whereas the yield of phenylisocyanide was only 10%. It was further shown that under the conditions used phenylisocyanide is not converted to benzonitrile. Similarly, only a low yield (10%) of aniline is obtained when the derivative is decomposed by concentrated sulfuric acid at room temperature; apparently more benzonitrile than phenylisocyanide is produced also under these conditions.

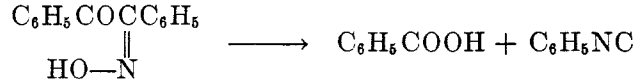
It has been found furthermore, that when the pure derivative in a solution of alcohol, water, and dioxane is allowed to stand in the presence of potassium hydroxide at room temperature, some (14%) of the original β-benzil monoxime (from which the derivative is prepared) is regenerated by hydrolysis of the derivative. On the basis of a similar result with the analogous benzenesulfonyl derivative of benzophenone oxime, Kuhara, Matsumiya, and Matsunami (2) concluded that the derivative had struc-

ture (V) and that structure (VI) is formed by a Beckmann rearrangement of (V); the rearrangement is effected by heat.

The results presented above show that the derivative obtained from β-benzil monoxime and benzenesulfonyl chloride has structure (II) and not structure (III) as was assumed by Werner and Piguet. The formation of the β-benzil monoxime can be explained only on the basis that the derivative has structure (II). The benzonitrile could result either from a direct cleavage of structure (II) (that is, by a so-called "Beckmann rearrangement of the second type") or by a preliminary isomerization of the derivative to the α-isomer, which then undergoes cleavage. The formation of phenylisocyanide involves a Beckmann rearrangement of (II) to (III), which then undergoes decomposition. Apparently, the rearrangement takes place to some extent even at room temperatures and, similar to the analogous rearrangement (2) of the benzophenone derivative, (V to VI), it presumably does not require the presence of reagents. The reactions described may be indicated as follows:



The equation for the reaction of β-benzil monoxime with benzenesulfonyl chloride in the presence of alkali has sometimes been represented as follows (4):



In the light of the results presented in the present paper this equation becomes misleading, since not only is the alkali not necessary for the formation of the phenylisocyanide, but the benzenesulfonyl derivative, which is first formed, decomposes to give also benzonitrile (possibly through a preliminary isomerization to the α-isomer), rather than only phenylisocyanide as implied by the equation.

EXPERIMENTAL

All melting points given are corrected.

Preparation of the benzenesulfonyl derivative of β-benzil monoxime. β-Benzil monoxime was prepared from α-benzil monoxime by the method of Taylor and Marks (5) and was purified by hydrolysis of its acetate as suggested by Barnes and Blatt (6); m.p., 111–112°.

The benzenesulfonyl derivative of β-benzil monoxime was prepared by a modification of the method described by Werner and Piguet (1). In a typical run, 11.25 g. of pure β-benzil monoxime was dissolved in 75 cc. of 4% sodium hydroxide (50% excess) and chilled to about 5° in an ice-bath. Ten grams of benzenesulfonyl chloride (13% excess) was added dropwise with efficient stirring and cooling during 80 minutes; stirring was continued 40 minutes longer. The mixture had a strong odor of phenylisocyanide. The derivative separated as an oil, which on standing overnight in a refrigerator crystallized to a white solid. It was filtered, washed with water and a little cold ether, and recrystallized from 175 cc. of a warm (below 50°) mixture of 3 volumes of absolute alcohol and 2 volumes of acetone. Several crops of crystals were obtained by evaporating the solvent at room temperature under reduced pressure; yield, 14.55 g., m.p. 120–121° with decomposition. After a second recrystallization from the same mixed solvent and washing with cold alcohol, the derivative melted at 122–123° with decomposition, when immersed in the bath at 120°. Some (1.08 g.) β-benzil monoxime (m.p. 109–111°) was recovered from the basic filtrate. Based on the amount of oxime used minus that recovered, the yield of derivative was 89%. The benzenesulfonyl derivative was also prepared by treating an ether suspension of the sodium salt of β-benzil monoxime at 0° with benzensulfonyl chloride. After recrystallization from ether, the derivative melted at 122–123° with decomposition. A mixed melting point of samples prepared by the two methods showed no depression.

Anal.[1] Calc'd for $C_{20}H_{15}NO_4S$: N, 3.83; S, 8.77.
Found: N, 3.64; S, 8.63.

Werner and Piguet reported that the derivative melted at 114°. We obtained a product melting at approximately this temperature when the reaction was carried out at room temperature, or at 5° using somewhat impure benzenesulfonyl chloride. Several recrystallizations were required to raise its melting point to 120°.

Reactions of derivative. (a) *Thermal decomposition.* When a few crystals of the derivative were dropped on a red hot platinum foil, they decomposed vigorously giving a strong odor of phenylisocyanide. On the other hand, when a few crystals were heated gradually to a point just above the melting point, they decomposed giving the odor of benzonitrile; the characteristic odor of phenylisocyanide was not detected under these conditions.

A large test tube was immersed in an oil-bath at 120–130° and 10 g. of the derivative was dropped into it in one-, to two-gram portions. Each portion melted, darkened, and "boiled," accompanied by a rise of temperature to about 190–200° as shown by a small thermometer within the test tube. The odor of benzonitrile was strong throughout, with only a faint isocyanide odor at one point. The tarry mass was extracted with ether, the ether boiled off, and the residue steam distilled. The distillate was made alkaline and extracted with ether. Evaporation of the ether gave 1.3 g. (45%) of benzonitrile, boiling at 189.5° (micro b.p.). The benzonitrile was further identified by hydrolysis to benzoic acid.

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[1] Microanalysis by R. L. Peck in this laboratory.

In another experiment, 4 g. (0.011 mole) of derivative was decomposed as described in the preceding experiment. The odor of isocyanide was perceptible once or twice during the experiment, whereas the odor of benzonitrile was strong throughout. The tarry mass was refluxed several hours with 20 cc. of water and 15 cc. of concentrated sulfuric acid. The mixture was diluted with water and extracted with ether. The ether solution on evaporation gave benzoic acid and benzonitrile, which was hydrolyzed with alkali to benzoic acid; the total yield of benzoic acid was 1.98 g. (74% of 0.022 mole). The aqueous acid solution, after making alkaline, gave a positive hypochlorite test for aniline. The aniline was extracted with ether, and isolated as the hydrochloride (0.11 g. or 8% of 0.11 mole) by pouring the dried ether solution into a saturated solution of hydrogen chloride in ether.

Like β-benzil monoxime itself (7), the derivative decomposed upon standing. An odorless sample left in the sunlight in a small vial decomposed in five months to a tarry liquid smelling of benzonitrile. A sample kept in the refrigerator one year was lowered in m.p. from 122–123° to 116–117°; upon washing the crystals with ether, the remaining crystals again melted at 122–123°, showing that decomposition had taken place only on the surface of the crystals.

(b) *Decomposition of derivative in the presence of sulfuric acid.* The derivative (5 g., 0.0137 mole) was dissolved in 100 cc. of concentrated sulfuric acid cooled in running water. After standing one week at room temperature, the amber solution was poured over crushed ice. A white precipitate was formed. The mixture was refluxed twenty-four hours, cooled, and shaken with ether, much of the precipitate remaining undissolved. The mixture was filtered. From the ether layer was obtained 1.83 g. of benzoic acid (56% of 0.0274 mole), by extraction with 5% sodium hydroxide solution, acidification with hydrochloric acid, extraction with ether, and evaporation of the ether. From the aqueous sulfuric acid layer, after making alkaline and extracting with ether, was obtained 0.16 g. of aniline hydrochloride or 9% of 0.0137 mole. It should be pointed out that benzonitrile in concentrated sulfuric acid gives products insoluble in ether (8); therefore it is probable that a portion of the benzonitrile formed from the derivative was not converted to benzoic acid.

(c) *Decomposition of derivative in the presence of potassium hydroxide.* The derivative (3.0 g.) was dissolved in 100 cc. of absolute ethanol and 30 cc. of absolute dioxane at room temperature. Upon adding 20 cc. of alcohol containing 4 g. of potassium hydroxide, the mixture turned yellow and the odor of isocyanide became evident; a white precipitate appeared which dissolved upon adding 20 cc. of water. After standing a week, most of the solvent was distilled off and 100 cc. of water added. The mixture was extracted with ether and the ether solution discarded. The alkaline aqueous solution was cooled and saturated with carbon dioxide. β-Benzil monoxime (0.25 g.) was obtained melting at 107–108°; yield 14%. After recrystallization from benzene and standing in air, the oxime melted at 111–112°; a mixed m.p. with an authentic sample of β-benzil monoxime (m.p. 111–112°) was the same.

In another experiment, 5 g. (0.0137 mole) of derivative was dissolved in 75 cc. of ethanol and 75 cc. of 10% potassium hydroxide added. A yellow color and the odor of isocyanide appeared at once. After two weeks at room temperature, the solution was acidified with sulfuric acid and refluxed twenty-four hours. The mixture was diluted with water and extracted with ether. From the ether layer was obtained benzoic acid; total yield of benzoic acid, 2.70 g. (81% of 0.0274 mole). From the aqueous acid layer, after making it alkaline and extracting with ether, was obtained approximately 0.1 g. of aniline or 8% of 0.0137 mole.

Alkaline treatment of phenylisocyanide. In order to show that under the conditions

used in the preceding experiment phenylisocyanide does not rearrange to benzonitrile, freshly prepared phenylisocyanide (9) (1.45 g.) was added to a mixture of 77 cc. each of 95% ethanol and 10% aqueous potassium hydroxide and allowed to stand two weeks at room temperature. The solution, smelling strongly of isocyanide, was made acid with sulfuric acid and refluxed four hours, using a condenser equipped with a hydrochloric acid trap to prevent loss of aniline. The mixture was made strongly alkaline with sodium hydroxide and refluxed four hours longer. The mixture was cooled, diluted with water, and extracted with ether. The ether layer was dried, filtered, and saturated with dry hydrogen chloride; the precipitate of aniline hydrochloride, m.p. 196–198°, weighed 1.47 g., (81%). From the aqueous alkaline layer only a trace of benzoic acid could be isolated. It is probable that the trace of benzonitrile, from which the benzoic acid was formed, was present in the phenylisocyanate used, since the method of preparation of the latter is reported to give some benzonitrile (3).

SUMMARY

Evidence has been presented that, contrary to the assumption of earlier workers, the derivative obtained from β-benzil monoxime and benezensulfonyl chloride in the presence of aqueous alkali is the unrearranged benzenesulfonyl derivative of the β-benzil monoxime. The derivative may undergo a Beckmann rearrangement, or it may cleave giving benzonitrile as one of the products; the cleavage might involve a preliminary isomerization to the α-isomer.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

EFFECT OF ORGANIC PEROXIDES IN CHLORINATION REACTIONS

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SATURATED HYDROCARBONS AND MONOCHLORIDES

A considerable accumulation of experimental evidence strongly indicates that, at least in many cases, the chlorination of saturated hydrocarbons proceeds by means of a chain mechanism involving chlorine atoms and free radicals (1). In general such chlorinations are expedited by agents which promote chain initiation in one of the two following ways:

(a) By the direct production of chlorine atoms. Heat, light, and traces of olefins (in "induced" substitutions on alkanes and alkyl chlorides) act in this way (2).

(b) By the formation of free radicals which then react with molecular chlorine to liberate chlorine atoms. In chlorinations, the catalytic effects of hexaphenylethane in the liquid phase, of azomethane in the vapor phase, and of tetraethyllead in both phases (3) are probably examples of this mechanism, although there is also the possibility of direct production of chlorine atoms.

In brominations and in hydrogen bromide additions to olefins, both oxygen and organic peroxides are well known to be effective catalysts, presumably because they initiate reaction chains by producing bromine atoms. Although liquid-phase addition of chlorine to olefins is but little affected by the presence of oxygen, the inhibitory effect of oxygen in vapor-phase chlorine substitution, has been well established (1, 3, 4). It is significant, however, that substitutive chlorination of olefins is facilitated by low (*ca.* 0.5%) oxygen concentrations at temperatures near 270° (5). Under proper experimental conditions, oxygen may be capable of initiating both bromine-atom and chlorine-atom chains. The inhibitory effect of high oxygen concentrations is attributed to the chain-breaking reaction

$$Cl\cdot + O_2 \rightarrow ClO_2\cdot$$

So far as is known, the analogous bromine-oxygen reaction does not take place. The effects of organic peroxides on the initiation of chlorine-atom chains remain to be investigated, and the present study is a preliminary effort towards that end.

General procedure. In an air-free system at 10^{-5} mm. a measured volume of chlorine was condensed (by the aid of liquid nitrogen) into a bomb tube containing the hydrocarbon to be chlorinated. The reaction tube was then sealed off and maintained at 0° in the dark for the desired length of time. Usually 0.05 mole (*ca.* 5.0 cc.) of hydrocarbon was treated with 0.005 mole of chlorine, although preliminary experiments showed that considerable variations in relative chlorine concentration do not significantly affect the results. At the completion of the experiment, analyses were made for free chlorine and for hydrogen chloride liberated; by these it was possible to account for all the chlorine originally introduced.

CHLORINATION OF ALIPHATIC AND ALICYCLIC HYDROCARBONS AND HALIDES

Cyclohexane. Air-free cyclohexane absorbed by substitution 25% of the chlorine to which it was exposed at 0° in the dark for 20 hours. The accelerative effect of light was demonstrated by control experiments; in systems illuminated by a 500 watt Mazda lamp at 20 cm., 100% of the chlorine was absorbed in one minute or less. The inhibitory effect of oxygen (2%) in the dark was shown by experiments in which no appreciable substitution took place at 0° in 120 hours. Ascaridole, unlike oxygen, markedly accelerated substitution in the dark in air-free systems. For example, the presence of as little as 1% of this perioxide brought about complete reaction in 15–20 minutes at 0°. Within the range of concentrations studied, the inhibitory effect of oxygen appears to outweigh the accelerative effect of ascaridole, for, in 20 hours at 0° in the dark, there was about 13% substitution in the presence of both reagents (oxygen 2–3%, ascaridol 2%) as compared to 25% substitution when both reagents were absent.

In supplement to the foregoing brief digest, the data on the chlorination of cyclohexane are summarized in Table I. The studies on *n*-heptane, *n*-butyl chloride, and cyclohexyl chloride thereafter reported in Table II follow essentially the same scheme.

AROMATIC HYDROCARBONS

It is well known that substitutive nuclear chlorination of aromatic hydrocarbons is facilitated by so-called halogen-carriers, among which are iodine, aluminum chloride, ferric chloride, iron, stannic chloride, activated charcoal, and aluminum oxide. On the other hand, side-chain chlorination is favored by light, by heat, and by the presence of peroxides, *i.e.*, in general, by the factors which facilitate the chlorination of saturated hydrocarbons. Nuclear and side-chain substitution may be simultaneous, as when chlorine is passed into toluene at room temperature. It has also been shown that under suitable conditions chlorine reacts by addition as well as by substitution with some aromatic nuclei, notably those of benzene and toluene (6).

So far as the present authors are aware, the addition of chlorine to *t*-butylbenzene or to *m*-xylene has not hitherto been reported.

In order to test the hypothesis that additive chlorination should be favored by low temperature and by relatively high initial chlorine concentrations, studies were made on benzene, chlorobenzene, toluene, *t*-butyl-

TABLE I

CHLORINATION OF CYCLOHEXANE[a]

(*In Vacuo* in the Dark)

DURATION OF REACTION	MOLE % OF ASCARIDOLE	% REACTION	NUMBER OF EXPERIMENTS	REMARKS
1–2 min.	—	1	6	
20 hours	—	25	10	
40 hours	—	40	4	
60 hours	—	60	4	
1 min.	—	100	6	Reaction illuminated
20 hours	—	0	5	2 mole % O_2 used
120 hours	—	0	5	2 mole % O_2 used
20 hours	2	100	6	
5 hours	2	100	3	
15 min.	1	100	2	
10 min.	0.5	98	1	
15 min.	0.1	85	1	
20 hours	0.5	12	1	2 mole % O_2 used
20 hours	2	13	1	3 mole % O_2 used

[a] No individual experiment deviated from the average by more than 2%.

TABLE II

CHLORINATION OF ALIPHATIC COMPOUNDS IN THE ABSENCE OF AIR AT 0°

SUBSTANCE	DARK	DARK 2 MOLE % OXYGEN	DARK 2 MOLE % ASCARIDOLE	ILLUMINATED
Heptane	10% in 20 hours	No reaction in 20 hours	100% in 20 min.	100% in 1 min.
Butyl chloride	7% in 20 hours	No reaction in 96 hours	85% in 20 hours	100% in 1 min.
Cyclohexyl chloride	3% in 20 hours	No reaction in 96 hours	52% in 20 hours	100% in 1 min.

benzene, and *m*-xylene at 0°. Exploratory experiments were conducted with toluene; hence, the chlorination of this hydrocarbon is described in detail. Table III gives a complete summary of the results obtained with toluene.

Toluene. Five cubic centimeters (0.032 mole) of toluene and 0.005 mole of chlorine were allowed to react in the dark at 0° in the absence of air.

At the end of 20 hours 99% of the chlorine had reacted, about 54% by substitution in the side chain, and about 45% by addition to the nucleus. Illumination accelerated the chlorine consumption markedly, the time for complete reaction being 30 seconds under illumination, as against 20–24 hours in the dark, but light did not appreciably alter the ratio of additive to substitutive chlorination (*cf.* expts. 186, 210). The illuminated reaction is not much affected by ascaridole, and is only moderately retarded by oxygen (expts. 208, 209, 210). The only factor investigated which materially affects the ratio of substitution to addition is the rate of chlorine introduction. In expt. 212, about 25 g. of chlorine was added in successive 5-g. portions to 150 cc. of toluene. Each chlorine addition was made at the temperature of a carbon dioxide-acetone mixture; the system was then

TABLE III

CHLORINATION OF TOLUENE

EXPT. NUMBER	GAS ADDED	TIME	LIGHT OR DARK	% REACTION		NO. OF EXPTS.
				Subst.	Add'n	
221	None	2 hrs.	D	50	25	1
182	None	20 hrs.	D	54	45	6
186	None	24 hrs.	D	55	45	4
203	None	36 hrs.	D	56	44	2
208[a]	None	30 secs.	L	58	42	2
210	None	30 secs.	L	55	45	2
209	1% O_2	1½ hrs.	L	55	45	2
213[b, c]	Air	—	L	75–85	15–20	1
212[b, c]	Air	—	L	40–45	50–55	1
211[b]	None	—	L	40–45	50–55	1

[a] Two mole per cent peroxide (ascaridole) used.

[b] One hundred fifty cubic centimeters of hydrocarbon and about 25 g. of chlorine.

[c] Difference in rate of introduction of chlorine (see text).

allowed to warm to 0°, and, when reaction ceased, the system was recooled and the process was repeated. In expt. 213, the presence at any time of an excess of chlorine was avoided by bubbling the chlorine slowly into the toluene held at 0°. The results indicate that addition is favored at the expense of substitution by relatively high chlorine concentrations.

t-*Butylbenzene.* About 5 cc. (0.032 mole) of hydrocarbon was treated with 0.005 mole of chlorine in the dark at 0° in the absence of air. After twenty hours, 87% of the chlorine had reacted, 59% by substitution, and 28% by addition. In a similar 2-hour run, 77% of the chlorine reacted, 51% by substitution, and 26% by addition. In 20-minute runs with 2% ascaridole, conducted in the dark at 0° in the absence of air, 84% of the chlorine reacted, 55% by substitution, and 29% by addition. Thus, or-

ganic peroxides accelerate both addition and substitution, but not so effectively as they accelerate the chlorination of saturated hydrocarbons.

Benzene. Benzene (150 cc., 1.67 moles) was cooled (as in expt. 212 with toluene) and 27 g. (0.38 mole) of chlorine was introduced in 4- to 5-g. portions. When the excess of benzene had been removed by distillation, the residue readily crystallized. The melting point (157°) indicated that the product was hexachlorocyclohexane, a conclusion further substantiated by analysis (Table IV, Experimental Part). At least 95% of the chlorine consumed was thus accounted for.

Chlorobenzene. Experiments similar to those with benzene were conducted with chlorobenzene. As with benzene, there was little substitution under the experimental conditions; about 85% of the chlorine consumed was accounted for in the form of heptachlorocyclohexane.

m-*Xylene.* In one experiment with this hydrocarbon, 25–26 g. (0.36 mole) of chlorine was passed rapidly into 150 cc. (1.2 moles) of *m*-xylene maintained at 0° in diffused light. Reaction was rapid, and there was profuse evolution of hydrogen chloride. Distillation of the resultant mixture under reduced pressure yielded, aside from *m*-xylene, a fraction which distilled over a range of about 20° and contained 27% of chlorine (evidently a mixture of monochloro substitution products), and a higher-boiling fraction which contained about 55% of chlorine.

In an otherwise similar experiment the xylene was maintained at about −55°, and the chlorine was added in 5-g. portions. When the addition was complete there was no perceptible chlorine coloration, and there had been practically no evolution of hydrogen chloride. Vigorous evolution of hydrogen chloride took place, however, when the mixture was warmed to room temperature. The final distillation fraction contained 52% of chlorine, and was shown by subsequent fractionation and analysis to consist of 4,6-dichloro-1,3-dimethylbenzene and a tetrachloro substitution (?) product of *m*-xylene.

In view of the observations recorded it seems probable that although there is undoubtedly some side-chain substitution, the initial reaction is principally addition. In all probability the unstable tetrachloro addition product, when warmed, loses hydrogen chloride to produce the 4,6-dichloro-*m*-xylene isolated. A similar process would also account satisfactorily for the tetrachloroxylene, which was shown to contain two atoms of nuclear chlorine.

The authors wish to express their appreciation to Dr. Frank R. Mayo for help in connection with this investigation.

EXPERIMENTAL PART

Materials. Chlorine (Ohio Chemical and Manufacturing Co.) was found to be 99% pure. In some experiments the chlorine from the tank was dried and distilled

before use, but the results in these instances did not differ from those in which the chlorine had not been so treated. Therefore, in subsequent experiments, the chlorine was used directly from the tank, precautions being taken to prevent the introduction of moisture.

Reagent grade cyclohexane (Eastman) was washed first with concentrated sulfuric acid and then with fuming sulfuric acid. The cyclohexane thus treated, after being washed with water and dried over calcium chloride, was distilled through a column and stored over sodium wire in a dark bottle: b.p. 80° at 750 mm.; n_D^{20} 1.4258.

n-Heptane (Eastman) was treated with concentrated sulfuric acid. The hydrocarbon was washed first with water, then with sodium carbonate solution, and finally with several portions of water. The *n*-heptane after being dried over calcium chloride, was distilled through a 35-cm. column. The fraction distilling at 97.2–97.4° at 746 mm. was collected and stored in a dark bottle over sodium wire; n_D^{20} 1.3870.

n-Butyl chloride (Eastman) was distilled through a column; the fraction boiling at 76–77° at 750 mm. was collected and stored in a dark bottle; n_D^{20} 1.4021.

Cyclohexyl chloride was prepared by the peroxide-catalyzed chlorination of cyclohexane with sulfuryl chloride (7). The product was distilled through a 30-cm. column. The fraction boiling at 141–143° at 750 mm. was collected and stored in a dark bottle; n_D^{20} 1.4610.

Toluene (reagent grade) was refluxed over sodium and then distilled through an 8-ball Schneider column. The fraction boiling at 109.5–110° at 750 mm. was stored over sodium wire; n_D^{20} 1.4949.

t-Butylbenzene was prepared by the Friedel-Crafts synthesis. The refractive index (n_D^{20} 1.4927) and the lack of reactivity of the product towards bromine established the purity of the fraction collected at 166.5–166.8° at 739 mm.

Benzene (best grade, thiophene-free) was distilled before use; b.p. 79.5–80° at 750 mm.; n_D^{20} 1.5005.

Chlorobenzene (best grade, Eastman) was distilled before use; b.p. 131–132° at 747 mm.; n_D^{20} 1.5241.

Bromobenzene (reagent grade, Merck) was distilled before use; b.p. 153–155° at 747 mm.; n_D^{20} 1.5579.

m-Xylene was distilled through a 30-cm. column. A fraction boiling at 138–139° at 750 mm. (n_D^{20} 1.4951) was used.

Apparatus. A vacuum line was used in the experiments conducted under air-free conditions. In most cases about 5 cc. of the hydrocarbon (or chloride) was by pipette into a 10-cc. bomb tube which was then cooled and sealed to the line. The sample was then thrice degassed. Chlorine was introduced from the tank into a chlorine chamber of known volume attached to the line, and was brought to atmospheric pressure by means of a sulfuric acid trap. The reaction tube was then cooled with liquid nitrogen, and by suitable manipulation of the stopcocks, the chlorine was distilled into this tube. Oxygen (when used) was introduced from a 2-l. chamber attached to the line, and brought to the required pressure (measured by a manometer).

In the vacuum-line experiments the extent of reaction was estimated by determining the unused chlorine and the hydrogen chloride evolved. In all experiments with saturated compounds the sum of the two in moles was found to equal the number of moles of chlorine originally introduced. Uncombined chlorine was determined by absorption in potassium iodide solution and titration of the liberated iodine. Sodium iodate was next added to the titrated portion; additional iodine, representing the hydrogen chloride formed in the substitution reaction, was thus liberated. It was titrated with standard sodium thiosulfate (8).

For the quantitative determination of total halogen, in such substances as the

toluene-chlorine product, the sodium and liquid ammonia method was used (9). About 0.3 g. of the substance to be analyzed was dissolved in ether. This solution was added to about 100 cc. of liquid ammonia in a 200–300-cc. round-bottomed flask. Small pieces of sodium were added until the blue color no longer faded. When this color had persisted for about one-half hour, it was discharged by the addition of ammonium nitrate. The ammonia was then allowed to evaporate. Ten cubic centimeters of ethyl alcohol was added to the residue, and the solution was evaporated to dryness. Ten cubic centimeters of water was then added, and the solution was boiled. The halide was titrated by the Mohr method.

Halogens in the side chains of aromatic compounds or in aliphatic or alicyclic hydrocarbons were determined by the use of alcoholic alkali (10). About 100 mg. of the substance to be analyzed was dissolved in 10 cc. of absolute ethyl alcohol. To this solution, 5 cc. of 1 *N* sodium methoxide in methyl alcohol was added. The resulting mixture was refluxed gently for one hour, and the halide was titrated by the Mohr method. The results of the analyses appear in Table IV.

TABLE IV

ANALYSES OF PRODUCTS

SUBSTANCE TREATED	PRODUCTS	TOTAL CHLORINE		CHLORINE REMOVED BY ALCOHOLIC NaOH	
		Found, %	Cal'd, %	Found, %	Cal'd, %
Toluene	Benzyl Chloride	27.0	27.0	27.0	27.0
	Chloromethylhexachlorocyclohexane	72.8	73.2	31.5	31.6
Benzene	Hexachlorocyclohexane	73.0	73.2	36.5	36.6
Chlorobenzene	Heptachlorocyclohexane	76.0	76.5	33.0	32.8
m-Xylene	4,6-dichloro-1,3-dimethylbenzene	40.4	40.6	None M.p. 68°	None M.p. 68°
	Tetrachloro-*m*-xylene (?)	57.5	58.0	29.0	29.0

SUMMARY

The chlorination of cyclohexane, *n*-heptane, *n*-butyl chloride, and cyclohexyl chloride proceeds slowly at 0° in the absence of light and catalysts. The presence of organic peroxides markedly accelerated substitution in the dark. The reactions are also tremendously accelerated by light. Oxygen completely inhibits chlorination.

Aromatic hydrocarbons are more readily chlorinated than aliphatic or alicyclic hydrocarbons. Chlorine absorption is relatively rapid in the dark at 0°; hence the effects of light and of peroxides are less marked. Oxygen inhibits reaction only slightly. Under the conditions described, aromatic chlorination takes place both by addition to the aromatic nucleus and by substitution. The percentage of addition product formed in the studies

here described is: for benzene, 100%; for chlorobenzene, over 90%; for toluene, 45%; for *t*-butylbenzene, 35%. At −50° chlorine adds to *m*-xylene, but at 0° the addition product loses hydrogen chloride to give substituted *m*-xylenes with two atoms of chlorine in the aromatic nucleus.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE BROMINATION OF CYCLOHEXANE, METHYLCYCLOHEXANE, AND ISOBUTANE

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Previous work (1) in this laboratory has shown that the side-chain bromination of toluene is favored by the presence of oxygen or peroxides, by low concentrations of bromine, and by the action of light. A chain mechanism involving bromine atoms was proposed to explain these effects. The present investigation was undertaken to determine whether or not similar factors control the bromination of aliphatic hydrocarbons. The hydrocarbons chosen for investigation were cyclohexane, methylcyclohexane, and isobutane. The present study makes possible a comparison of the relative reactivities of primary, secondary, and tertiary hydrogen atoms towards substitution by bromine atoms.

PREVIOUS WORK[2]

Markownikow (3) reported that cyclohexane reacts only slowly with bromine at 100°, and that at 110° an equimolecular mixture of the reactants gives chiefly polybromides and unchanged cyclohexane. Bodroux and Taboury (4) found that the bromination of boiling cyclohexane is accelerated by sunlight and ultraviolet light.

The photochemical vapor-phase bromination of cyclohexane has been studied by Pusch (5), Noddack (6), Wood and Rideal (7), and Jost (8). Both Pusch and Noddack employed radiation corresponding to the continuous absorption of bromine, worked at room temperature, and recorded no precautions to exclude oxygen. They agree that one molecule of bromine reacts per quantum of light absorbed.[3] Wood and Rideal employed glass apparatus at room temperature and used radiation corresponding to the band absorption of bromine. They observed a slow reaction in the dark. Because their reaction products consisted mostly of di- and

[1] This paper is an abstract of a dissertation submitted by William Hered in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The University of Chicago, 1939.

[2] See Ref. 2 for references on the bromination of pure and impure hydrocarbons with and without metal catalysts.

[3] Pusch records that under the same conditions, the quantum yields in the bromination of toluene, hexane, and heptane exceed one and range as high as sixty.

tri-bromocyclohexanes, they suggested that cyclohexyl bromide was produced in an activated state such that it would easily react with molecular bromine. Jost worked with quartz apparatus at 73–106°, found no reaction in the dark, and concluded that the thermal reaction of Wood and Rideal must have been a wall reaction. He employed both types of radiation previously mentioned and found no difference between them. This was taken as an indication that an activated bromine molecule would eventually dissociate into atoms, even if not in a single step. Wood and Rideal and Jost are in agreement that the rate of the reaction in any single experiment is proportional to the light absorbed, and that the reaction is inhibited by oxygen. Jost records that in a series of experiments the rates of reaction also depend on the cyclohexane concentration. He states that in the absence of oxygen, the quantum yields varied from 12 to 37, in its presence, from 3 to 7. A temperature coefficient of about 2 for a range of 30° indicated that the quantum yield would have been about 2 at room temperature, in fair agreement with the work of Pusch and of Noddack. From the relations between the light absorbed and the extent of reaction and from the phenomenon of oxygen inhibition, Jost concludes that the vapor-phase photochemical bromination of cyclohexane is a chain reaction involving bromine atoms.

Markownikow (9) found that pure liquid methylcyclohexane does not react with bromine in diffused light. The reaction in sunlight is slow at 100°, moderate at 115°.

Isobutane and bromine in equimolecular quantities in daylight are reported by Butlerow (10) to give polybromides and unchanged isobutane.

The chlorination of isobutane and other paraffin hydrocarbons has been studied by Hass and co-workers, and some interesting generalizations have been reported (11). One of these is that the order of increasing activity of hydrogen atoms is primary, secondary, tertiary, and that their relative reactivities in the thermal vapor-phase chlorination at 300° are represented by the series 1.00, 3.25, 4.33. The series approaches 1, 1, 1 as the temperature increases, and is not affected by the presence of any catalysts investigated. The results of liquid-phase chlorination correspond to those obtained at a higher temperature in the vapor phase.

EXPERIMENTAL

A study has been made of the factors which influence the bromination of cyclohexane, methylcyclohexane, and isobutane in the liquid phase. Mixtures of bromine and of the hydrocarbon (containing no solvent) were allowed to react near room temperature in glass-stoppered or sealed containers. The progress of the reaction of cyclohexane or methylcyclohexane in sealed tubes was estimated with a precision of ±3% by comparison with standard solutions of bromine in carbon tetrachloride, and in stoppered tubes with a precision of better than 1% by titration with potassium

iodide and sodium thiosulfate. Reactions in sealed tubes were usually allowed to proceed until the mixtures became colorless, when 100% reaction was assumed. The extent of the bromination of isobutane was determined by titration when the reaction did not reach completion.

Experiments in the dark were carried out in a large, stoppered, water-filled Dewar vessel maintained between 20° and 25°. Experiments in the light were usually carried out at a distance of 16 cm. (center to center) from a 300 watt incandescent lamp. The reaction vessel was suspended in a water-bath with a plane glass window. Tap water was circulated through this bath at a rate such that its temperature was maintained near 20°. In experiments lasting up to seven hours, the maximum variation was ±2°, in longer experiments, ±5°. To avoid any complications from a photochemical vapor-phase reaction, the reaction tubes were entirely screened from light above the level of their liquid contents.

Materials. Eastman Kodak Co. cyclohexane was washed with fuming sulfuric acid, dried over calcium chloride, fractionally distilled, and stored over sodium or phosphorus pentoxide. The fraction used has the following constants: m.p. 5.8°; b.p. 80.2–80.5° at 750 mm.; n_D^{20} 1.4256. The work of Seyer, Wright, and Bell (12) indicates that such material might contain a small amount of methylcyclohexane. Fractionation through a Podbielniak column yielded a fraction of m.p. 6.0° and n_D^{20} 1.4258 (recorded for cyclohexane (12), 6.47°, 1.42635) which was indistinguishable in bromination experiments from the material usually employed.

Methylcyclohexane and 99.5% isobutane were generously supplied by the Universal Oil Products Co. The methylcyclohexane was purified according to the procedure used for cyclohexane: b.p. 100.2–100.8° at 746 mm.; n_D^{20} 1.4231.

Procedure. Experiments with cyclohexane and methylcyclohexane in the presence of air were carried out in glass-stoppered vessels which were opened periodically for titration of samples. Isobutane experiments, usually employing 1.3 g. of hydrocarbon, were carried out according to the procedure described by Kharasch, Fineman, and Mayo (13) for cyclopropane, with provisions for admission of measured pressures of oxygen before the reaction tubes were sealed. The reported uncorrected oxygen pressures were measured while the reaction tubes were partially immersed in a bath at −80°.

Experiments with cyclohexane and methylcyclohexane in the absence of air, and with measured pressures of oxygen, were performed in much the same manner except that 5 cc. of the dry liquid hydrocarbon was introduced into the reaction tube with the aid of a pipette.

Analysis of products from isobutane and methylcyclohexane. The proportion of tertiary bromide in the bromination products was estimated from the extent of reaction with water at room temperature (14). The proportion of dibromide in the bromination products was estimated by removing the unsubstituted hydrocarbon and analyzing for bromine.

RESULTS

Effect of oxygen and light. The individual effects of light and oxygen on the bromination of cyclohexane, methylcyclohexane, and isobutane are shown in Table I. It is evident that in the absence of oxygen and light, all three hydrocarbons react only to the extent of 1% per month. In the dark, but in the presence of oxygen, cyclohexane and methylcyclohexane react much faster, about 10% per day. In the case of these two hydro-

carbons, illumination in the absence of oxygen is approximately as effective in accelerating the reaction as oxygen in the absence of illumination, the factor being of the order of 500 in either case. The rate of bromination of isobutane (at a higher bromine concentration) is increased to a greater extent by light but to a lesser extent by oxygen.

The combined effects of oxygen and light are best illustrated with the cyclic hydrocarbons by experiments (Table II) in which the initial bromine concentration was 0.20 molar and the oxygen pressure was 5–15 cm. These data show that oxygen and light together cause the reaction to

TABLE I

EFFECT OF LIGHT AND OXYGEN ON BROMINATION OF HYDROCARBONS[a]

	INITIAL CONCENTRATION Br_2 (MOLES/LITER)	ABSENCE OF LIGHT		LIGHT PRESENT OXYGEN ABSENT
		Oxygen Absent	Oxygen Present	
Cyclohexane	0.05			40% in 70 hours (2)
	.20	5% in 8 months (2)	60% in 5 days[b] (2) 75% in 4 days[e] (2) 55% in 4 days[f] (2)	60% in 136 hours (2)
Methylcyclohexane	.05			100% in 2–3 hours (3)
	.20	8% in 6 months (3)	50% in 5 days[b] (2)	100% in 60–78 hours (3)
Isobutane	1.0			100% in 8 hours
	2.0	<2% in 2 months (2)	50% in 20 days[c] 70% in 20 days[d]	100% in 13–15 hours (2)
	5.0			100% in 35 hours

[a] Numbers in parentheses indicate total number of experiments in which substantially the same result was obtained.

[b] Air at 1 atmosphere pressure.

[c, d, e, f] Oxygen at 1, 10, 15 or 37 cm. (of mercury) pressure, respectively.

proceed several hundred times as fast as either agent alone. Their combined effect approximates the product, rather than the sum, of their individual effects. Experiments with 1.0 or 2.0 molar bromine solutions in isobutane indicate that the photochemical bromination of isobutane is accelerated by oxygen by a factor of only 20 to 25, depending on the bromine concentration.

The accelerating effect of oxygen on the photochemical reaction varies with its pressure. Data on cyclohexane experiments at an initial bromine concentration of 0.20 molar in Table II are amplified in Figure 1. Similar data on methylcyclohexane are given in Table II and Figure 2. It is

TABLE II

COMBINED EFFECTS OF LIGHT AND OXYGEN ON BROMINATION OF HYDROCARBONS

	INITIAL CONCENTRATION Br_2	OXYGEN PRESSURE IN CM. MEASURED AT −80°						AIR AT 1 ATM.
		1	5	10	15	37	76	
Cyclohexane	0.05	90% in 10 min. (2)	85% in 10 min. (2)		80% in 10 min. (2)	70% in 10 min. (2)		85% in 1 hr. (3)
	.20	50% in 30 min. (4)	70% in 30 min. (4)		55% in 30 min. (2)	35% in 30 min. (4)	20% in 30 min. (2)	85% in 3 hrs. (5)
	1.0			100% in 7 hrs. (2)				85% in 5 hrs. (2)
	5.0							50% in 65 hrs. (2)
Methylcyclohexane	.05							85% in 5 min. (3)
	.20	80% in 5 min. (2)	90% in 5 min. (2)		80% in 5 min. (2)	70% in 5 min. (2)		85% in 15 min. (4)
	1.0			100% in 3 hrs. (2)				85% in 2 hrs. (2)
	5.0							50% in 48 hrs. (2)
Isobutane	1.0		100% in 20 min. (3)	100% in 20 min. (3)				
	2.0	90% in 4 hrs. (2)	90% in 45 min. (3)	90% in 45 min. (2)	90% in 45 min.	90% in 25 min. (2)		
	5.0			100% in 23 hrs. (3)				
Toluene	.20		100% in 2–4 sec. (2)		100% in 5–7 sec. (2)	100% in 10–12 sec. (2)	100% in 15–20 sec. (2)	
	1.0		100% in 20 sec. (2)		100% in 40 sec. (2)	100% in 2 min. (2)	100% in 3 min. (2)	

shown that oxygen exerts its maximum effect on the photochemical bromination of cyclohexane and methylcyclohexane at about 5 cm. pressure, and that higher oxygen pressures retard the reaction. The data indicate that the optimum oxygen pressure may be higher (with 2.0 molar bromine) for isobutane.

That oxygen retards as well as promotes the bromination of toluene had not been observed previously (1). The highest rate of bromination of toluene is obtained at low oxygen pressures (Table II).

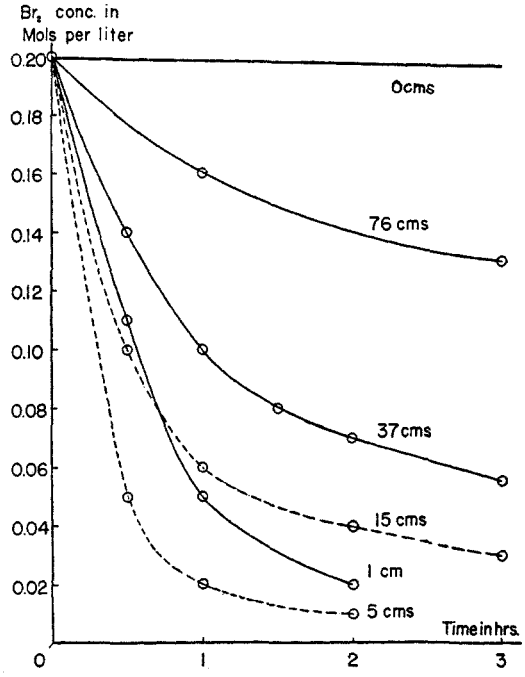

FIG. 1. PHOTOBROMINATION OF CYCLOHEXANE AT VARIOUS OXYGEN PRESSURES

On the basis of the data presented, valid comparison of the relative rates of bromination of cyclohexane, methylcyclohexane, and isobutane is possible only for the photochemical reaction with 10 cm. pressure of oxygen and an initial bromine concentration of 1.0 molar. The times required for complete reaction of bromine are in the approximate relationship: cyclohexane, 20; methylcyclohexane, 9; isobutane, 1.

Effect of bromine concentration. Comparative data on the effect of bromine concentration are available only for the photochemical reactions recorded in Tables I and II. Table I indicates that in the absence of oxygen, the proportion, but not the absolute amount, of bromine reacting with

cyclohexane is greater in the more dilute solution. With methylcyclohexane under the same conditions, both the proportion and absolute amount of bromine reacting is greater in the more dilute solution. Isobutane was studied only at higher concentrations, and in the absence of oxygen the absolute amount of bromine reacting seems to be nearly independent of the initial bromine concentration, over the concentration range studied.

The most extensive study of the effect of bromine concentration was made in photochemical experiments in the presence of air, as shown in the

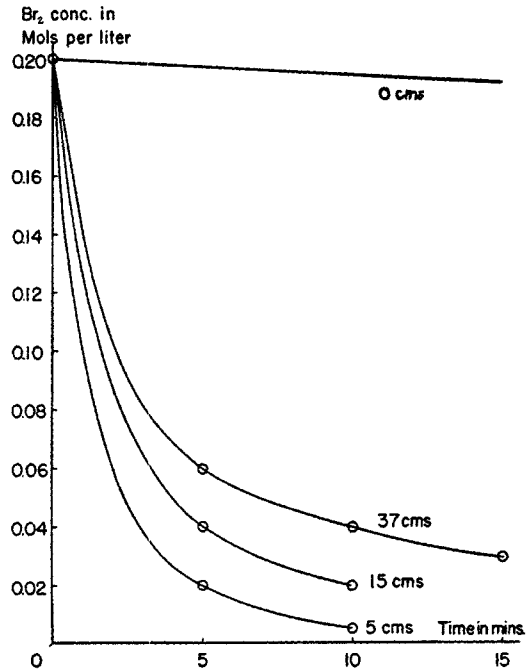

FIG. 2. PHOTOBROMINATION OF METHYLCYCLOHEXANE AT VARIOUS OXYGEN PRESSURES

last column of Table II. With both cyclohexane and methylcyclohexane, the time required for complete reaction decreases as the initial bromine concentration is decreased, and both the absolute amount and proportion of bromine reacting in a given time is lower at 5.0 than at 1.0 molar initial bromine concentration. Similar effects with both these hydrocarbons and isobutane are shown under various oxygen pressures in Table II. It is evident that bromination is actually retarded by high concentrations of bromine.

Effect of peroxides. Although organic peroxides markedly increased the

rate of side-chain bromination of toluene, no detectable acceleration was noted in the rate of bromination of the other three hydrocarbons employed in the present study. Experiments were carried out in the presence and absence of air and light, at initial bromine concentrations of 0.05 to 2.0 molar, using benzoyl peroxide, lauroyl peroxide, and ascaridole in proportions from 0.02 to 3 mole per cent per mole of bromine. The peroxides were added in one or in several portions to all three hydrocarbons. In a few experiments a slight retardation of the bromination was noted.

Effect of inhibitors. As in the case of toluene, the rate of bromination of these hydrocarbons can be retarded by small amounts of organic inhibitors (Table III). All of the experiments were carried out in the light, and 0.02 mole of the inhibitor per mole of bromine was employed. It is

TABLE III

THE EFFECT OF INHIBITORS ON BROMINATION OF HYDROCARBONS

	INITIAL CONCENTRATION Br_2	OXYGEN PRESSURE	INHIBITOR	EXTENT OF REACTION
Cyclohexane	0.2	5 cm.	None (control)	90% in 1 hour
			diphenylamine	85% in 3 hours
			ethanol	60% in 3 hours
			thiophenol	80% in 14 hours
			isoamyl nitrite	<2%[a] in 74 hours
Methylcyclohexane	0.2	5 cm.	None (control)	100% in 15 min.
			isoamyl nitrite	<2%[a] in 60 hours
Isobutane	2.0	10 cm.	None (control)	100% in 1 hour
			isoamyl nitrite	<2%[a] in 50 hours

[a] Determined by titration of bromine.

noteworthy that isoamyl nitrite inhibits the reaction nearly completely, and that thiophenol, ethanol, and diphenylamine are less effective inhibitors.

Products of reaction. In the case of each hydrocarbon, several lots of reaction products were combined, fractionally distilled, and analyzed as described in the experimental part. Cyclohexane yielded only cyclohexyl bromide. Methylcyclohexane gave about 75% mono- and 25% dibromides. Isobutane gave a mixture of about 60% tertiary butyl bromide and 40% 1,2-dibromo-2-methylpropane. Because significant quantities of isobutyl bromide were not found it is thought that the dibromide may come from isobutene formed by loss of hydrogen bromide from tertiary butyl bromide.

Effect of reaction products. Figures 1 and 2, together with other data

which cannot be economically presented in this paper, indicate that in the photochemical, oxygen-catalyzed brominations of cyclohexane and methylcyclohexane where the initial bromine concentration was 0.20 molar, the last quarter of the reaction was slower than in experiments where the initial bromine concentration was 0.05 molar. Tests indicated that cyclohexyl bromide and hydrogen bromide formed could have only a barely perceptible effect on the reaction, and it seemed likely that the product of the photochemical reaction of oxygen and cyclohexane produced an inhibitor for the bromination reaction. This was demonstrated by the following experiments. Cyclohexane with no previous treatment, or which had been previously illuminated in the absence of oxygen, reacted to the extent of 85% in 45 minutes. Cyclohexane which had been previously illuminated for four hours under one atmosphere pressure of oxygen required four hours for the same extent of reaction.[4] Accelerated formation of this inhibitor may explain the retarding effect of high oxygen pressures shown in Table II and Figures 1 and 2.

DISCUSSION OF RESULTS

The effects of visible light, oxygen, and inhibitors on the bromination of cyclohexane, methylcyclohexane, and isobutane, together with previous work on bromination reactions (1, 8) suggests that the reaction proceeds through a chain mechanism involving essentially the following steps:

$$\text{(a)}\quad Br_2 + h\nu \rightarrow 2Br\cdot$$
$$\text{(b)}\quad R\text{–}H + Br\cdot \rightarrow R\cdot + HBr$$
$$\text{(c)}\quad R\cdot + Br_2 \rightarrow R\text{–}Br + Br\cdot$$

Results of the present study indicate that tertiary hydrogen atoms are replaced in preference to the more numerous secondary hydrogen atoms of methylcyclohexane or primary hydrogen atoms of isobutane. The bromination of cyclohexane, which has no tertiary hydrogen atoms, is significantly slower than that of the other two hydrocarbons. The low reactivity of primary hydrogen atoms is further demonstrated in the unusually difficult bromination of neopentane (2,2-dimethylpropane) and trimethylacetic acid (15).

Thermal data indicate that reaction c is definitely exothermic, regardless of the variations in strength of the R–Br bonds formed. The results presented are wholly in agreement with the assumptions that the activation energy of reaction b is positive but small and that it varies with the strength of the carbon-to-hydrogen bond concerned. Tertiary and secondary

[4] The initial bromine concentration was 0.20 molar and the oxygen pressure 5 cm. in these experiments.

carbon-to-hydrogen bonds are estimated to be weaker than primary carbon-to-hydrogen bonds by 4.4 and 2.5 kcal. per mole, respectively, while the corresponding carbon-to-bromine bonds are stronger than the primary bonds. Adding these differences has led to the estimate by Conn, Kistiakowsky, and Smith (16) that substitution of tertiary and secondary aliphatic hydrogen atoms by bromine is more exothermic by 5.5 and 3.1 kcal., respectively, than substitution of a primary hydrogen atom.

Differences in the activation energy of reaction b corresponding to those in the strength of carbon-to-hydrogen bonds may well be critical in limiting the chain length in bromination reactions at low temperature (0–25°), so that comparatively long chains can be formed if tertiary hydrogen atoms are present, only shorter chains in other cases. Capture of bromine atoms by bromine molecules may be one of the chain-terminating reactions and may account for the retardation of the reaction at high bromine concentrations (1).

The slow reaction of aliphatic hydrocarbons as compared with the side-chain bromination of toluene is apparently due to shorter chain lengths, not to the initiation of fewer chains. This interpretation is consistent with the failure of small quantities of peroxides to affect the bromination of the aliphatic hydrocarbons. Even if the peroxide is 100% efficient in producing free radicals in any manner, or bromine atoms from hydrogen bromide, a chain length of 5 or 10 would prevent 3 mole per cent of peroxide from exerting an effect greater than about 30% on the total reaction. If the efficiency is low, as is more likely, the effect would not be detectable in the present work. Similar reasoning leads to the conclusion that in the bromination of toluene, where small quantities of peroxides exert large effects, the chain lengths must be in the hundreds or thousands. Clearly the methyl group in toluene is more reactive than aliphatic methyl groups. A possible explanation is that since the benzyl radical formed in reaction b may be stabilized by resonance, less energy is required for separation of the hydrogen atom, and the activation energy of reaction b is, therefore, lower.

Consideration of a similar mechanism in the chlorination of aliphatic hydrocarbons shows that the reaction corresponding to b would be exothermic regardless of the nature of R. The activation energy for this step is probably so low that differences in the strength of the R–H bond are less important, particularly at high temperatures (11). Brominations at high temperatures, where bromine atoms could easily acquire the necessary activation energy, should show similar effects.

The inhibition of aliphatic-type chlorinations and of the vapor-phase bromination of cyclohexane (7, 8) by oxygen is well known. This paper shows that excess oxygen retards the liquid-phase bromination of cyclo-

hexane, methylcyclohexane, isobutane, and toluene, but even at the highest oxygen pressures employed, the brominations are much faster than in the absence of all oxygen. Part of the retarding effect of oxygen is due to the formation of an oxidation product of cyclohexane but part may also be due to competition of oxygen and bromine molecules for the free radicals in step c, neither reaction having an appreciable activation energy. The latter explanation applies quantitatively to the vapor-phase bromination (7, 8) of cyclohexane.

The fact that the combined effects of light and oxygen on the bromination of cyclohexane, methylcyclohexane, and isobutane approximate the product, rather than the sum, of their individual effects leads to several tentative hypotheses. Of these, the most attractive is that light serves to initiate chains by dissociating bromine into atoms and that oxygen (but not peroxides) serves to increase the average length of the chains. Oxygen might protect the bromine atoms by formation of the unstable oxide BrO_2, or this oxide may decompose to give another oxide Br_2O (17) which serves as the brominating agent in a chain reaction. Some such explanation is also consistent with our observations that small quantities of peroxides are ineffective in aliphatic brominations.

We hope that further work will explain the combined effect of light and oxygen.

SUMMARY

1. Cyclohexane, methylcyclohexane, and isobutane react very slowly with bromine in the absence of light and oxygen.

2. The reactions are greatly accelerated by either light or oxygen, and the combined effects of light and oxygen are much greater than the sum of the individual effects.

3. The effects of bromine concentration, peroxides, and inhibitors have been studied.

4. An explanation for the phenomena observed is suggested.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

THE ACTION OF CHLORAL HYDRATE ON ALIPHATIC ORTHOESTERS

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The formula of chloral hydrate is usually presented as including two hydroxyl groups attached to the same carbon, thus $CCl_3CH(OH)_2$. If this formula is correct, chloral hydrate should react with aliphatic orthoesters with exchange of one or two hydroxyl groups for the same number of alkoxyls. If chloral hydrate consists of chloral with a molecule of water attached in some other manner, and more loosely, then the orthoester would not be expected to react to give an acetal or hemiacetal unless the chloral were sufficiently reactive in the absence of the usual catalysts such as ammonium chloride, ammonium nitrate, sulfuric acid, or hydrochloric acid. Under the influence of these compounds, orthoesters react with most aldehydes to form acetals (1).

$$CH_3CHO + HC(OC_2H_5)_3 \rightarrow HCOOC_2H_5 + CH_3CH(OC_2H_5)_2$$

Strong precedents exist for assuming that if two alcoholic hydroxyl groups are present in the chloral molecule, radical interchange would be expected with the orthoester as outlined above (2, 3, 4).

In this work certain selected orthoesters were refluxed with chloral and chloral hydrate for various periods of time with results which are best indicated by inspection of Table I.

In this work, reactions 8 and 9 were carried out using chloral instead of the hydrate and in addition, two drops of concentrated sulfuric acid were added to 9 as a catalyst. There was, however, no reaction in either case. The molar ratio of orthoester to chloral or chloral hydrate was 1:1 in each case mentioned in Table I.

In all runs save 6 and 7 qualitative determination of the by-products permitted the writing of an equation as shown below:

$$CCl_3CH(OH)_2 + HC(OC_2H_5)_3 \rightarrow CCl_3CH(OH)OC_2H_5 + C_2H_5OH + HCOOC_2H_5.$$

The by-products from reaction 7 appeared as a gel. Yields were determined by repeated fractional distillation, using an especially designed column.

In checking the identity of the major products, recourse was had to the preparation of the hemiacetals by an adaptation of a method already in the literature. Several workers in the past have prepared hemiacetals of

TABLE I

INTERACTION OF ORTHOESTER AND CHLORAL HYDRATE AT REFLUX TEMPERATURES

ORTHOESTER	PRODUCT	TIME, MIN.	YIELD, %
1. $HC(OC_2H_5)_3$	$CCl_3CH(OH)OC_2H_5$	105	25
2. $HC(OC_2H_5)_3$	$CCl_3CH(OH)OC_2H_5$	45	50
3. $HC(OC_3H_7)_3$	$CCl_3CH(OH)OC_3H_7$	60	68
4. $HC(OC_4H_9)_3$	$CCl_3CH(OH)OC_4H_9$	60	28
5. $HC(OC_4H_9)_3$	$CCl_3CH(OH)OC_4H_9$	45	30
6. $HC(SC_2H_5)_3$	$CCl_3CH(OH)SC_2H_5$	60	5
7. $Si(OC_2H_5)_4$	$CCl_3CH(OH)OC_2H_5$	240	4.1
8. $HC(OC_3H_7)_3$	none	45	0
9. $HC(OC_3H_7)_3$	none	45	0

TABLE II

HEMIACETALS FROM THE INTERACTION OF CHLORAL HYDRATE AND ALCOHOLS AT REFLUX TEMPERATURES

ALCOHOL	PRODUCT	TIME, MIN.	YIELD, %
10. C_2H_5OH	$CCl_3CH(OH)OC_2H_5$	60	56
11. C_2H_5OH	$CCl_3CH(OH)OC_2H_5$	45	52
12. C_2H_5OH	$CCl_3CH(OH)OC_2H_5$	1440	38
13. C_2H_5OH	$CCl_3CH(OH)OC_2H_5$	72	52
14. C_2H_5OH	$CCl_3CH(OH)OC_2H_5$	60	75
15. C_3H_7OH	$CCl_3CH(OH)OC_3H_7$	45	100
16. C_3H_7OH	$CCl_3CH(OH)OC_3H_7$	60	77
17. C_4H_9OH	$CCl_3CH(OH)OC_4H_9$	60	28
18. C_4H_9OH	$CCl_3CH(OH)OC_4H_9$	45	54
19. C_2H_5SH	$CCl_3CH(OH)SC_2H_5$	60	8.1

chloral by the interaction of chloral and the proper alcohol (5, 6, 7, 8, 9, 10, 11, 12). Chloral hydrate was here used directly, with good results,

$$CCl_3CH(OH)_2 + C_2H_5OH \rightleftharpoons CCl_3CH(OH)OC_2H_5 + HOH$$

The reaction between chloral hydrate and various alcohols at room temperature did not prove satisfactory in that too long a time was required to attain appreciable yields. The same may be said of the reaction using chloral itself.

Runs 12 and 13 were carried out at room temperatures. Run 14 was a trial run using small amounts.

Although, as has been pointed out before, many orthoesters react with alcohols in the absence of any known catalyst with resultant interchange of radicals (2, 3, 4), there is no record that acetals undergo the same reaction. It seemed of interest to check the results already in the literature on this reaction and to apply it to the hemiacetals of chloral prepared as outlined above (13, 14). In nearly every case a different hemiacetal was formed.

In reaction 24 the molar ratio was 1:1, in all others reported in Table IV, the ratio was hemiacetal:alcohol: :1:2.

Inasmuch as orthoesters react with each other with interchange of alkoxyl radicals, in the absence of known catalysts, it was considered desirable to ascertain whether or not this type of reaction could be

TABLE III

HEMIACETALS FROM THE INTERACTION OF CHLORAL AND ALCOHOLS AT REFLUX TEMPERATURES

ALCOHOL	PRODUCT	TIME, MIN.	YIELD, %	MOLE RATIO CHLORAL: ALCOHOL
20. C_2H_5OH(95%).....	$CCl_3CH(OH)OC_2H_5$	120	71.3	0.64:1
21. C_3H_7OH(anhyd.).....	$CCl_3CH(OH)OC_3H_7$	120	90	1:1

TABLE IV

INTERACTION OF HEMIACETAL AND ALCOHOL AT REFLUX TEMPERATURES

HEMIACETAL	ALCOHOL	PRODUCT	TIME, MIN.	YIELD, %
22. $CCl_3CH(OH)OC_2H_5$	+ C_3H_7OH	$\rightleftharpoons$ $CCl_3CH(OH)OC_3H_7$.....	60	40
23. $CCl_3CH(OH)OC_2H_5$	+ C_4H_9OH	$\rightleftharpoons$ $CCl_3CH(OH)OC_4H_9$.....	45	50
24. $CCl_3CH(OH)OC_2H_5$	+ C_6H_5OH	none	72	0
25. $CCl_3CH(OH)OC_3H_7$	+ C_2H_5OH	none	45	0
26. $CCl_3CH(OH)OC_3H_7$	+ C_4H_9OH	$\rightleftharpoons$ $CCl_3CH(OH)OC_4H_9$.....	45	40
27. $CCl_3CH(OH)OC_4H_9$	+ C_2H_5OH	none	45	0
28. $CCl_3CH(OH)OC_4H_9$	+ C_3H_7OH	none	45	0

carried out between orthoester and chloral hemiacetal. Fair yields were obtained in the two reactions attempted.

For further identification of the hemiacetals, the tetrachloro ether was prepared from two of them by the action of phosphorus pentachloride.

$$CCl_3CH(OH)OC_2H_5 + PCl_5 = HCl + POCl_3 + CCl_3CHClOC_2H_5$$

The reactants were mixed in the molar ratio of 1:1. Complete directions may be found in the literature (17, 21).

EXPERIMENTAL PART

Orthoformates used in this work were purchased from the Eastman Kodak Co. Their simple physical properties were found to be satisfactory. Ethyl orthothio-

formate was prepared by the action of formic acid on ethyl mercaptan in the presence of anhydrous hydrochloric acid, according to the method outlined by Holmberg (15). The yield amounted to 26%, b.p. 234°, literature 235° (15). Chloral and chloral hydrate were also purchased and found to be satisfactory.

Chloral ethylhemiacetal, $CCl_3CH(OH)OC_2H_5$, was prepared as described above and in Tables I, II, and III. It was a white crystalline solid, m.p. 47.5°, literature 46.0° (16, 17), 46.6° (18), 50° (19), 56–57° (5). The boiling point was 111.0° at 741.4 mm., literature 115–116° at 771 mm. (5), 116.8° at 771 mm. (17). In this reaction ethyl formate was isolated, b.p. 53.6–54.4°, $n_D^{25.6}$ 1.3583, also ethyl alcohol b.p. 77.5–78.5°, n_D^{25} 1.3622. The hemiacetal prepared from ethyl alcohol and chloral hydrate by reflux was shown by mixed melting point to be identical with the product obtained by the action of ethyl orthoformate. The product formed by the action of ethyl orthosilicate on chloral hydrate melted at 47–48°.

TABLE V

INTERACTION OF ORTHOESTER AND HEMIACETAL

(refluxed 60 minutes, molar ratio 1:1)

	HEMIACETAL	ORTHOESTER	PRODUCT	YIELD, %
29.	$CCl_3CH(OH)OC_2H_5$	+ $HC(OC_3H_7)_3$.....	$CCl_3CH(OH)OC_3H_7$	32
30.	$CCl_3CH(OH)OC_2H_5$	+ $HC(OC_4H_9)_3$.....	$CCl_3CH(OH)OC_4H_9$	20
31.	$CCl_3CH(OH)OC_3H_7$	+ $HC(OC_2H_5)_3$.....	$CCl_3CH(OH)OC_2H_5$	16
32.	$CCl_3CH(OH)OC_3H_7$	+ $HC(OC_4H_9)_3$.....	$CCl_3CH(OH)OC_4H_9$	30
33.	$CCl_3CH(OH)OC_4H_9$	+ $HC(OC_2H_5)_3$.....	$CCl_3CH(OH)OC_2H_5$	37
34.	$CCl_3CH(OH)OC_4H_9$	+ $HC(OC_3H_7)_3$.....	$CCl_3CH(OH)OC_3H_7$	64

TABLE VI

TETRACHLORO ETHERS FROM THE HEMIACETALS USING PCl_5

	HEMIACETAL	PRODUCT	YIELD, %
35.	$CCl_3CH(OH)OC_2H_5$.....	$CCl_3CHClOC_2H_5$	40
36.	$CCl_3CH(OH)OC_3H_7$.....	$CCl_3CHClOC_3H_7$	36

Chloral propylhemiacetal, $CCl_3CH(OH)OC_3H_7$, was prepared like the corresponding ethyl compound, b.p. 119–121° (742.4 mm.), $d_4^{25.7}$ 1.2996, n_D^{25} 1.4622, literature b.p. 120–122° (5). The compound was further identified by checking its physical properties with the same compound obtained by the action of propyl alcohol on chloral hydrate.

Chloral butylhemiacetal, $CCl_3CH(OH)OC_4H_9$, was prepared and checked like the ethyl compound, m.p. 49°, literature 49° (20), b.p. 129–130° (742 mm.).

Chloral ethylmercaptohemiacetal, $CCl_3CH(OH)SC_2H_5$, was prepared by the action of chloral hydrate on ethyl orthothioformate and on ethyl mercaptan, m.p. 68–69.5°. The preparation from ethyl mercaptan had been previously carried out by Martius and Mendelssohn-Bartholdy (11).

1,2,2,2-Tetrachlorodiethyl ether, $CCl_3CHClOC_2H_5$, was prepared according to the method of Nehr and Foster (21) by the action of phosphorus pentachloride on chloral hemiacetal, b.p. 184° (738 mm.), literature 189.7° (758.7 mm.) (21).

1,2,2,2-Tetrachloroethyl propyl ether, $CCl_3CHClOC_3H_7$, was similarly prepared

from chloral propylhemiacetal and phosphorus pentachloride according to the method given by Paterno and Pisanti (17), b.p. 201–202°, literature 204.8° (17).

DISCUSSION

It has been shown that chloral hydrate reacts with an aliphatic ortho-ester to form a hemiacetal, the by-products being alcohol and ester. Unfortunately a definite mechanism cannot be postulated on the basis of the evidence at hand, nor can any of the data here presented be said to throw any light on the structure of chloral hydrate. Some investigators have assumed, in spite of contradictions by others, that chloral hydrate, in its reactions, dissociates reversibly into chloral and water. If this is true, then alcohol may be assumed to act by combination with chloral to form the hemiacetal.

On the basis of this assumption, the water which is set free would be expected to hydrolyze the orthoformate, and the ethyl alcohol thus formed could easily add to the chloral molecule to form the hemiacetal. It is not

TABLE VII

PERCENTAGE YIELD OF NEW HEMIACETAL

HEMIACETAL	ALCOHOL		
	C_2H_5	C_3H_7	C_4H_9
C_2H_5	X	40	50
C_3H_7	0	X	40
C_4H_9	0	0	X

impossible however, to visualize an exchange of radicals between chloral hydrate and orthoformate, perhaps through some co-ordinated intermediate.

In one case it was shown that sulfur moves with its ethyl radical from orthoformate to hemiacetal but even this reaction could be explained by several different mechanisms.

There is every indication that prolonged refluxing of chloral hydrate with propyl or butyl orthoformate tends to decrease the yield of hemiacetal. Apparently there is some secondary reaction by which hemiacetal is removed, although the nature of this reaction is unknown. The hemiacetals themselves are quite stable at their boiling temperatures. When the hemiacetals were prepared from alcohols instead of orthoformates the same tendency was noted. In both cases, also, the yields of propylhemiacetals were higher than ethyl or butyl.

Consistently, this work has substantiated the results of others to the effect that the hydroxyl group of these three hemiacetals is unreactive toward metathetical reactions with other alcohols, ethers, or polyethers.

Radical interchange between an alcohol and a hemiacetal of chloral will not take place if the radical represented in the alcohol is lighter in weight than that in the ethereal section of the hemiacetal.

In Table VIII, percentage yields of new hemiacetal are listed against the compounds used. The reaction is that of a chloral hemiacetal with an orthoformate. It will be noted that reading down in all three columns the yields increase. Reading from left to right, the yields decrease for chloral ethylhemiacetal but increase markedly for the other two.

TABLE VIII

PERCENTAGE YIELD OF NEW HEMIACETAL

HEMIACETAL	ORTHOFORMATE		
	C_2H_5	C_3H_7	C_4H_9
C_2H_5	X	32	20
C_3H_7	16	X	30
C_4H_9	37	64	X

SUMMARY

1. A reaction has been presented between an alkyl orthoformate and chloral hydrate by which a chloral hemiacetal is formed together with alcohol and formate. Ethyl orthothioformate also reacts in this manner with moderate facility. Ethyl orthosilicate does not react without formation of gels. Chloral does not so react, even in the presence of sulfuric acid catalyst.

2. Hemiacetals of chloral have also been prepared by direct action of an alcohol on chloral hydrate. This is probably an equilibrium reaction.

3. Radical interchange has been shown to take place between (a) hemiacetal and alcohol and (b) hemiacetal and orthoformate.

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[CONTRIBUTION FROM THE DIVISION OF BIOCHEMISTRY, MAYO FOUNDATION]

STUDIES ON STEROID α-KETOLS. I. THE PARTIAL SYNTHESIS OF 16-KETOTESTOSTERONE ACETATE

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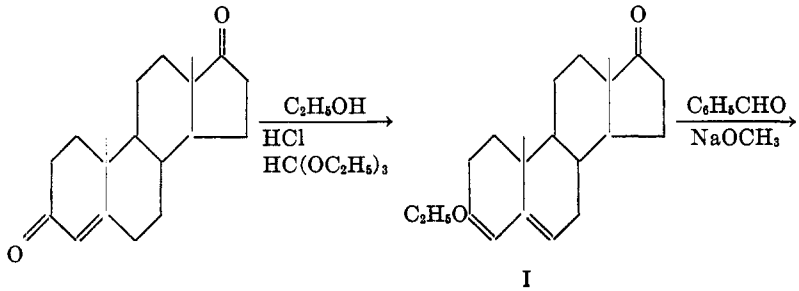
The amorphous fraction of the extract of the adrenal cortex which has the greatest effect on the metabolism of certain inorganic electrolytes so far has resisted all attempts at crystallization or separation into pure components. The high lability of the material has been the main reason for lack of success in this and other laboratories.

Perhaps the most striking property of the amorphous fraction is its high solubility in water compared with that of any of the numerous crystalline compounds already isolated from the adrenal cortex. This behavior led Butenandt and Peters (1) to prepare steroids with hydroxylated side chains in the hope that water-soluble compounds with the characteristic physiologic activity might be obtained. Although a steroid with three hydroxyl groups in the side chain was synthesized, it was only slightly soluble in water and did not have the desired physiologic activity. More recently Zwemer and Lowenstein (2) suggested that the most active hormone of the adrenal cortex may contain the ascorbic acid moiety.

Attention so far, then, has been centered on the probability that there is present a highly hydroxylated side chain attached to the steroid nucleus. The other obvious possibility is the presence of hydroxyl groups on the steroid nucleus itself, and since studies in this laboratory indicate that the amorphous fraction may contain such compounds, we have made a start in that direction. Although it is known that all the compounds separated from the adrenal cortex which produce a physiologic effect have an α-ketol side chain at position 17, it seemed desirable to prepare first a steroid which has the ketol structure at positions 16 and 17. This paper, which describes the preparation of 16-ketotestosterone acetate, is one of a series which deals with nuclear hydroxylation.

The 16-ketotestosterone acetate was prepared by the following series of reactions:



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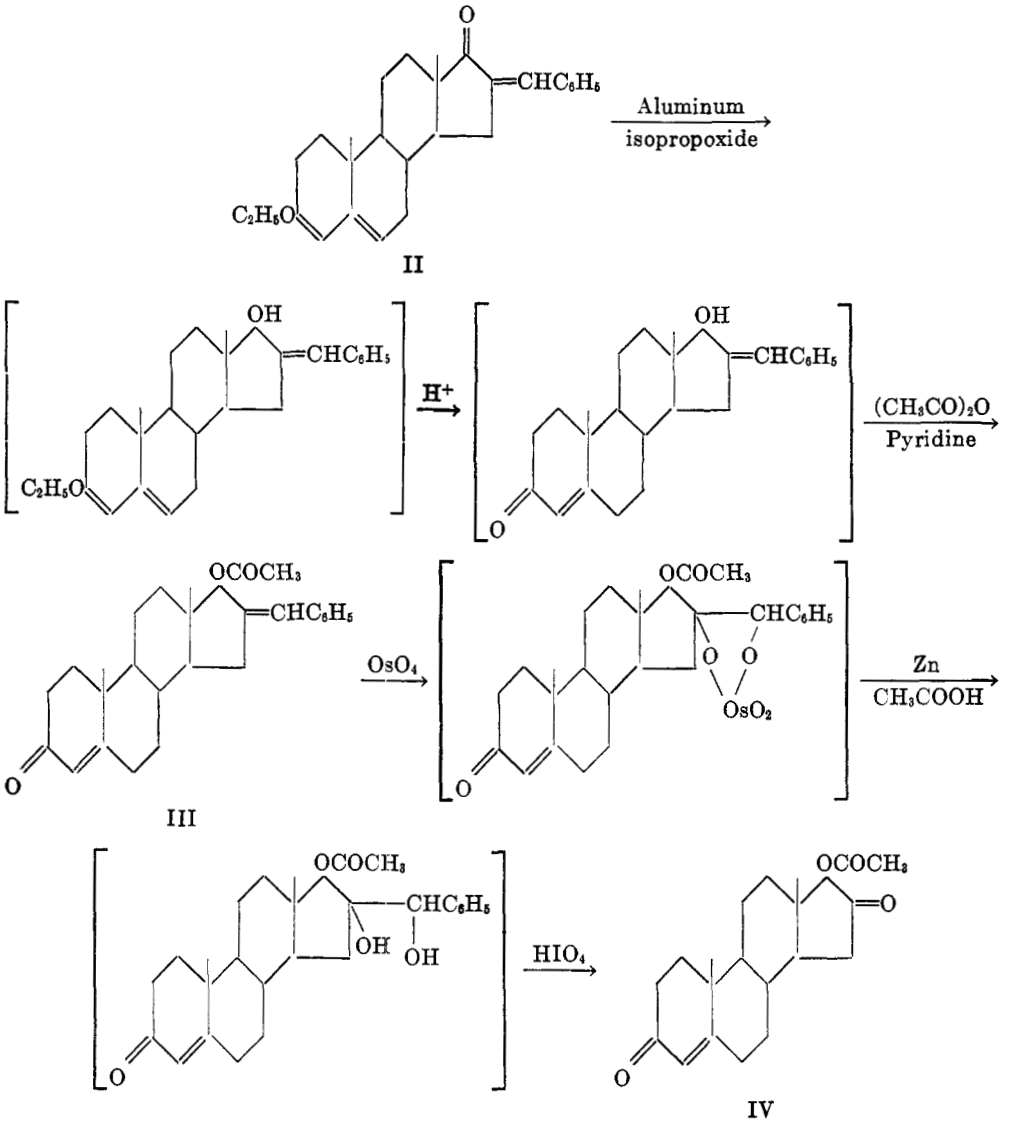

The decomposition of the osmium addition product without hydrolysis of the acetoxyl group on carbon atom 17 was accomplished by reduction with zinc dust and acetic acid at 45–50°. The methods of Criegee (3) and Reich, Sutter, and Reichstein (4), which involve refluxing with either sodium sulfite, formaldehyde, or ascorbic acid, are not applicable here.

Some difficulty was encountered in the cleavage of the glycol with periodic acid because of traces of osmium which could not be removed.

Apparently the activity of the periodic acid is increased catalytically by the osmium to such an extent that other points in the molecule are oxidized. This step is being studied further on more easily available compounds.

The preparation of 16-ketotestosterone acetate has permitted a study of its physiologic effects which will be reported elsewhere. The results obtained indicate that the characteristic physiologic effect of the amorphous fraction is not due to this type of compound.

EXPERIMENTAL

All melting points are uncorrected.

The benzal compound (II). Androstene-3,17-dione 3-enol ethyl ether (I) was prepared by the method of Serini and Köster (5). This enol ether (1.89 g. or .00601 mole) was dissolved in 75 cc. of boiling methyl alcohol and 15 cc. of methyl alcohol which contained 0.0132 mole of sodium methoxide was added. To this solution 1.50 cc. (0.0148 mole) of benzaldehyde was added dropwise. Crystals began to appear after the solution had been refluxed for forty-five minutes, and after another half hour of heating the solution was diluted with water to give 2.38 g. of crude benzal compound which melted at 177–182°. A product so obtained is sufficiently pure for the next step; further purification is to be avoided because of the instability of the enol ether. For analysis a sample which had been prepared previously was crystallized in the form of long bars from acetone which contained a little pyridine. The compound sintered at 177° and melted at 181–186°.

Anal. Calc'd for $C_{28}H_{34}O_2$: C, 83.54; H, 8.51.
Found: C, 83.45; H, 8.68.

16-Benzaltestosterone acetate (III). The crude benzal compound (2.38 g.) was dissolved in 10 cc. of dry benzene and added to 12 cc. of a benzene solution of aluminum isopropoxide (0.31 g. per cc.). The solution was refluxed for three hours, concentrated to one-half its volume to remove acetone, and refluxed for two hours more. The solution was made up to the original volume with dry benzene and refluxed for one hour. This process of concentration, dilution, and refluxing was repeated two more times. After cooling, ether and potassium hydroxide solution were added. The ether was washed until neutral to litmus and concentrated to an oil. To convert the enol ether to the ketone, this residue was dissolved in warm acetic acid and kept overnight at room temperature. The solution was concentrated in a vacuum, and the residue was dissolved in 8 cc. of pyridine and 10 cc. of acetic anhydride and warmed at 60° for half an hour. After standing at room temperature for twenty-four hours, the acetylation mixture was worked up in the usual manner. Repeated crystallization from acetone-water gave 0.860 g. of prisms which melted at 178–179°. Some samples melted almost completely at this point, then solidified and remelted at 197–198°.

Anal. Calc'd for $C_{28}H_{34}O_3$: C, 80.34; H, 8.19.
Found: C, 80.41; H, 8.17.

16-Ketotestosterone acetate (IV). One hundred and fifty milligrams (0.000358 mole) of 16-benzaltestosterone acetate was dissolved in 4 cc. of carbon tetrachloride and a solution of 100 mg. (0.000394 mole) of osmium tetroxide in 4 cc. of carbon tetrachloride was added dropwise. The resulting brown solution was kept in the dark at room temperature for three days, at the end of which time there was a heavy black precipitate. After concentration to dryness the residue was dissolved in 5 cc. of acetic acid. One cubic centimeter of water was added and the solution

kept at 45–50° while 1.5 g. of zinc dust was added in small portions over a period of one hour. From time to time during this addition small portions of water and acetic acid were added to rinse the sides of the flask and hold most of the zinc acetate in solution. At the end of the reaction the total volumes of the acetic acid and water were 15 cc. and 8 cc. respectively. Enough water was then added to dissolve all the zinc acetate and the solution was heated at 40° for fifteen minutes. After two hours standing at room temperature, 90% of the remaining acetic acid was neutralized with a strong solution of potassium carbonate. The resulting solution was extracted twice with ether and the washed ether extracts were filtered through a pad of Norit on glass wool to remove finely divided osmium. On concentrating the ethereal solution, a white powder was obtained which weighed 185 mg. A sample of 8 mg. reduced 92% of the theoretical amount of periodic acid.

The remaining 150 mg. was dissolved in 2 cc. of alcohol to which 10 cc. of periodic acid solution (0.001 mole HIO_4 in 60% alcohol) was added. After standing overnight the solution was concentrated in a vacuum to a small volume and diluted with water. This solution was extracted with ether. The ether was washed first with sodium bicarbonate solution and then with water. On concentrating it in a vacuum, 104 mg. of a pale yellow oil was obtained. The oil was dissolved in 2 cc. of benzene, and petroleum ether was added until the solution became slightly turbid. The solution was passed through a column of Al_2O_3 (3 g.). Oily material which weighed 4 mg. was removed from the column with petroleum ether. A mixture of benzene and petroleum ether 1 to 3 was then passed through the column and after this was concentrated 58 mg. of crystals separated. One milligram of oily material was separated from the column with this same concentration of benzene and petroleum ether. The 58 mg. of material was recrystallized from a mixture of acetone and petroleum ether. Thirty-four milligrams of crystals with jagged edges were obtained.[1] These crystals melted at 188–190° and gave analytical figures for carbon and hydrogen in good agreement with the calculated values. Further crystallization raised the melting point to a constant value of 194–195°.

Anal. Calc'd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19.
Found: C, 73.05; H, 8.20.

This compound has a levorotation $[\alpha]_{4361}^{25}$ −56° (10 mg. in 4 cc. of 95% alcohol). It produces a deep purple color with concentrated sulfuric acid.

SUMMARY

The preparation and properties of 16-ketotestosterone acetate are described.

ROCHESTER, MINN.

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(3) CRIEGEE, *Ann.*, **522**, 81 (1936).
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(5) SERINI AND KÖSTER, *Ber.*, **71**, 1766 (1938).

[1] The low yield (29%) prompted the use of lead tetraacetate for the cleavage of similar glycols. Much more satisfactory results were obtained. These will be reported in the third paper of this series.

[CONTRIBUTION FROM THE DIVISION OF BIOCHEMISTRY, MAYO FOUNDATION]

STUDIES ON STEROID α-KETOLS. II. A NEW PARTIAL SYNTHESIS OF 5-ANDROSTENE-3,16,17-TRIOL: AN INTERMEDIATE IN THE PREPARATION OF 16-HYDROXYTESTOSTERONE

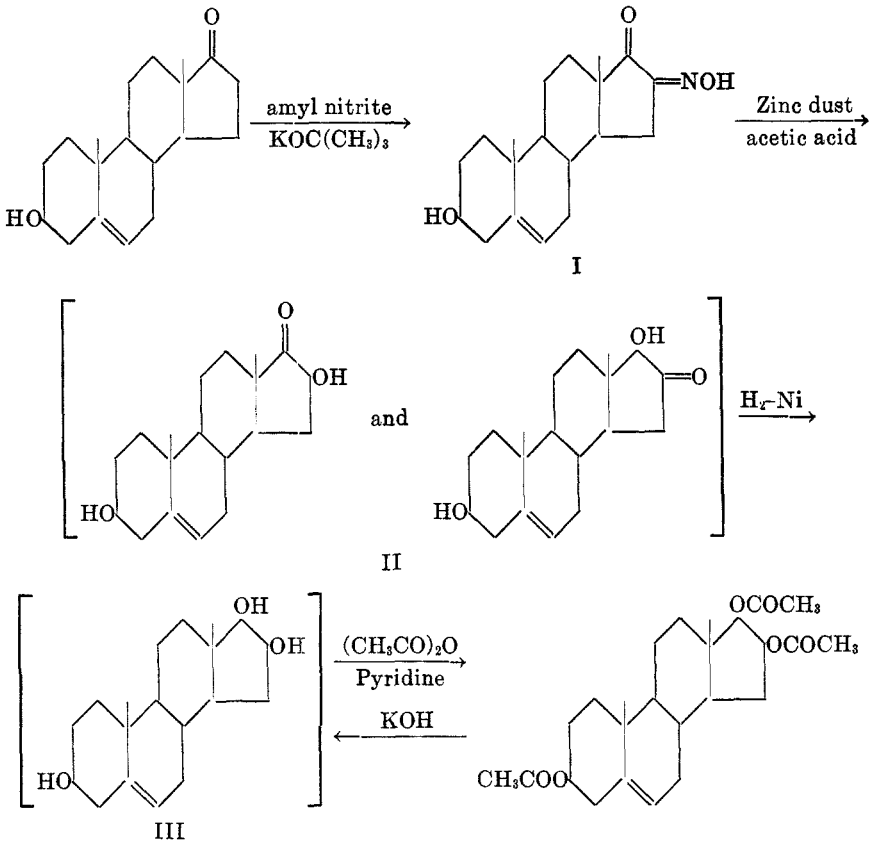
FRANK H. STODOLA, EDWARD C. KENDALL, AND BERNARD F. McKENZIE

Received June 18, 1941

In 1939, Butenandt and co-workers (1) synthesized 16-hydroxytestosterone and investigated its sex hormone activity. Unfortunately the synthesis devised by these workers was long, laborious, and costly. Moreover the yields were so low that investigation of all the intermediate compounds was not possible. For these reasons we believe that any improvement in this synthesis would be welcomed by those who wish to prepare this compound for further study of its hormonal activity. We are able to report such an improvement as a result of synthetic work in this laboratory on steroid derivatives which have an α-ketol grouping in ring D. We have found that the 3,16,17-triol required in the synthesis by the method of Butenandt and co-workers can be prepared easily by a new method so satisfactory that the yield of 16-hydroxytestosterone can be increased almost ten-fold by its use.

The essential contribution of the new method involves the reduction of the isonitroso derivative of dehydroisoandrosterone with zinc dust and acetic acid. The reduction of the isonitroso group was attempted with the reasonable expectation that the α-amino ketone would be formed, since that type of compound results from the reduction of isonitrosocamphor (2). The fact that a neutral product was obtained suggested that formation of an α-ketol had taken place. This was confirmed by conversion of the ketol to a diacetate which agreed in melting point with that given by Butenandt and co-workers. For further confirmation the ketone group of the diacetate was reduced, and the resulting compound characterized as the triacetate. It appeared worth while, in view of the difficulties of the synthesis by the method of Butenandt and co-workers, to make use of this unusual reduction for the synthesis of the intermediate 5-androstene-3,16,17-triol required in the preparation of 16-hydroxytestosterone.

The following method was found most suitable:



The yield of the triol by our method was 24.7% compared with 2.50% by the method of Butenandt and co-workers. This reduction of an isonitroso ketone to an α-ketol provides a very satisfactory method for the introduction of a hydroxyl group next to a keto group in the steroid nucleus. The reaction is being studied further with other isonitroso ketones.

EXPERIMENTAL

All melting points are uncorrected.

Isonitrosodehydroisoandrosterone (*I*). The method of Litvan and Robinson (3) was used. Potassium (0.50 g. or 0.0128 atom) was dissolved in 20 cc. of *tert.* butyl alcohol and 2.00 g. (0.00693 mole) of dehydroisoandrosterone was added. Nitrogen was passed over the well-stirred solution for one hour and then 1.90 cc. (0.0138 mole) of freshly prepared *n*-amyl nitrite was added dropwise. A precipitate appeared in less than a minute and the solution became red. After the solution had been stirred for two hours under nitrogen the reaction mixture was kept overnight at room tem-

perature. It was then diluted with water and extracted twice with ether. The aqueous layer was separated, acidified with acetic acid, and extracted with chloroform. The chloroform extract was shaken once with a dilute solution of potassium carbonate to remove impurities. It was then extracted repeatedly with 0.1 *N* sodium hydroxide solution until the alkaline extracts were no longer yellow. Acidification of the combined aqueous extracts gave 1.51 g. of pale yellow crystals (65.5% yield) sufficiently pure for the reduction with zinc in acetic acid. The compound was difficultly soluble in alcohol or chloroform but easily soluble in chloroform which contained a little alcohol. For analysis a sample was crystallized from isopropyl alcohol in the form of almost colorless needles. The compound sinters at 240° and melts at 248–249° with evolution of gas.

Anal. Calc'd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41.
Found: C, 72.14; H, 8.82; N, 4.37.

3-Acetoxyisonitrosodehydroisoandrosterone. One hundred milligrams of the isonitroso ketone (I) was dissolved in 5 cc. of pyridine and 1.5 cc. of acetic anhydride and kept at room temperature for two days. From this reaction mixture 109 mg. of a crystalline white solid was isolated. Recrystallization from acetone-water gave long needles which melted at 183–184°.

Anal. Calc'd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90.
Found: C, 70.02; H, 8.29; N, 4.15.

Reduction of the isonitroso ketone (I). The isonitroso ketone (1.50 g.) was suspended in 50 cc. of acetic acid and 3 cc. of water. Four grams of zinc dust was added in small portions while the temperature of the solution was kept at 40–45°. The compound soon dissolved and the solution became yellow. After the addition of 20 cc. of water, the solution was refluxed for one hour during which time it became colorless. It was then cooled and filtered to remove zinc dust. To the filtrate sufficient strong potassium carbonate solution was added to neutralize about 90% of the remaining acetic acid. The acid solution was extracted five times with chloroform. The combined chloroform extracts were shaken first with 50 cc. of 1 *N* sulfuric acid to remove a small amount of amine. After an extraction with dilute potassium hydroxide, the chloroform solution was thoroughly washed with water and concentrated in a vacuum to a white powder which consisted of a mixture of α-ketols (II) and weighed 1.38 g. (95.9% conversion).

Reduction of the ketols (II) to the triol (III). The mixture of ketols (1.00 g.) was hydrogenated in alcohol in the presence of Raney nickel catalyst until no more hydrogen was absorbed. The reduction product was dissolved in acetic anhydride and pyridine and kept at room temperature for twenty-four hours. From this acetylation mixture was obtained 651 mg. of crude triacetate (m.p. 209–213°) which was saponified by refluxing with alcoholic potassium hydroxide for thirty minutes. The triol was isolated and crystallized from an alcohol-water-pyridine mixture in the form of blocks; m.p. 273–275°. The melting point reported by Butenandt and co-workers was 273–275°. The yield was 395 mg. (39.2%).

Acetylation of the ketol mixture (II). The ketol mixture (II) was dissolved in 5 cc. of pyridine and 3 cc. of acetic anhydride and kept at room temperature for twenty-four hours. The diacetate was isolated and crystallized from dilute alcohol in the form of needles. The yield was 285 mg. (59.9%); m.p. 124–125°. Butenandt and co-workers report the melting point 123°. This compound is either 3,16-diacetoxy-5-androstene-17-one or 3,17-diacetoxy-5-androstene-16-one.

Anal. Calc'd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30.
Found: C, 70.78; H, 8.13.

Reduction of the diacetate. The diacetate (100 mg.) was hydrogenated in alcohol for four hours in the presence of Raney nickel catalyst. Acetylation of the reduction product gave 66 mg. of triacetate which was crystallized from methyl alcohol in large plates. Repeated recrystallization did not raise the melting point of 214–215° although the value given by Butenandt and co-workers is 224–226°.

Anal. Calc'd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39.
Found: C, 69.27; H, 8.56.

SUMMARY

A new method is described for the preparation of 5-androstene-3,16,17-triol from isonitrosodehydroandrosterone. By the use of this method it is now possible to obtain 16-hydroxytestosterone in a yield ten times that previously reported.

ROCHESTER, MINN.

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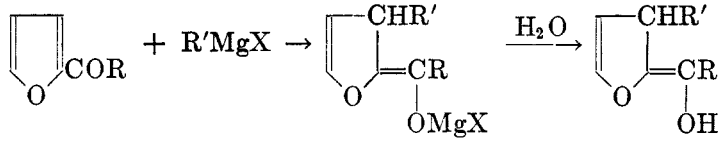
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A GRIGNARD REACTION INVOLVING THE FURAN NUCLEUS

REYNOLD C. FUSON, E. W. KAISER,[1] AND S. B. SPECK

Received June 30, 1941

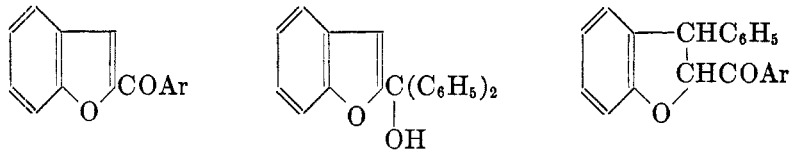
A study of the mode of addition of the Grignard reagent to 2-furyl ketones was initiated in the hope of finding a method of preparing mono ethers of enediols. A compound of the desired type (I) would result if a Grignard reagent could be condensed in the 1,4-manner with a 2-furyl ketone.



I

The proposed condensation is novel in that it involves a double bond of the furan nucleus.

In the present work the action of phenylmagnesium bromide on 2-benzofuryl aryl ketones (II) has been studied. The phenyl ketone (II, Ar = C_6H_5) reacted entirely in the 1,2-manner, yielding the corresponding carbinol (III). The structure of the product was established by oxidative degradation to benzophenone in an 83% yield.



II III IV

The mode of addition to the corresponding mesityl and 2,4,6-triisopropylphenyl ketones, however, was 1,4, producing unstable enolic intermediates (V). That from mesityl 2-furyl ketone appeared to form an enol peroxide, which spontaneously decomposed at room temperature to give equimolecular amounts of the known 3-phenylisocoumaranone (VI) and mesitoic acid.

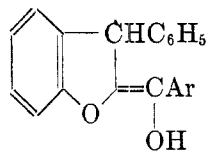
Oxidation of the triisopropylphenyl compound proceeded with more

[1] du Pont Post-Doctorate Fellow, 1939–1940.

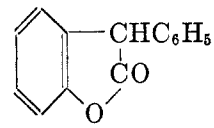
difficulty, and a small amount of triisopropylbenzoic acid was the only product isolated. By analogy with the mesityl ketone, however, it seems safe to conclude that the mode of addition was 1,4.

When the reaction with the two hindered ketones took place in the absence of oxygen, and opportunity was given for the enolic intermediates to rearrange, the products were the corresponding 2-aroyl-3-phenyl-2,3-dihydrofurans (IV).

An attempt was made to synthesize these ketones by an independent method. 3-Phenylcoumarilic acid was reduced by sodium amalgam to yield two isomeric dihydrocoumarilic acids. Attempts to convert these to the desired ketones by condensing the acid chlorides with mesitylene and triisopropylbenzene gave only amorphous products.



V



VI

It is of interest that the mesityl and 2,4,6-triisopropylphenyl-2-benzofuryl ketones were made from coumarilyl chloride by condensation with the aromatic hydrocarbon in the presence of aluminum chloride. The use of the Friedel-Crafts method in the synthesis of aryl 2-furyl ketones appears not to have been reported previously.

EXPERIMENTAL

2-Benzoylbenzofuran was prepared in 69% yield according to the method of Stoermer, Chydenius, and Schinn (1), except that phenacyl chloride was used instead of the bromide.

α-Benzofuryldiphenylcarbinol. Approximately 0.05 mole of phenylmagnesium bromide was added over a period of fifteen minutes to a well-stirred, refluxing solution of 8.12 g. of 2-benzoylbenzofuran in 130 cc. of absolute ether. At first, a tan colored solid separated. On continued refluxing, this solid gradually went into solution and, after refluxing for two hours, a white, finely divided solid separated from the solution. The reaction mixture was poured on a mixture of 150 g. of ice-water and 10 g. of ammonium chloride. The ether solution was washed with 25 cc. of saturated sodium bicarbonate solution containing a few crystals of sodium thiosulfate and dried over anhydrous magnesium sulfate. The solution was concentrated to a small volume, and 200 cc. of petroleum ether (b.p. 30–60°) was added. The solvent was allowed to evaporate on a water-bath until crystallization had started. Cooling gave 8.9 g. of the carbinol—a colorless crystalline solid melting at 129–132°. Recrystallization of the product from benzene-petroleum ether (b.p. 60–110°) and from dilute ethanol gave colorless crystals melting at 133–134°.

Anal. Calc'd for $C_{21}H_{16}O_2$: C, 83.97; H, 5.36.
Found: C, 83.86; H, 5.49.

The carbinol gave no semicarbazone, oxime, acetate, or benzoate.

Oxidation with sodium dichromate. To a solution of 2.1 g. of α-benzofuryldiphenylcarbinol in 55 cc. of glacial acetic acid, 17 g. of technical sodium dichromate was added. The mixture was warmed until a vigorous reaction had begun and, after this initial reaction had subsided, was heated on a water-bath for twelve hours. An additional 3 g. of sodium dichromate was added, and heating was continued another hour. The reaction mixture was poured into 350 cc. of water and was steam distilled until all of the oil was carried over. The benzophenone obtained melted at 47.5–49° and weighed 1.05 g. A mixture with an authentic sample of benzophenone showed no lowering of the melting point.

Coumarin dibromide. The procedure was an adaptation of that used by Karrer, Glattfelder, and Widmer (2) for 5-acetoxycoumarin. A solution of 333 g. of bromine in 270 g. of chloroform was added dropwise over three and one-half hours to a well-stirred solution of 300 g. of coumarin in 650 g. of chloroform at room temperature. After concentration to one-half the volume in a rapid stream of air, the reaction mixture was filtered and the coumarin dibromide was washed with four 80-cc. portions of absolute ether. Further concentration of the filtrate gave additional amounts of product. The colorless crystals weighed 357 g. and melted at 103–107°.

Coumarilic acid. This compound was prepared from coumarin dibromide by a method similar to that of Karrer, Glattfelder, and Widmer (2). The acid, after recrystallization from 50% alcohol, melted at 190–193°; yield 90%.

Coumarilyl chloride. The chloride, boiling at 146–148° (19 mm.), was obtained in 94% yield by the method of Tadeus and Reichstein (3).

2-Mesitoylbenzofuran. A. *From coumarilyl chloride.* A solution of 53 g. of coumarilyl chloride in 140 cc. of carbon disulfide was added over a period of one hour to a suspension of 44 g. of anhydrous aluminum chloride in a mixture of 40 g. of mesitylene and 110 cc. of carbon disulfide at 0°. The reaction mixture was stirred at this temperature for an additional forty minutes after the chloride had been added. The resulting suspension was poured on a mixture of 400 g. of ice and 30 cc. of concentrated hydrochloric acid, and 200 cc. of ether was added. The ether-carbon disulfide layer was removed, and the aqueous layer was extracted with several portions of fresh ether. The combined extracts were washed with three 100-cc. portions of saturated aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The solvent was distilled; the 2-mesitoylbenzofuran, after recrystallization from 95% ethanol (60 cc.), weighed 57 g. It was white and melted at 74.5–76.5°.

Anal.[2] Calc'd for $C_{18}H_{16}O_2$: C, 81.78; H, 6.11.
Found: C, 81.94; H, 6.12.

B. *From salicylaldehyde.* 2-Mesitoylbenzofuran was also prepared according to the general method of Stoermer, Chydenius, and Schinn (1) for 2-acylbenzofurans. A solution of 9.4 g. of salicylaldehyde in 10 cc. of 95% ethanol was added to a solution of 4.3 g. of potassium hydroxide in 50 cc. of 95% ethanol, and the mixture was warmed until the salt was dissolved. A hot solution of 15 g. of ω-chloroacetomesitylene in 50 cc. of 95% ethanol was added in portions over a period of ten minutes to the warm solution of the aldehyde salt. After being refluxed for two and a quarter hours, the reaction mixture was filtered, and the filtrate diluted with an equal volume of water. The diluted filtrate was then steam-distilled until a distillate of 200 cc. had been collected. The residue was extracted with six 50-cc. portions of ether, and the

[2] The microanalyses were carried out by Mr. L. G. Fauble, Dr. W. H. Taylor, Miss Mary S. Kreger, and Mr. C. W. Beazley.

combined ethereal extracts, after being washed with 10% sodium hydroxide solution and with water, were dried over anhydrous magnesium sulfate. The ether was then removed by distillation. Addition of petroleum ether (b.p. 30–60°) gave 4.5 g. of a solid which, after repeated recrystallizations from benzene-petroleum ether (b.p. 60–110°), dilute methanol, and dilute ethanol, separated as colorless crystals, melting at 172–173°.

Anal. Calc'd for $C_{18}H_{18}O_4$: C, 72.48; H, 6.08.
Found: C, 71.90; H, 5.86.

This compound was not identified.

Evaporation of the petroleum ether from the filtrate and addition of 95% ethanol gave 3 g. of a colorless solid which, after two recrystallizations from 95% ethanol, melted at 74.5–76.5°. A mixture of this compound with 2-mesitoylbenzofuran prepared by method A melted at 74.5–76.5°.

2-Mesitoyl-3-phenyl-2,3-dihydrobenzofuran. An ether solution containing approximately 0.1 mole of phenylmagnesium bromide, prepared under nitrogen, was added gradually over a period of thirty-five minutes to a refluxing solution of 17.5 g. of 2-mesitoylbenzofuran in 200 cc. of absolute ether. The reaction was carried out in a nitrogen atmosphere and with stirring. When the addition of the Grignard reagent was nearly complete, the color of the mixture changed from red to light green. After being heated under reflux for an additional thirty-five minutes, the mixture was cooled, and 100 cc. of 1.2 *N* hydrochloric acid was added cautiously. The mixture was stirred at reflux temperature for five hours, during which the ether was removed by a stream of nitrogen. The resulting suspension was heated at 75° for thirty-six hours and cooled. The 2-mesitoyl-3-phenyl-2,3-dihydrobenzofuran, after repeated crystallization from 95% alcohol, absolute alcohol and benzene-petroleum ether, melted at 148–154°. A sharp melting point could not be obtained.

Anal. Calc'd for $C_{24}H_{22}O_2$: C, 84.16; H, 6.48.
Found: C, 83.95; H, 6.52.

When this reaction was carried out without using an inert atmosphere, only cleavage products of 2-mesitoyl-3-phenyl-2,3-dihydrobenzofuran were obtained. Approximately 0.1 mole of phenylmagnesium bromide in 75 cc. of absolute ether was added, with stirring, to a refluxing solution of 13.1 g. of 2-mesitoylbenzofuran in 200 cc. of absolute ether over a period of twenty minutes. After an additional thirty-five minutes of refluxing, the reaction mixture was decomposed in the usual manner with ice-ammonium chloride solution. The moist ether solution was condensed to a volume of 75 cc. in a rapid stream of air and was then warmed until the spontaneous evolution of heat had begun. After the mixture was refluxed for an additional thirty minutes and allowed to stand overnight at room temperature, sufficient ether was added to bring the material into solution. Extraction of this solution with three 150-cc. portions of saturated aqueous sodium bicarbonate solution and acidification of the resulting bicarbonate solution with hydrochloric acid, gave 4.6 g. of mesitoic acid melting at 150–152°. The melting point of a mixture of this compound with an authentic sample of mesitoic acid showed no depression.

The ethereal layer, after being dried over anhydrous magnesium sulfate, was concentrated to 50 cc., and an equal volume of petroleum ether (b.p. 60–110°) added. Fractionation of this solution to remove the ether gave a solution which on standing deposited 6 g. of colorless crystals, melting at 98–116°. Recrystallizations of this solid from methanol and from benzene-petroleum ether (b.p. 60–110°) gave colorless needles, melting at 114–115°.

Anal. Calc'd for $C_{14}H_{10}O_2$: C, 79.96; H, 4.81.
Found, C, 79.63; H, 4.96.

A mixture of this compound with a sample of 3-phenylisocoumaranone (m.p. 110–114°), prepared by the method of Bistrzycki and Flatau (4) (from phenol and mandelic acid), melted at 112–115°. Bromination of this compound by the procedure of Bistrzycki and Flatau (4) gave a product melting at 70–72°.[3] Further concentration of the mother liquor from this product gave only a viscous oil which could not be crystallized.

One experiment was carried out in which the reaction mixture was divided into two equal parts. One of these was exposed to air and the other was worked up under nitrogen. The relative amounts of products were the same as when they originated from different reaction mixtures. This shows that the enol is the parent substance of the 2-mesitoyl-3-phenyl-2,3-dihydrobenzofuran as well as of the cleavage products.

2-(2,4,6-Triisopropylbenzoyl)benzofuran. A solution of 33 g. of coumarilyl chloride in 110 cc. of carbon disulfide was added to a well-stirred suspension of 26 g. of anhydrous aluminum chloride in a mixture of 39 g. of 2,4,6-triisopropylbenzene,[4] in 70 cc. of disulfide at 0° over a period of thirty minutes. The ice-bath was removed and the reaction mixture was stirred for four and one-half hours at room temperature. A vigorous evolution of hydrogen chloride took place when the reaction mixture had attained room temperature, and the solid gradually went into solution. The reddish-brown solution was poured on 200 g. of cracked ice and 10 cc. of concentrated hydrochloric acid, and the aqueous layer was extracted with ether (two 75-cc. portions), and after the solution was dried over anhydrous magnesium sulfate, the solvents were distilled. The residue, on treatment with petroleum ether (b.p. 30–60°), gave 45 g. of a colorless, crystalline solid melting at 92–100°. Recrystallization from a benzene-petroleum ether mixture and 95% alcohol gave 2-(2,4,6-triisopropylbenzoyl)benzofuran melting at 103–105°. Evidence was obtained for two crystalline forms of this substance. When these crystals were heated very slowly, they softened and resolidified, finally melting at 117–118°. The higher-melting form when recrystallized from 95% alcohol melted at 103–105°.

Anal. Calc'd for $C_{24}H_{28}O_2$: C, 82.71; H, 8.10.
Found: C, 82.59; H, 7.89.

2-(2,4,6-Triisopropylbenzoyl)-3-phenyl-2,3-dihydrobenzofuran. Approximately 0.1 mole of phenylmagnesium bromide, prepared in the usual manner under nitrogen, was added slowly (forty minutes) to a well-stirred, refluxing solution of 25 g. of 2-(2,4,6-triisopropylbenzoyl)benzofuran in 250 cc. of absolute ether in an atmosphere of nitrogen. After being refluxed for three hours, the reaction mixture was poured on 100 g. of cracked ice and 20 cc. of glacial acetic acid and the aqueous layer removed. The ethereal layer was washed free of acid with saturated sodium bicarbonate solution, containing a few crystals of sodium thiosulfate, and then was washed with water. The ether solution was dried and the solvent distilled. The residue was dissolved in 150 cc. of low-boiling petroleum ether and the solution kept at 0° for several days. The crude 3-phenylcoumaranone (m.p. 107–132°) which separated weighed 21 g. Recrystallization from absolute alcohol gave colorless plates, melting at 140–141°.

Anal. Calc'd for $C_{30}H_{34}O_2$: C, 84.45; H, 8.05.
Found: C, 84.67; H, 8.16.

The foregoing experiment was carried out without rigid exclusion of oxygen, and

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[3] The melting point reported by these authors was 70°.

[4] The 2,4,6-triisopropylbenzene used was Alkazene-13 obtained from the Dow Chemical Company.

through the ether solution of the product (enol) a stream of air was passed for one hour. The product proved to be a mixture; a small amount of 2,4,6-triisopropylbenzoic acid was the only pure compound which could be obtained from it.

3-Phenylcoumarilic acid.[5] To a solution of 4.83 g. of sodium in 75 cc. of absolute alcohol was added 19.7 g. of phenol. The mixture was cooled in an ice-bath and 56 g. of ethyl α-bromobenzoylacetate was added dropwise, with stirring. The ice-bath was removed and the stirring continued for five hours. After standing twelve hours, the mixture, then neutral to litmus, was poured into 800 cc. of cold water. The product was dissolved in ether and the solution washed with 5% sodium bisulfite solution and with water and dried over anhydrous magnesium sulfate.

The oily residue left after the ether had been distilled was added slowly, with shaking, to 100 cc. of concentrated sulfuric acid. The reaction mixture was kept at 0° during the addition and for one hour afterward; it was then allowed to stand at room temperature for three hours. It was finally poured into 800 g. of cracked ice. The product was taken up in ether, washed with water, 5% sodium thiosulfate solution and water, and dried over anhydrous magnesium sulfate.

The impure ester, obtained by evaporating the ether, was saponified by heating on a steam-cone for one and one-half hours with 13 g. of sodium hydroxide and 100 cc. of water. The mixture was filtered and the filtrate acidified with 100 cc. of 6 *N* hydrochloric acid. The 3-phenylcoumarilic acid, after two recrystallizations from dilute ethanol, weighed 9 g. and melted at 228–231°. After several additional crystallizations from dilute ethanol, the acid melted at 232–233°, with decomposition.

Anal. Calc'd for $C_{15}H_{10}O_3$: C, 75.60; H, 4.24; neut. equiv., 238.1.
Found: C, 75.27; H, 4.60; neut. equiv., 240, 245.

Catalytic hydrogenation of 3-phenylcoumarilic acid. A solution of 3.1 g. of 3-phenylcoumarilic acid in 13 cc. of 1 *N* sodium hydroxide solution was hydrogenated under a pressure of 5000 lbs. (340 atm.) at 75°, Raney nickel being used as a catalyst. At the end of four hours the catalyst was removed, and concentrated hydrochloric acid added to precipitate the organic acid. The product weighed 2.8 g. and melted at 130–145°. Repeated recrystallization from benzene and from dilute ethanol gave colorless crystals melting at 160–162°. The compound had the composition of an octahydro derivative of 3-phenylcoumarilic acid; it was not studied further.

Anal. Calc'd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.35.
Found: C, 73.19; H, 7.46.

3-Phenyl-2,3-dihydrocoumarilic acid (m.p. 147°). A. *From 3-phenylcoumarilic acid.* Twenty-five grams of 3% sodium amalgam was added over a period of five hours to a water suspension of 0.5 g. of 3-phenylcoumarilic acid. The temperature was kept at 70° during the addition and for an additional eighteen hours. Ten grams more of the amalgam was added to the filtered solution and the temperature maintained at 70° for another twelve hours. The mixture was allowed to stand for twenty-four hours at room temperature, decanted through a filter and the mercury washed with water. Acidification of the filtrate gave 0.5 g. of crude acid melting at 130–134°. Recrystallization from dilute ethanol and from a benzene-petroleum ether mixture yielded colorless needles of 3-phenyl-2,3-dihydrocoumarilic acid melting at 146–147°.

Anal. Calc'd for $C_{15}H_{12}O_3$: C, 74.97; H, 5.04.
Found: C, 75.17; H, 5.29.

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[5] This procedure is an adaptation of that used by Hantzsch (5) for the preparation of 3-methylcoumarilic acid.

When the reduction was effected at room temperature, the product was an isomeric acid melting at 186–188°. When heated slowly this acid melted partially, resolidified and melted to a clear liquid at 195–196°.

Anal. Calc'd for $C_{15}H_{12}O_3$: C, 74.97; H, 5.04.
Found: C, 75.18; H, 5.13.

B. *From coumarilic acid.* The dihydrocoumarilic acid, melting at 147°, was also prepared by the procedure of King[6] by adding benzene to coumarilic acid in the presence of aluminum chloride. The product melted at 146–148° and proved to be identical with that from method A.

Anal. Calc'd for $C_{15}H_{12}O_3$: C, 74.97; H, 5.04.
Found: C, 75.17; H, 5.29.

SUMMARY

Phenylmagnesium bromide has been found to add in the 1,4-manner to mesityl 2-benzofuryl ketone and to 2,4,6-triisopropylphenyl 2-benzofuryl ketone. The condensation is novel in that it involves a double bond of the furan nucleus.

URBANA, ILL.

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[6] The acid described here is identical with that of King (6) incorrectly reported as 2-phenyl-2,3-dihydrocoumarilic acid.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

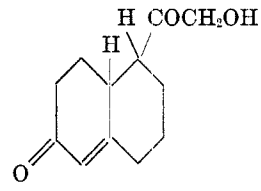
STRUCTURAL MODELS OF CORTIN COMPOUNDS IN THE NAPHTHALENE SERIES

LOUIS LONG, JR.[1] AND ALFRED BURGER

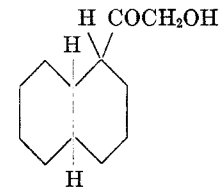
Received July 5, 1941

All of the potent crystalline compounds isolated from the adrenal cortex contain a ketol side chain, an α,β-unsaturated keto group, and a steroid nucleus. It is the purpose of the present investigation to synthesize a model compound in which a decahydronaphthalene skeleton will be substituted for the cyclopentanophenanthrene structure.

Attempts were made initially to prepare the octahydronaphthalene derivative I. As certain difficulties arose in the course of the synthesis, the



I



II

decahydronaphthalene ketol II was synthesized in order to gain experience in handling the totally hydrogenated naphthalene nucleus.

As a starting material for compound I, it was desired to prepare 6-hydroxydecahydro-1-naphthoic acid. Two routes to this substance were examined. In one, 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene (III) (1, 2) was hydrogenated to 1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV), and various methods were tried to convert the tetralol IV to the corresponding halide for a subsequent nitrile synthesis of 6-methoxy-1,2,3,4-tetrahydro-1-naphthoic acid. The method was abandoned after isolating 6-methoxy-3,4-dihydronaphthalene (V) from the reaction mixture resulting from the treatment of the tetralol with phosphorus tribromide or hydrobromic acid. This indicated the marked tendency for dehydration of this α-tetralol in the presence of halogenating agents. Also, using dry hydrogen chloride (3, 4), a product was obtained which could not be converted into the acid through the nitrile.

In the other route, hydrogenation of 6-hydroxy-1-naphthoic acid (IX)

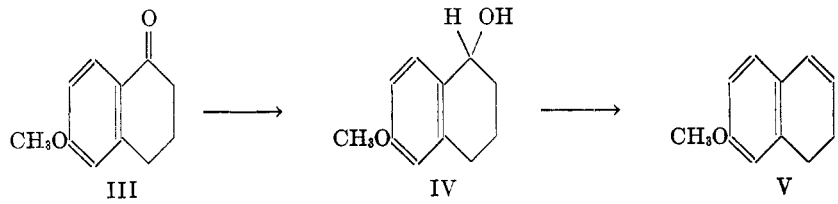
[1] Smith, Kline & French Research Fellow.

(5) was tried. 6-Methoxy-1-naphthoic acid[2] (VIII) was prepared by conversion of 6-methoxy-1-iodonaphthalene (VI) (7, 8, 9) to the nitrile VII with cuprous cyanide, followed by hydrolysis of the nitrile group with propanolic potassium hydroxide. The methoxyl group was hydrolyzed with a boiling hydrobromic acid-glacial acetic acid mixture.

Various conditions of hydrogenation were tested using platinum oxide (10) as a catalyst at atmospheric pressure. In all experiments in which the naphthalene nucleus was reduced completely, the hydroxyl group in position 6 was lost. The removal of the hydroxyl group during hydrogenation had not been anticipated for this compound because of the analogy to the hydrogenation under similar conditions of β-naphthol and 1-hydroxy-2-naphthoic acid to hydroxydecahydronaphthalenes by Hückel (11, 12). A possible explanation of this unexpected result may be the fact that in our case substituent groups are present in both rings of the naphthalene nucleus. The hydrogenation experiments included the use of various solvents, various amounts of reagents, and different reaction temperatures, as well as attempted protection of the hydroxyl group by acetylation and methylation. In a few reductions the effect of the esterification of the carboxyl group was tried, but the course of the hydrogenation could not be altered by this procedure.

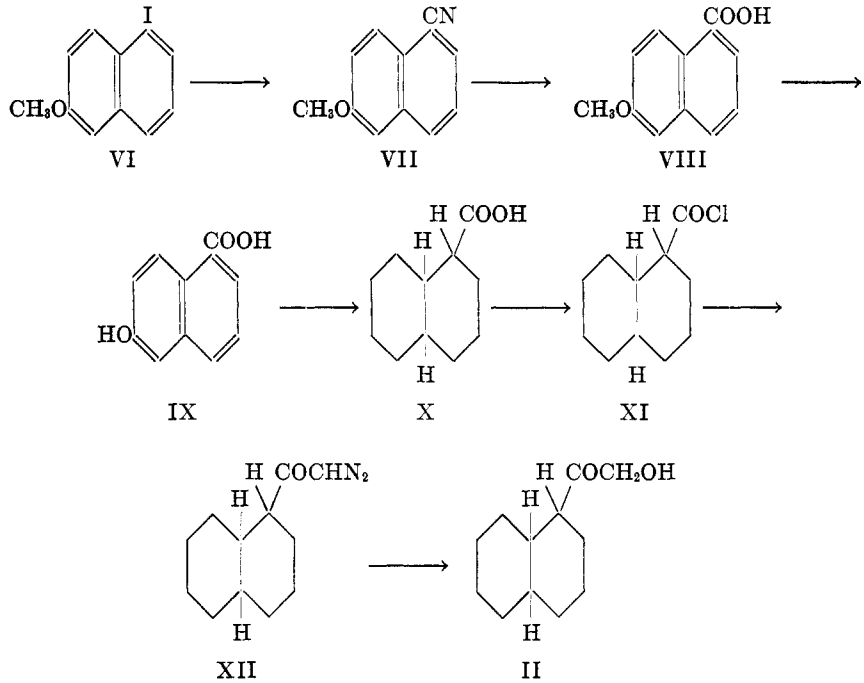
As a result of these numerous hydrogenation experiments, an amount of decahydro-1-naphthoic acid (X) (13) accumulated which was sufficient for the synthesis of the ketol II. The diazo ketone XII was prepared by the Arndt-Eistert synthesis (14, 15), and the ketol was obtained from the diazo ketone by treatment with dilute sulfuric acid (16).

The physiological action of the ketol II has been tested by Professor S. W. Britton of the University of Virginia. The compound had no apparent toxic effects, but exhibited no influence on life maintenance and growth of adrenalectomized animals.



III IV V

[2] Professor Henry Gilman of Iowa State College very kindly communicated to us the details of the preparation of this compound from furoic acid and anisole [*cf.* McCorkle and Turck (6)], but the method outlined in the text was adopted after comparative experimentation.



EXPERIMENTAL[3]

1-Hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV). A mixture of 5.0 g. of 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene (III) (1, 2), 100 cc. of 95% ethanol, and 0.1 g. of platinum oxide catalyst was shaken with hydrogen at atmospheric pressure and room temperature for ten hours. The catalyst was reactivated by shaking with air twice, and additions of 1 cc. of 0.1 *M* ferrous sulfate and 0.2 g. of platinum oxide catalyst were made during the course of the reduction. After absorption of 1.1 mole of hydrogen, the catalyst was filtered, the solvent was removed in vacuum, and the residual viscous, slightly yellow oil was fractionated at a pressure of 1 mm. The distillate was a clear, colorless oil, b.p. 109° (1 mm.). The yield was 4.9 g. (97%).

Anal. Calc'd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92.
Found: C, 73.87; H, 7.84.

The α-naphthylurethan was formed by heating the tetralol with an equivalent amount of α-naphthyl isocyanate on the water-bath for two minutes with exclusion of moisture. Extraction with ligroin and crystallization from the same solvent yielded colorless micro needles, m.p. 131–133°.

Anal. Calc'd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09.
Found: C, 76.42; H, 6.11.

6-Methoxy-3,4-dihydronaphthalene (V). To 1 g. of 1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV) placed in a 25 cc. Erlenmeyer flask with an elongated neck, cooled in an ice-water-bath, was added 9.2 cc. of 48% hydrobromic acid. The

[3] Microanalyses by Mrs. Elizabeth Johnson Mathers.

flask was sealed at atmospheric pressure and placed on a shaking machine overnight. The reaction mixture was diluted with water, and the solid extracted with ether. The ether layer was washed with 5% sodium bicarbonate solution and water. After drying over anhydrous sodium sulfate, the ether was removed in a vacuum. The residual viscous, tan material was distilled at 1 mm. and crystallized from hexane. It melted at 70–73°; the yield was 0.35 g. (40%). For purification, crystallization from petroleum ether and sublimation in a high vacuum gave colorless shiny clusters, m.p. 73–74°.

Anal. Calc'd for $C_{11}H_{12}O$: C, 82.46; H, 7.55.
Found: C, 83.13; H, 7.86.

Since the possibility of the formation of 2-methoxynaphthalene (m.p. 72°) by dehydrogenation of our dihydro derivative could not be excluded, a mixture melting point of the two compounds was taken. A 20° depression was observed.[4]

In an attempted synthesis of 6-methoxy-1,2,3,4-tetrahydro-1-naphthoic acid, 2.9 g. of the tetralol IV was dissolved in 30 cc. of dry benzene, 1.5 g. of anhydrous calcium chloride was added (3, 4), and a rapid stream of dry hydrogen chloride was passed in at 0° for fifteen minutes. The red solution was filtered and allowed to evaporate. The oily residue, freed from hydrogen chloride, was treated with potassium cyanide, potassium iodide, and cupric sulfate at 0° according to the method of Ziegler and Hechelhammer (17). After standing overnight, the solution was boiled under reflux for five minutes, and poured into 45 cc. of 20% ethanolic potassium hydroxide solution. The mixture was boiled for 48 hours, and worked up in the customary way. Besides 0.3 g. of a resinous alkali-soluble material which could not be purified, the reaction product consisted largely of an alkali-insoluble oil which after distillation weighed 1.5 g. The colorless oil showed b.p. 107–108° (2 mm.), n_D^{25} 1.5080. It formed a low-melting red crystalline picrate which was not further investigated. The analysis agreed with the empirical formula $C_{14}H_{16}O$, but no compound which might be predicted from the reactions outlined could be fitted to these data.

Anal. Calc'd for $C_{14}H_{16}O$: C, 83.96; H, 8.05.
Found: C, 83.86; H, 8.07.

6-Methoxy-1-naphthonitrile (VII). Fifty grams of 1-iodo-6-methoxynaphthalene (VI) (7, 8, 9) was heated in a distilling flask with 20 g. of freshly prepared, dry cuprous cyanide at 220–230° for eight hours. The nitrile was distilled from the reaction mixture at 2 mm. pressure and purified by redistillation. The yield of crude material was 41 g. (82%), m.p. 78–79°.[5]

6-Methoxy-1-naphthoic acid (VIII). A hot solution of 15 g. of potassium hydroxide in 150 cc. of *n*-propanol was poured into a flask containing 9 g. of 6-methoxy-1-naphthonitrile (VII), and boiling under reflux was continued for forty-eight hours. After cooling, the solution was evaporated to dryness in a vacuum. The residue was dissolved in water, the aqueous solution was extracted with chloroform and ether, and the acid was liberated by acidification with concentrated hydrochloric acid, yielding 9.2 g. (93%) of crude product, m.p. 181–182°. Crystallization from 95% ethanol gave small colorless rods, m.p. 182–182.5° (6).

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[4] The preparation of 3,4-dihydro-6-methoxynaphthalene by a route similar to ours has been mentioned without experimental details by Salzer (18).

[5] Butenandt and Schramm (8) reported the preparation of the same compound, m.p. 79°, in 18% yield from 6-methoxy-1-naphthylamine hydrochloride by the Sandmeyer reaction.

Several experiments were made in an endeavor to obtain the maximum yield of the acid. The use of either ethanolic or isopropanolic potassium hydroxide gave approximately equal amounts of the acid and of *6-methoxy-1-naphthamide*. Crystallization of the amide from benzene yielded colorless rectangular prisms, m.p. 201–203°.

Anal. Calc'd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51.
Found: C, 71.98; H, 5.35.

6-Hydroxy-1-naphthoic acid (IX). A solution of 10 g. of crude 6-methoxy-1-naphthoic acid (VIII) in 150 cc. of 48% hydrobromic acid and 150 cc. of glacial acetic acid was boiled under reflux for five hours. The crystals which formed as the solution cooled to room temperature were collected and purified by crystallization from water with Norit. Almost colorless, thin rectangular prisms [8.4 g. (90%)] were obtained, which melted at 212.5–213° (5).

Ethyl-6-hydroxy-1-naphthoate was prepared by saturating an absolute ethanolic solution of 2 g. of the acid IX with dry hydrogen chloride, boiling under reflux for five hours, and working up the mixture in the usual manner. The crude product was crystallized from benzene and distilled at 1 mm., to yield 1.3 g. (57%) of colorless flat plates, m.p. 105–107°.

Anal. Calc'd for $C_{13}H_{12}O_3$: C, 72.20; H, 5.59.
Found: C, 71.92; H, 5.91.

Hydrogenation of 6-hydroxy-1-naphthoic acid (IX). A mixture of 1.0 g. of 6-hydroxy-1-naphthoic acid, 50 cc. of glacial acetic acid, and 1.0 g. of platinum oxide catalyst was shaken with hydrogen at atmospheric pressure and room temperature for five and one-half hours. The amount of hydrogen calculated for six moles was absorbed, the catalyst was filtered, the solvent removed in a vacuum, and the residual white waxy solid was dissolved in 20 cc. of 5% sodium bicarbonate solution. After filtration, the acid was precipitated by acidification with 10% hydrochloric acid. The yield of crude precipitate was 0.58 g. [55%, calculated as decahydro-1-naphthoic acid (X)]. Purification was accomplished by sublimation under 1 mm. pressure followed by crystallization from 95% ethanol, to yield colorless small rhomboids, m.p. 96–123°, which melted at 112–115° after resolidification. It is assumed that our decahydro acid consisted of a mixture of stereoisomers, and that partial interconversion took place during melting.

Anal. Calc'd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95.
Found: C, 72.64; H, 10.00.

Numerous hydrogenation experiments were completed in attempts to isolate 6-hydroxydecahydro-1-naphthoic acid from the reaction mixture. The temperature of hydrogenation, the amount and composition of the solvent, the amount of catalyst, and the starting material [including the use of ethyl 6-hydroxy-1-naphthoate and 6-acetoxy-1-naphthoic acid (5)] were varied without detecting in any reaction product the presence of an alcoholic hydroxyl group or its acetate.

1-(1'-Keto-2'-hydroxyethyl)decahydronaphthalene (II). Sixty-nine hundredths gram of decahydro-1-naphthoic acid (X) was added to an ice-cold solution of 1.5 cc. of thionyl chloride in 4 cc. of dry benzene to which 2 drops of dry pyridine had been added. After standing at room temperature for thirty minutes, the clear yellow solution was warmed to 40° for ten minutes. The benzene was evaporated under reduced pressure, 2 cc. of dry benzene added, and the solution again evaporated to dryness in vacuum. The residual acid chloride XI, a yellow oil, was dissolved in 16 cc. of dry benzene and added dropwise to an ice-cold solution of diazomethane in absolute ether (prepared from 4.5 cc. of N-nitroso-N-methylurethan using *n*-propanolic potassium hydroxide). After standing at room temperature for one hour, the solution was evaporated to dryness under reduced pressure, leaving a yellow

crystalline residue of the diazo ketone XII. This method was patterned after that of Bachmann, Cole, and Wilds (15).

The diazo ketone was dissolved in 11 cc. of dioxane and 8 cc. of 2 *N* sulfuric acid was added (16). There was a slight evolution of gas. The solution was warmed to 40° for half an hour, when gas evolution appeared to have ended. Sixty cubic centimeters of water was added, and the emulsion was extracted with ether. The ether extract was washed with water, sodium bicarbonate solution, and water, successively, dried over sodium sulfate, filtered, and the ether removed under reduced pressure. The residue crystallized in long, light yellow needles. After washing with absolute ether, and drying at 1 mm. over phosphorus pentoxide, the yellow crystalline ketol II melted at 83–84°; yield, 0.3 g. (40%). Sublimation at 1 mm. and 110° yielded thick colorless rectangular prisms, m.p. 82.5–83°.

Anal. Calc'd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27.
Found: C, 73.46; H, 10.56.

The ketol II, dissolved in methanol, reduced readily ammoniacal silver nitrate solution.

SUMMARY

A decahydronaphthalene derivative with a ketol side chain at position 1 has been synthesized as a simple model of the cortin series.

6-Methoxy-1-naphthoic acid was synthesized from 6-methoxy-1-iodonaphthalene by the nitrile synthesis in satisfactory yield.

1-Hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene has been prepared and the relative ease of its dehydration has been demonstrated.

The hydrogenation of 6-hydroxy-1-naphthoic acid with Adams' catalyst at room temperature and atmospheric pressure has been investigated, and the loss of the hydroxyl group under these conditions is reported.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

REDUCTION OF THE 2-NITROPHENYL ESTERS OF CERTAIN ACIDS

L. CHAS. RAIFORD AND WILLIAM G. HUEY

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Hübner and Stünkel (1) reduced 2-nitrophenyl benzoate with tin and hydrochloric acid, dissolved the resulting tin double salt in alcohol, decomposed it cold with hydrogen sulfide, and obtained 2-phenylbenzoxazole, which had previously been prepared by Ladenburg (2) by treatment of 2-aminophenol with benzoyl chloride and subsequent distillation of the first product. Böttcher (3) repeated and confirmed the observations of the previous workers but found, in addition, that when the tin double salt was decomposed in hot alcoholic solution it gave mainly 2-benzoylaminophenol mixed with but a small portion of 2-phenylbenzoxazole. The formation of these products may involve intermediates I and II, neither of which was isolated.

The formation of 2-benzoylaminophenol in that experiment represents the migration of acyl from oxygen to nitrogen, which was found later to occur in many other cases. Bender (4) reduced 2-nitrophenyl ethyl carbonate and obtained what he thought was the corresponding 2-aminophenyl derivative, but noted that the substance showed no basic properties. Ransom (5), working under the direction of Stieglitz, proved that Bender's compound is 2-hydroxyphenylurethan and must have been formed by the migration of the carboethoxy radical from oxygen to nitrogen. Similarly, Lellmann and Bonhöffer (6) reduced the 2-nitrophenyl ester of diphenylcarbamic acid and obtained a compound that had the expected composition, and which they regarded as 2-aminophenyl diphenylcarbamate with the structure later assigned by Herzog (7) to a product he obtained by the action of diphenylcarbamyl chloride on 2-aminophenol. More recent work by Raiford and Alexander (8) indicates that Lellmann and Bonhöffer's compound cannot have the structure they assigned, but is 2-diphenylcarbamylaminophenol, and must have been formed by a migration of acyl from oxygen to nitrogen in the 2-amino compound which was the first product of reduction.

The tendency of 2-N-acylaminophenols to form cyclic compounds is also well known. Following Ladenburg's work, Hübner and Stünkel (1) found that heating 2-benzoylaminophenol above its melting point converts it

into 2-phenylbenzoxazole. Groenvik (9) heated 2-hydroxyphenylurethan above 200° and found that alcohol was eliminated and benzoxazolone was formed. In later work Moore (10) found that reduction of the methyl, ethyl, *n*-propyl, and *n*-butyl 2-nitro-4-bromo-5-methylphenyl carbonates gave the corresponding 2-amino compounds which, under the usual laboratory conditions, promptly rearranged to the isomeric 2-hydroxyphenylurethans, as found by Ransom for the unsubstituted compound. In addition, Moore showed that under the conditions of his work portions of the urethans containing the ethyl, propyl, and butyl radicals lost the ele-

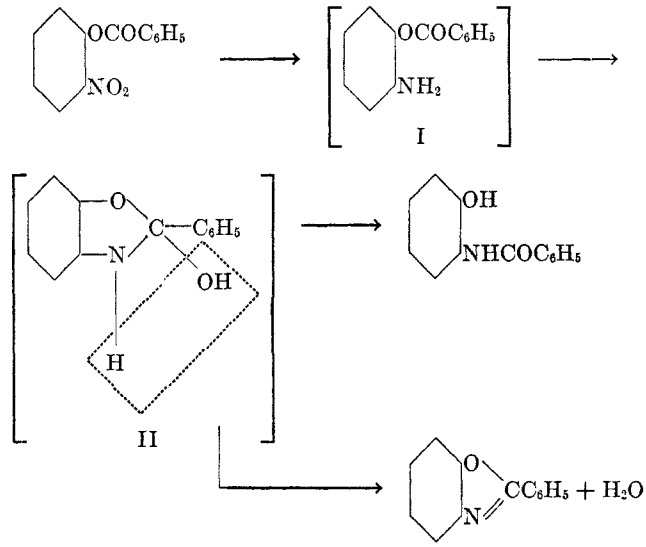
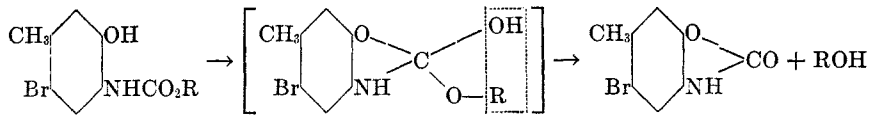
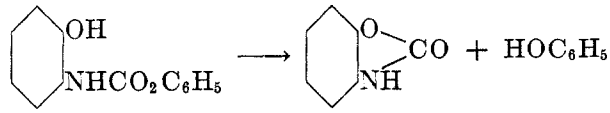


FIG. 1

ments of the related alcohols and suffered ring closure to give benzoxazolone. This type of change was also observed by Raiford and Inman



(11) who found that when the N-carboaryloxy derivatives of 2-aminophenol and its substitution products are dissolved in caustic alkali solution they are converted into benzoxazolone and a phenol is eliminated. In some



instances the change takes place slowly when the product is stored at room temperature (12).

In the light of the above observations it was of interest to extend this work and, in particular, to test the reaction of an *o*-nitrophenyl ester of a heterocyclic acid. 2-Nitrophenyl furoate and several of its substitution products were prepared and their behavior studied. Reduction of the unsubstituted compound at the temperature of an ice-bath gave chiefly 2-(α-furyl)benzoxazole, m.p., 85–87°, and a small portion of an alkali-soluble product, m.p., 225–226°, which was found not to be identical with 2-furoylaminophenol, m.p., 161°, nor with N-furoylbenzoxazolone, m.p., 141–143°, either of which might have been expected under the conditions. The product in question contains chlorine, and is still under investigation. When reduction was carried through at a higher temperature the chief product was 2-furoylaminophenol, along with a smaller portion of furylbenzoxazole, and none of the high-melting compound. This might occur as indicated in Figure 1. It was of interest here to note the effect of halogen as a substituent. Reduction of 2-nitro-4-bromophenyl and 2-nitro-4-bromo-5-methylphenyl furoate, respectively, at low temperatures gave mixtures of the corresponding benzoxazoles and the 2-furoylaminophenols, but chiefly the latter in each case. When two bromine atoms were present none of the benzoxazole was obtained. Thus, reduction of 2-nitro-4,6-dibromophenyl furoate and 2-nitro-4-bromophenyl 5-bromofuroate, respectively, gave only the related 2-furoylaminophenols.

EXPERIMENTAL

2-Nitrophenyl alkyl carbonates. These compounds were obtained by the interaction of a caustic alkali solution of the required nitrophenol and the necessary alkyl chlorocarbonate. To the phenolate solution an ether solution of the carbonate was added and the mixture was shaken until the red color of the phenolate had disappeared. The ether layer containing the desired product was removed, dried over potassium carbonate, the ether distilled, and the residue purified by crystallization from a suitable solvent. Analytical data and other properties for these products are given in Table I.

Reduction of the o-nitrophenyl alkyl esters. This was carried out in accordance with the general directions of Ransom (5) with the modifications indicated below. The nitrophenyl alkyl carbonate was ground to a fine powder and was then added to concentrated hydrochloric acid. For each gram of ester, 15–18 cc. of acid was used, the mixture was stirred rapidly, and an excess of granulated tin was added in small quantities during a period of half an hour, while the temperature of the mixture was kept below 20°. Within three-fourths hour the blue-green color of the carbonate had disappeared and there remained in the flask the tan to nearly colorless product in the form of the amine hydrochloride.

To determine whether the reduction was complete the following test was made. A small portion of the reaction mixture, held on the end of a glass rod or thermometer, was brought into a test tube containing some 50% solution of potassium hydroxide at

about −10°. If reduction was incomplete a red color was produced. This color was probably due to the potassium salt of the *o*-nitrophenol that had been formed by hydrolysis of the carbonate used as starting material. When the color test was negative the whole reduction mixture was cooled to about −12° and slowly poured

TABLE I

2-NITRO-4-BROMOPHENYL ALKYL CARBONATES

ALKYL	YIELD, %	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANAL., HALOGEN	
						Calc'd	Found
Methyl.....	48[a]	Alcohol	Pale yellow needles	61–63	$C_8H_6BrNO_5$	28.98	29.12
Ethyl.....	74[a]	Alcohol	Pale yellow needles	75–77[b]	$C_9H_8BrNO_5$	27.58	27.91
n-Propyl.....	91	Alcohol	Nearly colorless blunt needles	49–51	$C_{10}H_{10}BrNO_5$	26.31	26.51
n-Butyl.....			Tan oil	181° 5–6 mm.	$C_{11}H_{12}BrNO_5$	25.15	25.23

[a] These refer to purified material.

[b] Upson (16) reported 76° for this compound but did not record analytical data.

TABLE II

2-CARBOALKOXYAMINO-4-BROMOPHENOL DERIVATIVES[a]

ALKYL	YIELD %[b]	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANAL., HALOGEN	
						Calc'd	Found
Methyl.....	40	Alcohol	Colorless plates	168[d]	$C_8H_8BrNO_3$	32.52	32.53
Ethyl.....	52	Alcohol	Colorless plates	141[d]	$C_9H_{10}BrNO_3$	30.76[e]	32.00
n-Propyl.....	30	Alcohol	Colorless plates	113–114[d]	$C_{10}H_{12}BrNO_3$	29.19	29.04
n-Butyl.....		Alcohol	Long colorless plates	121–123[d]	$C_{11}H_{14}BrNO_3$	27.77	27.94

[a] These compounds do not suffer ring closure on standing at room temperature, as was found by Huey (12), in the study of the corresponding aryl compounds.

[b] These values represent purified material.

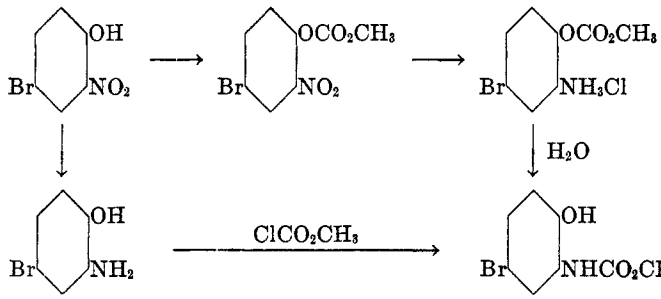
[c] This compound was previously obtained by Upson (16) who reported that it melted at 140–142° and gave a satisfactory analysis for carbon and hydrogen.

[d] The melting points of the hydrochlorides of the isomeric 2-aminophenyl alkyl carbonates were: methyl, 147–148°; ethyl, 141–143°; *n*-propyl, 136°; *n*-butyl, 138°.

with stirring into an excess of the 50% alkali solution, also cooled to −12°. The cold alkali mixture was then extracted three times with ether (25–30 cc. used each time), the extract washed three times with ice-water and then dried for some hours over anhydrous sodium sulfate. The dry ether solution was decanted and dry hydrogen chloride was bubbled through it. A flocculent colorless solid, the amine hydro-

chloride, was deposited. This salt was next dissolved in warm alcohol, the solution was allowed to stand for a short time, and was then diluted with an equal volume of water. The water caused hydrolysis of the salt to the 2-aminophenyl alkyl carbonate which then rearranged to the isomeric 2-hydroxyphenylurethan.

To establish the structure of this and other rearranged products in this group, each was prepared in another way. A portion of the corresponding *o*-aminophenol, dissolved in dioxane, was mixed with dimethylaniline, and to this liquid was slowly added the required alkyl chlorocarbonate with cooling and stirring. The mixture was then warmed to about 50°, allowed to stand for one hour, and poured into a large volume of water. The solid that separated was collected, dissolved in 5% caustic alkali solution, and the liquid treated with dilute hydrochloric acid. The product that separated was crystallized from a suitable solvent. Data for these products are given in Table II.



FUROIC ACID DERIVATIVES

N-Furoylbenzoxazolone. Thirteen and five-tenths grams of benzoxazolone (13) was dissolved in 80 cc. of pyridine, and to this was slowly added with stirring and cooling 10% more than one molecular proportion of furoyl chloride. The reaction flask was then allowed to stand in an ice-bath until no more solid separated after which four volumes of water was added, the mixture was stirred and allowed to remain for half an hour, and was then filtered. A yield of 83% was obtained. Crystallization from alcohol gave colorless glistening needles that melted at 141–143°.

Anal. Calc'd for $C_{12}H_7NO_4$: N, 6.11. Found: N, 6.20.

5-Bromofuroic acid. This compound has previously been prepared by a number of workers. Canzoneri and Oliveri (14) obtained a product that melted at 185–186°, and gave acceptable analyses for C, H, and Br. They recorded no yield. Hill and Sanger (15) treated dry furoic acid with bromine vapor at an elevated temperature and obtained yields between 40% and 60% of the desired product, which they found to melt at 183–184°. In the present work the bromination was carried out at the temperature of a boiling water-bath in the apparatus described below. One end of a piece of glass tubing about 50 mm. long and 25 mm. inside diameter was sealed to the middle of the inside of the base of a one-liter Erlenmeyer flask so as to provide a separate well. The flask was fitted by a ground glass joint to a long Allihn condenser, the inner tube of which extended down into the well for about 1 cm. when the condenser was in place. The upper end of the condenser was connected with a train of three wash bottles containing water, lime water, and sodium hydroxide solution, respectively.

Twenty grams of powdered furoic acid was placed in the flask and distributed as uniformly as possible over the bottom in such a way that none entered the well. Into the latter was introduced, by means of a long-stemmed tap funnel, 33 g. of bromine,

the condenser was attached, the flask was placed in a bath of boiling water, and heating was continued until the vapors of bromine had disappeared, usually five to seven hours. The average yield for nine runs was 85% of a product that showed a melting range of 165–172°. This solid was dissolved in the minimum quantity of boiling water, decolorizing carbon was added, and the mixture was boiled and filtered. The compound that separated was further purified by four additional crystallizations, and was obtained in large colorless foliated flakes that melted at 190–191°. The average yield of material purified in this way was 54%.

Anal. Calc'd for $C_5H_3BrO_3$: Br, 41.88. Found: Br, 41.90.

5-Bromofuroyl chloride. A mixture of 38.2 g. of furoic acid and 100 cc. of thionyl chloride was placed in a suitable flask, connected to a return condenser by a ground glass joint and heated at about 80° for four hours. The mixture was transferred to a distilling flask, unchanged thionyl chloride was removed under reduced pressure, until a dark colored crystalline residue was obtained. The condenser was then replaced by a distilling flask which was kept immersed in an ice-bath, and the distillation continued at still lower pressure. The product passed over at 89° and 8 mm. and was obtained in the form of colorless irregularly-shaped plates that melted at 54–56°.

Anal. Calc'd for $C_5H_2BrClO_2$: Hal., 55.13. Found: Hal., 54.66.

5-Bromofuranilide. To a solution containing 1.9 g. of aniline in 10 cc. of dioxane, 2.1 g. of the required acid chloride was added, the mixture was allowed to stand for an hour, a few cc. of dilute hydrochloric acid was added, and the whole was poured with stirring into several volumes of water. Repeated crystallization of the product from alcohol gave long colorless needles that melted at 145°.

Anal. Calc'd for $C_{11}H_8BrNO_2$: Br, 30.07. Found: Br, 30.04.

2-Nitrophenyl furoate and substitution products. To obtain these products the required nitrophenol was heated with a solution of an equimolecular proportion of caustic potash until all was dissolved, the liquid was stirred and cooled to about 30° so as to cause most of the salt to separate in the form of fine crystals, after which one molecular proportion of furoyl chloride was slowly dropped in with stirring, and the resulting mixture was stirred for some hours, until the red color of the potassium salt had almost disappeared. The solid product was collected by filtration, and purified by crystallization from a suitable solvent. Analytical data and other properties are given in Table III.

Reduction of 2-nitrophenyl furoic acid esters. Two and thirty-three hundredths grams of 2-nitrophenyl furoate was dissolved in 10 cc. of boiling alcohol, and the solution was stirred and cooled in an ice-bath to favor the formation of small crystals. When the temperature was between 5° and 0°, 12.5 cc. of a hydrochloric acid solution of stannous chloride (prepared by dissolving the dihydrate in concentrated hydrochloric acid, in the proportion of 1 g. to 1 cc.) was added dropwise, the mixture was stirred until all solid dissolved, which sometimes required as long as ten hours, and was then set aside at room temperature for two days. Next, two volumes of concentrated hydrochloric acid was added and the mixture was cooled in an ice-bath for several hours. The green crystals that appeared were removed, washed with cold dilute hydrochloric acid, and finally with ice-water. On the theory that the product was 2-furoylaminophenol, the yield was 85%. The material showed a melting range of 70° to 170°, indicating a mixture. The solid was shaken with 5% solution of sodium hydroxide, the mixture was filtered and the filtrate (F) was reserved. The alkali-insoluble portion was dissolved in concentrated hydrochloric acid and from this liquid it was precipitated unchanged by neutralization or large dilution, which suggested that it might be 2-aminophenyl furoate. It was identified as 2-(α-furyl)

TABLE III

2-NITROPHENYL FUROATE AND SUBSTITUTION PRODUCTS

ADDITIONAL SUBSTITUENTS IN PHENYL	SUBSTITUENT IN FUROYL	YIELD %	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANALYSES			
							Halogen		Nitrogen	
							Calc'd	Found	Calc'd	Found
Unsubs.		Nearly quant.	Absolute alcohol	Pale green needles	83–84	$C_{11}H_7NO_5$			6.01	6.15
4-Bromo-		Nearly quant.	Absolute alcohol	Pale green needles	88–89	$C_{11}H_6BrNO_5$	25.64	25.56[a]		
4-Bromo-	5-Bromo-	85	Absolute alcohol	Cream plates	135	$C_{11}H_5Br_2NO_5$	40.92	41.07		
4,6-Dibromo-		Nearly quant.	Carbon tetrachloride	Pale green cubes	133–134	$C_{11}H_5BrNO_5$	40.92	41.26		
4-Bromo-5-methyl-		95	Alcohol	Pale green plates	74–76	$C_{12}H_8BrNO_5$	24.54	24.46		

[a] When this product was purified by crystallization from carbon tetrachloride, analysis for halogen gave 26.26%, indicating adsorption of some solvent.

TABLE IV

2-(α-FURYL)BENZOXAZOLES

SUBSTITUENTS IN PHENYL	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANALYSES			
					Halogen		Nitrogen	
					Calc'd	Found	Calc'd	Found
Unsubstituted	60% Alcohol	Colorless plates	83–85	$C_{11}H_7NO_2$	—	—	7.56	7.68
5-Bromo-	Alcohol	Pale brown prisms	92–93	$C_{11}H_6BrNO_2$	30.30	30.58	—	—
5-Bromo-6-methyl-	80% Alcohol	Colorless needles	122–124	$C_{12}H_8BrNO_2$	28.77	28.83	—	—

TABLE V

SUBSTITUTION PRODUCTS OF 2-FUROYLAMINOPHENOL

SUBSTITUENT IN PHENYL	SUBSTITUENT IN FUROYL	YIELD %	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANALYSES			
							Halogen		Nitrogen	
							Calc'd	Found	Calc'd	Found
Unsubstituted		95	Alcohol	Tan plates	161–162	$C_{11}H_9NO_3$	—	—	6.89	7.01
4-Bromo-		58	Alcohol	Nearly colorless needles	238	$C_{11}H_8BrNO_3$	28.36	27.62	—	—
4-Bromo-5-methyl-		60	Alcohol	Fine colorless needles	239–240	$C_{12}H_{10}BrNO_3$	27.02	27.14	—	—
4-Bromo-	5-Bromo-	Nearly quant.	Acetone	Small needles	282–284 decomp.	$C_{11}H_7Br_2NO_3$	44.32	44.65	—	—

benzoxazole. Analytical data for this and others obtained in a similar way are shown in Table IV.

When filtrate (F) was acidified, it gave a product that melted at 225–226°, but which was not the expected 2-furoylaminophenol. To obtain the latter the following experiments were carried through. To a solution of 10 g. of 2-aminophenol in a mixture of 32.6 cc. of pyridine and 25 cc. of dioxane was added with cooling and stirring 30 g. of furoyl chloride in 30 cc. of dioxane, the mixture was allowed to stand overnight, one volume of water was added, and the liquid was made faintly acid with hydrochloric acid. A 93% yield of product separated. Crystallization from absolute alcohol gave heavy brown needles that melted at 113–114° and were identified as 2-furoylaminophenyl furoate.

Anal. Calc'd for $C_{16}H_{11}NO_5$: N, 4.71. Found: N, 4.68.

A mixture of 16.8 g. of the above diacyl derivative and 100 cc. of 6% caustic alkali solution was warmed until all solid had dissolved, the liquid was cooled and acidified. The yield of product was 95%. Analytical data and other properties for this and related *o*-furoylaminophenols are given in Table V.

SUMMARY

1. A number of 2-nitrophenyl alkyl esters of carbonic acid have been reduced in acid solution. In each case the 2-amino derivative was isolated and its direct rearrangement to the isomeric 2-hydroxyphenylurethan was observed. The latter were found to be stable under the conditions of these experiments.

2. Reduction of 2-nitrophenyl furoate at the temperature of the ice-bath gave chiefly 2-(α-furyl)benzoxazole. When a bromine atom was present in the phenyl residue some of the corresponding benzoxazole was again obtained, but the chief product was the 2-furoylaminophenol. When the dibromo compounds were used, the furoylaminophenols only could be isolated.

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[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

THE TRANSAMINATION REACTION. THE EFFECT OF ESTERIFICATION OF THE REACTANTS ON THE MECHANISM OF THE REACTION[1]

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The transamination reaction may be defined broadly as the transfer of an amino group together with a hydrogen atom, or a proton, from a compound carrying an amino group in the *alpha* position with respect to a carboxyl group to a compound with a ketonic carbonyl group in the *alpha* position relative to a carboxyl group. Recently the term transamination reaction has been applied primarily to the special case where the reactants are an *alpha* amino acid and an *alpha* keto acid. However, it may be remarked that this is only one example of a more general reaction. Reactions such as those between *alpha* amino acids and alloxan or isatin (1) and triketohydrindene (ninhydrin) (2) fall into this general category.

The reaction between *alpha* keto acids and *alpha* amino acids has been shown to lead to the formation of a new amino acid, carbon dioxide, and the aldehyde derived from the original amino acid by oxidative deamination and decarboxylation (3, 4). The latter may be accompanied by the aldehyde formed by simple decarboxylation of the keto acid.

$$\begin{array}{lcl} RCHNH_2COOH & & RCHO + CO_2 + R'CHNH_2COOH \\ + & \nearrow & \\ R'COCOOH & \searrow & RCHNH_2COOH + CO_2 + R'CHO \end{array}$$

The mechanism of this reaction was discussed in an earlier communication (4).

An analogous reaction has been found to occur in a number of biological systems by Braunshtein and Kritsman (5) and by Virtanen and Laine (6) and has been extensively studied by Cohen (7). The enzyme catalyzed reaction which takes place in biological systems differs from the uncata-

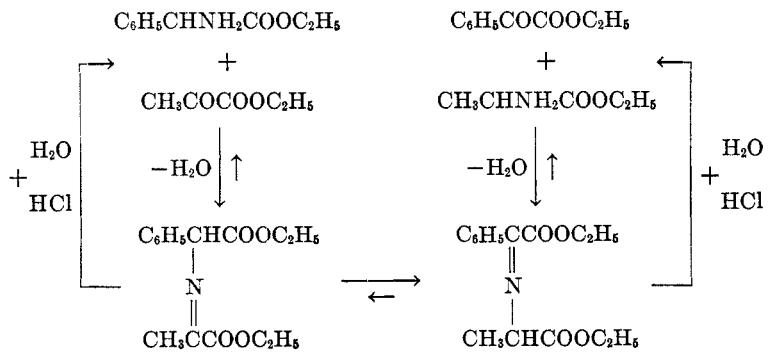
[1] Abstracted from a thesis presented by Stuart D. Brewer to the faculty of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

lyzed reaction formulated above in two ways, first no carbon dioxide is eliminated and second, the system appears to be reversible.

$$\begin{array}{ccc} RCHNH_2COOH & & RCOCOOH \\ + & \rightleftharpoons & + \\ R'COCOOH & & R'CHNH_2COOH \end{array}$$

Although earlier work (4) had shown that decarboxylation was an essential step in the uncatalyzed transamination reaction, it was of interest to determine whether transamination would proceed in systems in which decarboxylation was prevented by suitable masking of the carboxyl groups of the reactants. Furthermore, in the absence of decarboxylation such systems would be more closely analogous to the enzyme catalyzed systems. As a step in this direction, a study of the effect of esterification of the reactants was undertaken.

When the ethyl esters of α-aminophenylacetic acid and pyruvic acid are mixed, as such or in solution, an immediate reaction takes place as evidenced by the evolution of heat and the elimination of water. These effects appear to be associated with the formation of a Schiff base type of compound containing the methyleneazomethine grouping. Attempts to isolate in pure form such an intermediate or a derivative thereof were unsuccessful, but its existence appears likely in view of the results reported in this paper, as well as Knoop and Martius' synthesis of octopine from pyruvic acid and arginine (8). On boiling an absolute alcoholic solution of the above reactants, a slow shift of a hydrogen atom, or proton, from the amino ester residue to the keto ester residue takes place. Analysis of the reaction mixture demonstrated the presence of considerable quantities of ethyl benzoylformate together with alanine ethyl ester. In the presence of a small amount of sodium ethoxide as catalyst the conversion to ethyl benzoylformate and alanine ester is complete in twenty-four hours, indicating that the reaction proceeds largely in one direction. The analogy between this reaction and the enzyme catalyzed reaction of the free acids is illustrated below.



It is interesting to note that Ingold and his collaborators (9) have described a large number of simple methyleneazomethine systems in which sodium ethoxide will catalyze the tautomeric shift of a proton (prototropy). Systems in which the shift will take place spontaneously have not been observed. However, in none of the systems studied by Ingold were carboxyl or carbethoxyl groups attached to the carbon atoms of the methyleneazomethine group. In our reaction, the presence of a small amount of sodium ethoxide greatly enhances the rate of tautomeric shift. The half time for the uncatalyzed reaction is about four days while that of the catalyzed reaction is about three and one-half hours. Mineral acids cause a very marked diminution in the speed of the reaction. The presence of the water eliminated from the reactants during the formation of the intermediate methyleneazomethine system appears to have little effect on the rate of tautomeric shift, nor does the presence of an excess of either of the reactants.

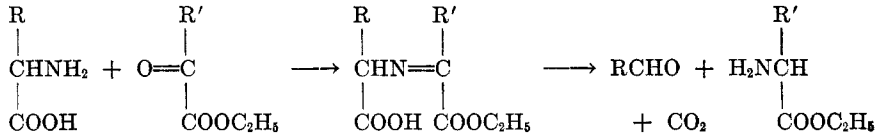
When the reverse reaction, that of ethyl benzoylformate with alanine ethyl ester was studied, no conversion to ethyl α-aminophenylacetate and ethyl pyruvate was observed although the reactants appeared to form the expected intermediate methyleneazomethine system. This result was not surprising in view of the fact that the reaction between α-aminophenylacetic acid and pyruvic acid is unidirectional (3, 4), being one of the few cases encountered that was not complicated by the formation of two aldehydic products.

Esterification of the carboxyl groups appears to alter the mechanism of transamination profoundly. The mobile hydrogen, or proton, in the uncatalyzed transaminations of systems in which the carboxyl groups of both reactants are free, may be drawn either from the aqueous reaction medium or from the *alpha* position of the original amino acid. The fact that certain amino acids in which the *alpha* carbon atom carries no hydrogen (α-amino-α-phenyl-*n*-butyric acid) undergo normal transamination with pyruvic acid (4) indicates that the medium is the more likely source of protons in these reactions. When both carboxyl groups are protected by esterification, the proton source appears to be limited to the *alpha* hydrogen of the amino ester, barring exchange with the medium during tautomeric shift. This conclusion is borne out by the fact that transamination with the free acids is completely inhibited in the presence of hydroxyl ions (3) while transamination with the esters is markedly catalyzed by the presence of ethoxide ions. Furthermore, the rate of uncatalyzed transamination with the free acids, neglecting the possible effect of about 20° in the reaction temperature, is approximately a hundred times that of the uncatalyzed ester reaction.

After determining that transamination takes place in systems in which both carboxyl groups were covered, it was of interest to investigate systems

in which only one of the carboxyl groups was protected. Langenbeck's (10) experiments indicated that decarboxylation of the keto acid should be expected when the carboxyl group of the amino acid alone was covered. On the other hand, Traube had shown that covering the carboxyl group of the keto acid, as in alloxan and isatin (1), caused oxidative deamination and decarboxylation of the amino acid with the liberation of ammonia and carbon dioxide. It was later shown (11) that a true transamination is involved as an intermediate stage in these reactions.

When a mixture of equimolar amounts of ethyl benzoylformate and alanine was heated, transamination ensued with the formation of ethyl α-aminophenylacetate, acetaldehyde, and carbon dioxide. This reaction is particularly interesting since it reverses the usual direction of the shift of the amino group that occurs between this pair of reactants when both carboxyl groups are either free or protected. The interaction of ethyl pyruvate and α-aminophenylacetic acid led to the formation of alanine ethyl ester, benzaldehyde, and carbon dioxide.



The intermediate of the Schiff base type postulated in the above scheme appears to be a likely stage in the reaction, and illustrates the analogy to other transaminating systems.

It may be concluded from these observations, as well as from data already in the literature, that the nitrogen of a transaminating system moves to, or remains attached to, that side of the system which carries the protected carboxyl group.

EXPERIMENTAL

α-Keto acids and esters. Benzoylformic acid was prepared by the oxidation of mandelic acid, following the procedure of Hurd and McNamee (12). Ethyl benzoylformate was likewise prepared from mandelic acid by the method of Corson, Dodge, Harris, and Hazen (13). Ethyl pyruvate was prepared by esterification of pyruvic acid following the directions of Simon (14).

α-Amino esters. The amino esters were isolated and stored as hydrochlorides. Alanine ethyl ester was prepared by a modification of Fischer's technique (15) based on observations of Johnson and Ticknor (16). Dry hydrogen chloride was passed into a suspension of 35 g. of alanine in 500 cc. of absolute ethanol until the alanine had completely dissolved and the evolution of heat had ceased. The solution was boiled under reflux for two hours and then evaporated to a thick syrup under reduced pressure at a water-bath temperature of 40–50°. To remove excess hydrogen chloride as completely as possible, the syrup was dissolved in 200 cc. of absolute ethanol and evaporated as before. Usually a crystalline residue remained, but if the residue

was a syrup it could be crystallized by dissolving in 50 cc. of absolute ethanol and layering the solution with anhydrous ether. On standing in the refrigerator for several days, alanine ethyl ester hydrochloride separated as a crystalline mass which could be easily broken up and washed with dry ether. After drying the product thoroughly in a vacuum desiccator over potassium hydroxide and calcium chloride, it could be stored in a well stoppered bottle without deterioration. The yield was generally 90–95%.

Ethyl α-aminophenylacetate hydrochloride was prepared in a similar manner by the esterification of α-aminophenylacetic acid (50 g.) with absolute ethanol (500 cc.). The greater part of the product separated from the reaction mixture on cooling. The remainder was obtained by concentrating the mother liquor as described for the alanine derivative. The yield of ester hydrochloride was 90–95%.

The free amino esters were prepared as required from the hydrochlorides by the technique recommended by Fischer (15).

Estimation of α-keto esters. A roughly quantitative estimation of the amounts of ethyl pyruvate and ethyl benzoylformate in reaction mixtures was essential to the success of the experiments described later. For this reason the quantitative nature

TABLE I

ESTIMATION OF KETO ESTERS AS 2,4-DINITROPHENYLHYDRAZONES

Twenty-five cubic centimeters of keto ester solution treated with equimolar quantity of 2,4-dinitrophenylhydrazine.

MOLARITY OF SOLUTION	2,4-DINITROPHENYLHYDRAZONES			
	Ethyl pyruvate		Ethyl benzoylformate	
	Grams	Yield, %	Grams	Yield, %
0.100	0.610	83	0.842	94
.075	.456	82	.671	95
.050	.317	85	.457	90

of the conversion of the keto esters into their 2,4-dinitrophenylhydrazones under standardized conditions was investigated. To 25-cc. portions of solutions of the keto esters in 95% ethanol of concentrations indicated in Table I, 1.25 cc. of concentrated hydrochloric acid and one molecular equivalent of 2,4-dinitrophenylhydrazine were added. The mixture was heated until the hydrazine reagent had dissolved. On cooling, the desired hydrazones separated from the solution in crystalline form. The results of a series of experiments at different concentrations of both keto esters are summarized in Table I.

Ethyl benzoylformate 2,4-dinitrophenylhydrazone[2] crystallizes from ethanol or from benzene on addition of petroleum ether in the form of orange needles. On rapid heating the orange product melts at about 156°, but on very slow heating the

[2] Allen and Richmond (17) reported that ethyl benzoylformate gives with 2,4-dinitrophenylhydrazine a compound of undetermined structure, possibly a pyridazine, rather than the expected hydrazone. Our product is the expected hydrazone. Dr. C. F. H. Allen kindly compared our product with his and reported the two substances to be identical. Dr. Allen suggested that faulty preparation for analysis might account for the discrepancy reported in his communication.

substance undergoes a transition to a yellow form at about 140°, especially if the temperature of the bath is held at this point for several minutes. If the conversion to the yellow form is complete, the product melts at 162–163.5°. The existence of several forms of 2,4-dinitrophenylhydrazones with different melting points has been observed in numerous instances (19). Recrystallization of the yellow form from either of the above solvents converts it into the orange form.

Anal. Calc'd for $C_{16}H_{14}N_4O_6$: N, 15.6. Found: N, 15.7.

Since the reactions described below were expected to lead to mixtures of ethyl pyruvate and ethyl benzoylformate, an attempt was made to separate the 2,4-dinitrophenylhydrazones of these compounds by the chromatographic adsorption technique, as suggested by Strain (18). Unfortunately the proper combination of solvent and adsorbent was not found. It was observed, however, that talc would remove traces of highly colored impurities from the solutions of the hydrazones in benzene-petroleum ether mixtures. This observation was useful in preparing mixtures of the derivatives for analysis.

The peculiar behavior of the dinitrophenylhydrazones on melting precluded the use of melting point diagrams, a technique successfully employed by Ingold and collaborators (9) for the determination of the composition of mixtures of similar derivatives. Since the calculated nitrogen values of the dinitrophenylhydrazones of ethyl pyruvate and ethyl benzoylformate are 18.95% and 15.64%, respectively, the approximate composition of the mixtures could be calculated from their nitrogen content.

Transamination Reactions

General procedure. The solvent used was in every case absolute ethanol. Solutions of known concentration of the various keto esters, amino esters, and sodium ethoxide were prepared. Appropriate amounts of the ester solutions and sodium ethoxide solution (when used) were mixed and diluted with absolute ethanol so that the final concentrations were 0.1 *M* (unless otherwise stated) with respect to each ester and 0.005 *M* respecting sodium ethoxide. Preliminary experiments had shown that higher concentrations of sodium ethoxide, although they increased the speed of the reactions, caused excessive formation of insoluble by-products.

The solutions were boiled under reflux on an oil-bath in an all glass apparatus. At suitable intervals, 25-cc. samples were withdrawn for analysis. The samples were treated immediately with 5 cc. of concentrated hydrochloric acid and diluted with 25 cc. of 95% ethanol. The test solution was then heated almost to boiling, 0.5 g. of 2,4-dinitrophenylhydrazine was added, and heating continued until the reagent had dissolved. After the solution had cooled to room temperature and crystallization of the hydrazone was complete, the precipitate was collected in a tared, sintered glass Gooch crucible, washed with 5 cc. of ethanol, dried in a vacuum desiccator, and weighed. The mixture of dinitrophenylhydrazones was recrystallized first from a small volume of hot ethanol, and then from benzene by the addition of petroleum ether after adsorption of a trace of impurities on powdered talc. The composition of the mixture was calculated on the basis of its nitrogen content.

Ethyl pyruvate and ethyl α-aminophenylacetate. The results of a typical reaction between ethyl pyruvate and ethyl α-aminophenylacetate in the presence of the water eliminated by Schiff base formation from the reactants are summarized in Table II. The concentrations of reactants and catalyst are indicated in the table.

In order to eliminate any effects due to the presence of the water formed by the condensation of the keto ester with the amino ester, a series of experiments was

carried out in which the water was removed from solutions of the two esters by addition of benzene, and distillation. Subsequently sodium ethoxide solution was added and the concentrations adjusted by dilution with the appropriate amount of absolute ethanol. The results of the reaction between ethyl pyruvate and ethyl

TABLE II

CATALYZED TRANSAMINATION WITH ETHYL PYRUVATE AND ETHYL α-AMINOPHENYLACETATE

(In presence of water eliminated by condensation)

0.100 *M* ethyl pyruvate, 0.100 *M* ethyl α-aminophenylacetate, 0.005 *M* sodium ethoxide—in absolute ethanol.

Twenty-five cubic centimeters of solution withdrawn at stated time intervals.

TIME (HOURS)	2,4-DINITROPHENYLHYDRAZONES			ETHYL BENZOYLFORMATE IN MIXTURE, %
	Grams	Yield, %[a]	Nitrogen, %	
3	0.420	52	17.41	46
6	.357	43	17.12	55
12	.195	23	16.67	68

[a] The yields are calculated with regard to the composition of the hydrazone mixture as determined by analysis.

TABLE III

CATALYZED TRANSAMINATION WITH ETHYL PYRUVATE AND ETHYL α-AMINOPHENYLACETATE

(In absence of water of condensation)

0.100 *M* ethyl pyruvate, 0.100 *M* ethyl α-aminophenylacetate, 0.005 *M* sodium ethoxide—in absolute ethanol.

Twenty-five cubic centimeters of solution withdrawn at stated time intervals. Water removed by benzene treatment.

TIME (HOURS)	2,4-DINITROPHENYLHYDRAZONES			ETHYL BENZOYLFORMATE IN MIXTURE, %
	Grams	Yield, %[a]	Nitrogen, %	
1.0	0.302	39	18.35	18
2.2	.317	40	17.76	36
3.1	.312	39	17.46	45
4.5	.307	37	17.12	55
17.3	.253	29	15.73	95
24.0	.321	36	15.51	103

[a] The yields are calculated with regard to the composition of the hydrazone mixture as determined by analysis.

α-aminophenylacetate catalyzed by sodium ethoxide under anhydrous conditions are set forth in Table III.

Comparison of the two tables shows that the yield of hydrazones is more constant in the absence of the water of condensation. In both cases the relatively low yields

of keto ester derivatives are probably due to competing reactions such as the self-condensation of ethyl pyruvate.

The effect of an excess of either of the reactants was found to be negligible. The results of several experiments in which the concentrations of the reactants were varied in the absence of catalyst and in both the presence and absence of water of condensation are summarized in Table IV.

The effect of mineral acids on the rate of transamination was determined by boiling a solution of 5.35 g. (0.025 mole) of ethyl α-aminophenylacetate hydrochloride and 2.9 g. (0.025 mole) of ethyl pyruvate in 500 cc. of absolute ethanol for 48 hours under reflux. The mixture of 2,4-dinitrophenylhydrazones obtained as previously described contained 18.6% of nitrogen, indicating the presence of about 9% of ethyl benzoylformate. The half time for the reaction calculated on the basis of this result would be greater than twelve days.

TABLE IV

EFFECT OF EXCESS OF A REACTANT ON THE RATE OF TRANSAMINATION WITH ETHYL PYRUVATE AND ETHYL α-AMINOPHENYLACETATE IN THE ABSENCE OF A CATALYST

Experiments 1, 2, and 3 in the presence of water of condensation.
Experiment 4 in the absence of water of condensation.

EXP. NO.	MOLARITY OF		TIME (HOURS)	2,4-DINITROPHENYLHYDRAZONES		ETHYL BENZOYLFORMATE IN MIXTURE, %
	Ethyl pyruvate	Ethyl α-aminophenylacetate		Yield, %[a]	Nitrogen, %	
1	0.092	0.103	6	47	18.44	15
			24	36	17.93	32
2	.100	.100	6	42	18.49	14
			24	34	17.78	35
3	.105	.095	24	32	18.02	32
4	.092	.103	24	43	17.85	33

[a] All yields were calculated on the basis of the limiting reagent and the composition of the hydrazone mixture.

The isolation of the alanine ethyl ester formed by the interaction of ethyl pyruvate and ethyl α-aminobenzoylformate was possible only after removal of all of the keto esters. A solution of ethyl pyruvate (11.6 g., 0.1 mole) and ethyl α-aminophenylacetate (17.9 g., 0.1 mole) in absolute ethanol was prepared. After removal of water by the benzene treatment, addition of sodium ethoxide and adjustment of the concentrations as previously indicated, the solution was boiled under reflux for 36 hours. Sufficient hydrochloric acid to neutralize the sodium ethoxide was added, and the volume reduced to 125 cc. by evaporation under reduced pressure. The resulting solution was subjected to catalytic hydrogenation over palladium oxide catalyst at room temperature at an initial pressure of 80 atmospheres of hydrogen. After 36 hours the pressure drop indicated 60% reduction of the keto esters originally present. Most of the alcohol was removed by distillation at atmospheric pressure, and the residual liquid was distilled under reduced pressure. The fraction coming

over below 100° at 10 mm., about 2 cc., contained most of the alanine ethyl ester. It was treated with an equal volume of concentrated hydrochloric acid and evaporated to dryness on the steam-bath. The residual solid was taken up in ethanol and treated with 1 cc. of pyridine. After standing in the refrigerator for several days 0.75 g. of alanine had separated.

Anal. Calc'd for $C_3H_7NO_2$: N, 15.7. Found: N, 15.8.

Ethyl mandelate was isolated from the high-boiling portion of the reaction mixture.

Ethyl benzoylformate and alanine ethyl ester. An absolute ethanol solution containing known equimolar amounts of ethyl benzoylformate and alanine ethyl ester was treated with benzene to remove water as previously described. Sodium ethoxide was added and the resulting solution was diluted with absolute ethanol so that it was 0.1 *M* with respect to the esters and 0.005 *M* with respect to sodium ethoxide. After boiling the solution under reflux for twenty-four hours, the keto esters were isolated as 2,4-dinitrophenylhydrazones in the previously described manner. Pure ethyl benzoylformate 2,4-dinitrophenylhydrazone was isolated in 75% yield and identified by observation of its transition to the yellow form and subsequent melting at 161.5–162.5°.

Ethyl benzoylformate and alanine. A mixture of 4.45 g. (0.05 mole) of alanine and 8.9 g. (0.05 mole) of ethyl benzoylformate was heated for four hours on an oil-bath at 160°. A stream of nitrogen was passed through the flask and the exhaust was directed first into a cooled trap containing ethanol and then into a trap containing 40% potassium hydroxide solution. On extraction of the dark brown viscous reaction mixture with hot ethanol, a solid residue equivalent to 34% of the original alanine remained. The material was indentified as alanine by conversion to α-phenylureidopropionic acid (20), m.p. 167.5–168° with decomposition.[3]

Half of the ethanol extract (100 cc.) was treated with 100 cc. of water and 50 cc. of concentrated hydrochloric acid and boiled under reflux for 24 hours. Removal of the ethanol by evaporation caused the separation of a tar which was not further investigated. The clear aqueous solution was evaporated to dryness and the residue taken up in 95% ethanol and treated with pyridine, which caused the precipitation of α-aminophenylacetic acid. The yield was 2.25 g., an aliquot equivalent of 60%. The identity of the product was established by conversion to α-phenylureidophenylacetic acid (21), m.p. 167.5–168.5° with decomposition.

Acetaldehyde was isolated from the contents of the first trap as the 2,4-dinitrophenylhydrazone m.p. 147° after recrystallization from 50% ethanol. Two forms of this derivative melting at 147° and 164° have been observed (19). The high-melting form is more frequently encountered.

Ethyl pyruvate and α-aminophenylacetic acid. A mixture of 5.8 g. of ethyl pyruvate and 7.5 g. of α-aminophenylacetic acid was heated for 1.75 hours in an oil-bath at 175° in the apparatus described above. The reaction mixture was taken up in 100 cc. of 85% ethanol. After standing overnight, a deposit of 0.45 g. of unreacted α-aminophenylacetic acid was filtered off. The filtrate was treated with 10 cc. of concen-

[3] All identifications based upon melting points were controlled by mixed melting point determinations with authentic substances. α-Phenylureidopropionic acid melts with decomposition over a wide range of temperatures depending on the rate of heating. Values ranging from 160° to 180° can be obtained with the same preparation. The values here reported were always controlled by the simultaneous determination of the decomposition point of the substance isolated, an authentic specimen, and their mixture.

trated sulfuric acid, diluted with 100 cc. of water, and boiled under reflux for four hours. After dilution with another 100 cc. of water, the ethanol was removed by distillation. From the distillate, after addition of phenylhydrazine, 1.2 g. of benzaldehyde phenylhydrazone (22) was isolated, m.p. 157–158° with decomposition.

After removal of a considerable amount of tar which had separated from the residual aqueous solution, sulfuric acid was removed by treatment with barium carbonate and the sulfate-free filtrate evaporated to a thin syrup under reduced pressure on the water-bath. Treatment of the concentrated aqueous solution with phenyl isocyanate under the usual conditions gave a mixture of phenylureides, which after several recrystallizations yielded 0.6 g. of α-phenylureidopropionic acid (20), m.p. 166.5° (decomp.). The phenylureide was converted by the usual treatment into 3-phenyl-5-methylhydantoin (23), m.p. 169–170°.

SUMMARY

1. Transamination takes place in systems in which the carboxyl groups of both the amino acid and the keto acid are masked by esterification. The systems ethyl pyruvate—ethyl α-aminophenylacetate and ethyl benzoylformate—alanine ethyl ester have been studied.

2. Transamination in these systems appears to be accomplished by the tautomeric shift of a proton characteristic of methyleneazomethine systems.

3. The mobility of the proton in a methyleneazomethine system is greatly enhanced by the presence of carbethoxyl groups as substituents on the carbon atoms of the system. The increase in mobility is so great that the tautomeric shift takes place at a conveniently measurable speed even in the absence of a catalyst.

4. In transaminating systems where only one of the carboxyl groups is masked, the amino group goes to that side of the system carrying the masked carboxyl group. The nature of other substituents on the *alpha* carbon atoms appears to have little influence upon the direction of shift of the amino group. The systems alanine—ethyl benzoylformate and α-aminophenylacetic acid—ethyl pyruvate were studied.

5. Ethyl benzoylformate 2,4-dinitrophenylhydrazone, which other workers had failed to recognize, has been prepared and found to exist in interconvertible dimorphic forms.

NEW YORK, N. Y.

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[Contribution from the William H. Nichols Laboratory, New York University]

CONDENSATION OF AMIDES WITH CARBONYL COMPOUNDS: BENZYL CARBAMATE WITH ALDEHYDES AND *alpha* KETO ACIDS[1]

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The condensation of amides with carbonyl compounds was observed as early as 1870 by Roth (1) who prepared benzylidenediacetamide by heating benzaldehyde with acetamide.

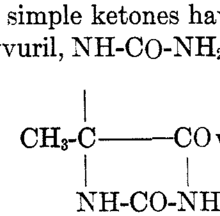
$$C_6H_5CHO + 2CH_3CONH_2 \rightarrow C_6H_5CH(NHCOCH_3)_2 + H_2O$$

Soon thereafter Bischoff (2) observed the formation of analogous compounds by the condensation of urethan with a series of aldehydes. Bischoff also noted that chloral and bromal reacted with only one mole of urethan forming compounds which appeared to be the products of simple addition of the urethan to the carbonyl group of the aldehyde. Mochelles (3) has described similar derivatives of chloral with a number of amides and succeeded in converting these into unsaturated compounds by the elimination of water.

$$RCHO + R'CONH_2 \longrightarrow R\overset{OH}{\overset{|}{C}}HNHCOR' \longrightarrow RCH{=}NCOR' + H_2O$$

More recently Noyes and Forman (4) studied the condensation of a series of aldehydes with acetamide, and obtained in yields of six to fifty-four per cent the products resulting from the condensation of two moles of amide with one mole of aldehyde.

Condensations of simple amides with simple ketones have not been observed. Aside from products such as pyvuril,



whose formation

[1] Abstracted from a thesis presented by Arthur E. Martell to the faculty of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

from urea and pyruvic acid was observed by Grimaux (5), it remained for Bergmann and Grafe (6) to initiate the study and demonstrate the usefulness for synthetic purposes of the condensation products of simple amides with *alpha* keto acids. These authors prepared α,α-diacetaminopropionic acid, $CH_3C(NHCOCH_3)_2COOH$, and α-acetaminoacrylic acid, $CH_2{=}C(NHCOCH_3)COOH$, by the interaction of acetamide and pyruvic acid and developed a method for the synthesis of pyruvylamino acids $RCH(NHCOCOCH_3)COOH$, from the former. More recently Shemin and Herbst (7) have studied the interaction of acetamide and phenylpyruvic acid, benzoylformic acid and α-ketoglutaric acid, and have reported the formation of α-acetaminocinnamic acid, α,α-diacetaminophenylacetic acid and α-acetamino-α-hydroxyglutaryl lactone, respectively.

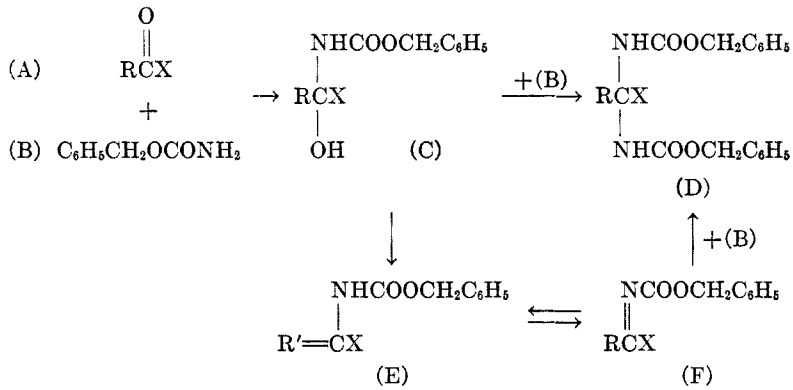
Methods of synthesizing peptides from such condensation products have been developed (8). However, the usefulness of these methods for the preparation of free peptides is impaired by the necessity of applying hydrolytic procedures for the removal of acyl groups. Such procedures usually cause a certain amount of splitting of the peptide linkages, even under carefully controlled conditions. Since Bergmann and Zervas (9) had demonstrated the ease with which the carbobenzoxyl group could be removed from derivatives of amino acids and peptides by catalytic hydrogenation, a study of the applicability of the carbobenzoxyamino derivatives of *alpha* keto acids in peptide syntheses was indicated. As the first step in this direction a study of the condensation of benzyl carbamate with aldehydes and *alpha* keto acids was undertaken.

Benzyl carbamate was found to condense readily with both aliphatic and aromatic aldehydes. Condensations were carried out with isovaleraldehyde, benzaldehyde, anisaldehyde, piperonal, and furfural. In all cases one mole of aldehyde reacted with two moles of benzyl carbamate. No attempt was made to isolate intermediates in the condensation reaction.

The condensation of benzyl carbamate with *alpha* keto acids led to a greater variety of products. From the reaction with pyruvic acid only α,α-dicarbobenzoxyaminopropionic acid could be isolated. However, two products were obtained by the interaction of benzyl carbamate with phenylpyruvic acid, depending upon the temperature at which condensation took place. After reaction at 95° only α,α-dicarbobenzoxyamino-β-phenylpropionic acid could be isolated, while at 135° the only product obtained was α-carbobenzoxyaminocinnamic acid. It was further observed that α,α-dicarbobenzoxyamino-β-phenylpropionic acid lost a molecule of benzyl carbamate on heating at 140° with the formation of α-carbobenzoxyaminocinnamic acid. The reverse of this reaction, addition of the amide to the aminocinnamic acid derivative, did not take place. When α-ketoglutaric acid was condensed with benzyl carbamate, the lac-

tone of α-carbobenzoxyamino-α-hydroxyglutaric acid was formed. The interaction of benzoylformic acid and benzyl carbamate gave only a small amount of carbobenzoxybenzalimine rather than the diaminophenylacetic acid derivative expected by analogy to the condensation with acetamide (7).

The course of the various condensation reactions is summarized in the accompanying scheme.



When X = H, R = $(CH_3)_2CHCH_2$—, C_6H_5—, (*p*)$CH_3OC_6H_4$—, 3,4-$CH_2O_2C_6H_3$—, or C_4H_3O—,
When X = COOH, R = CH_3—, $C_6H_5CH_2$—, —CH_2CH_2COOH, or C_6H_5—.
R′ = R minus H except for C_6H_5, where formula (E) is structurally impossible.

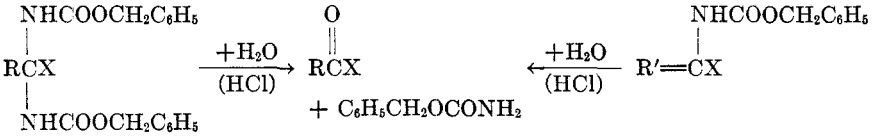
The primary reaction is the addition of benzyl carbamate to the carbonyl group of the ketonic compound with the formation of an intermediate of type (C). This intermediate may be stabilized by the formation of a lactone as in the case of α-ketoglutaric acid.

The second step in the reaction may be either the direct replacement of the hydroxyl group of (C) by another benzyl carbamate residue, or the elimination of a molecule of water with the formation of unsaturated intermediates of types (E) or (F). In the latter case the reaction is completed by the addition of a second molecule of benzyl carbamate at the site of unsaturation. The second addition reaction probably involves saturation of a carbon-nitrogen double bond as in (F). The failure of α-carbobenzoxyaminocinnamic acid to react with benzyl carbamate may be cited in support of this interpretation. Other aminocinnamic acid derivatives have shown similar unreactivity towards the further addition of amides (7). On the other hand the addition of acetamide (7) as well as benzamide and propionamide (10) to α-acetaminoacrylic acid with the formation of α,α-diacylaminopropionic acid derivatives has been observed.

This apparent discrepancy may be ascribed to the tendency of the phenyl group in the aminocinnamic acid derivatives to hold the side chain double bond in a position conjugated with the aromatic ring and thus prevent the tautomeric shift of the double bond to the carbon-nitrogen position.

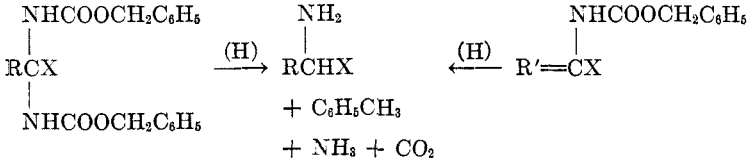
In certain cases the facts permit a choice between the several possible routes. The formation of α,α-dicarbobenzoxyamino-β-phenylpropionic acid from phenylpyruvic acid probably involves the direct replacement of the hydroxyl group of intermediate (C) by a benzyl carbamate group. The intervention of an unsaturated intermediate may be ruled out in this case. A similar mechanism is probably involved in the formation of the diacylamino derivatives of aldehydes. The fact that carbobenzoxybenzalimine, $C_6H_5CH{=}NCOOCH_2C_6H_5$, could exist in a reaction mixture in the presence of an excess of benzyl carbamate supports this view. However, this postulate still lacks rigorous experimental verification. In the case of α-ketoglutaric acid the stabilization of the intermediate of type (C) by lactone formation determines the route followed, while in the case of pyruvic acid the data do not permit designation of a choice.

The condensation products of both aldehydes and keto acids were hydrolytically decomposed into their components by merely boiling for a few minutes with dilute aqueous hydrochloric acid. Simply boiling its aqueous solution sufficed to decompose α-carbobenzoxyamino-α-hydroxyglutaryl lactone into α-ketoglutaric acid and benzyl carbamate.



X = H or COOH

Catalytic hydrogenation of the products on the other hand led to the formation of primary amines from the aldehyde derivatives and *alpha* amino acids from the keto acid derivatives.



X = H or COOH

Benzylamine, anisylamine, and piperonylamine were obtained in excellent yield by hydrogenation of the respective dicarbobenzoxyamino derivatives over palladium oxide catalyst. On similar treatment the

analogous derivatives of isovaleraldehyde and furfural failed to yield simple amines. The nature of the products formed has not been established. Application of the same technique to α,α-dicarbobenzoxyaminopropionic acid led to the formation of alanine, while α,α-dicarbobenzoxyamino-β-phenylpropionic acid and α-carbobenzoxyaminocinnamic acid were both converted in good yield into β-phenylalanine. α-Carbobenzoxyamino-α-hydroxyglutaryl lactone failed to behave in the same way. On reduction, most of the nitrogen was recovered as ammonia, both with the hydrogenation technique successfully employed in the above cases and with the method previously applied with success to the acetamide analog (7).

EXPERIMENTAL

Benzyl carbamate. Benzyl chlorocarbonate was prepared by a method essentially that of Bergmann and Zervas (9). The amide was prepared by slowly pouring the acid chloride obtained from 100 g. of benzyl alcohol into a liter of ice-cold aqueous ammonia (d = 0.90) with rapid stirring [comp. Thiele (11)]. The amide formed rapidly with heat evolution, and precipitated. After the reaction mixture had stood at room temperature for half an hour, the product was filtered off by suction, washed thoroughly with cold water, and air dried. The yield of practically pure benzyl carbamate was 139 g. (95%), m.p. 86°. By recrystallization from toluene (200 ml.) the product was obtained in the form of glistening rectangular plates (130 g.), m.p. 87°. Recrystallization from water also gave a satisfactory product.

α-Keto acids. Benzoylformic acid was prepared by the oxidation of mandelic acid as suggested by Acree (12). The purity of the product was greatly enhanced by recrystallization from dry toluene.

Phenylpyruvic acid was prepared by the hydrolysis of α-acetaminocinnamic acid, following the directions of Herbst and Shemin (13).

α-Ketoglutaric acid was prepared from ethyl succinate and ethyl oxalate by the method of Neuberg and Ringer (14).

Condensation of Benzyl Carbamate with Aldehydes and α-Keto Acids

General procedure. Ten grams of benzyl carbamate was heated without solvent for varying lengths of time under reflux with the aldehyde or keto acid. The amount of carbonyl compound used, the conditions employed, and the results obtained in each case are summarized in Table I. All condensations except those with isovaleraldehyde were carried out under reduced pressure (10–15 mm.). The condensation products of benzyl carbamate with aldehydes were purified by crystallization from benzene or toluene, while the *alpha* keto acid derivatives were crystallized from ethyl acetate with the addition of petroleum ether when necessary. The purification of α,α-dicarbobenzoxyaminopropionic acid was greatly simplified by carefully washing the crude product with cold water prior to recrystallizing from ethyl acetate. It was also found advantageous with α,α-dicarbobenzoxyamino-β-phenylpropionic acid and α-carbobenzoxyaminocinnamic acid to separate the products from unreacted benzyl carbamate by extracting the reaction mixture with cold dilute aqueous alkali. Acidification of the alkaline aqueous extracts liberated the free acids, which were then recrystallized as just indicated.

TABLE I

CONDENSATION OF BENZYL CARBAMATE WITH CARBONYL COMPOUNDS

COMPD. NO.	CARBONYL COMPOUND	GRAMS[a] CARBONYL COMPD.	TEMP., °C.	TIME OF REACTION (HRS.)	PRODUCT	M.P., °C.	YIELD, %
I	Isovaleraldehyde	4	100	4	Dicarbobenzoxy-3-methylbutylidenediamine	124	55
II	Benzaldehyde	4	80	1	Dicarbobenzoxybenzylidenediamine	175	68
III	Anisaldehyde	5	100	4	Dicarbobenzoxy-*p*-methoxybenzylidenediamine	193	65
IV	Piperonal	5	110	5	Dicarbobenzoxy-3,4-methylenedioxybenzylidenediamine	204	63
V	Furfural	4	100	3	Dicarbobenzoxyfurfurylidenediamine	163	49
VI	Pyruvic acid	4	70	2	α,α-Dicarbobenzoxyaminopropionic acid	139	85
VII	Phenylpyruvic acid	6	95	4	α,α-Dicarbobenzoxyamino-β-phenylpropionic acid	141	48
VIII	Phenylpyruvic acid	6	135	3	α-Carbobenzoxyaminocinnamic acid	160	71
IX	α-Ketoglutaric acid	10	80	4	α-Carbobenzoxyamino-α-hydroxyglutaryl lactone	176	90
X	Benzoylformic acid	5	125	12	Carbobenzoxybenzalimine	240	25

[a] Ten grams of benzyl carbamate was used in each case.

TABLE II

ANALYSES OF CONDENSATION PRODUCTS

COMPD. NO.	EMPIRICAL FORMULA	CALCULATED				FOUND			
		C, %	H, %	N, %	Neut. equiv.	C, %	H, %	N, %	Neut. equiv.
I	$C_{21}H_{26}N_2O_4$	68.1	7.1	7.6		68.2	6.8	7.4	
II	$C_{23}H_{22}N_2O_4$	70.7	5.7	7.2		70.6	5.7	7.1	
III	$C_{24}H_{24}N_2O_5$	68.7	5.8	6.7		68.6	5.7	6.5	
IV	$C_{24}H_{22}N_2O_6$	66.4	5.1	6.4		66.4	5.0	6.4	
V	$C_{21}H_{20}N_2O_5$	66.3	5.3	7.4		66.3	5.4	7.5	
VI	$C_{19}H_{20}N_2O_6$	61.3	5.4	7.5	372	61.4	5.6	7.3	386
VII	$C_{25}H_{24}N_2O_6$	66.9	5.4	6.2	448	67.1	5.4	6.2	453
VIII	$C_{17}H_{15}NO_4$	68.9	5.0	4.7	297	68.9	5.2	4.6	291
IX	$C_{13}H_{13}NO_6$	55.9	4.7	5.0	140	55.7	4.5	5.0	140
X	$C_{15}H_{13}NO_2$	75.3	5.4	5.9		75.6	5.4	5.8	

Both types of products usually crystallized in the form of needles. Exceptions were the products derived from benzaldehyde and furfural, which separated from hot benzene as gelatinous masses that disintegrated to colorless powders on drying. Both products were precipitated from ethyl acetate as colorless powders on addition of petroleum ether. The lactone of α-carbobenzoxyamino-α-hydroxyglutaric acid crystallized from ethyl acetate as hard, dense prisms, but separated from the same solvent on the addition of petroleum ether as fine needles. All of the products were insoluble in petroleum ether, ligroin, and cold water, but showed appreciable solubility in hot benzene, toluene, ethyl acetate, and ethyl alcohol.

In Table II are summarized the results of elementary analyses of the compounds described in Table I.

α-Carbobenzoxyaminocinnamic acid from α,α-dicarbobenzoxyamino-β-phenylpropionic acid. α,α-Dicarbobenzoxyamino-β-phenylpropionic acid (1.0 g.) was heated on an oil-bath at 140° for one hour. The reaction mixture was extracted with cold dilute aqueous alkali. Upon acidification of the aqueous extract and recrystallization of the precipitate from ethyl acetate and petroleum ether, 0.45 g. (68% yield) of α-carbobenzoxyaminocinnamic acid, m.p. 159°, was obtained. A small amount of benzyl carbamate, m.p. 85°, was isolated by recrystallization of the alkali-insoluble residue from hot water and from toluene.

Benzyl carbamate with α-carbobenzoxyaminocinnamic acid. A mixture of 0.15 g. of benzyl carbamate and 0.25 g. of α-carbobenzoxyaminocinnamic acid was heated on an oil-bath at 95° for 16 hours. A small amount (47%) of benzyl carbamate, m.p. 86°, and 0.23 g. (92%) of unchanged α-carbobenzoxyaminocinnamic acid, m.p. 160°, were recovered from the reaction mixture by the procedure described above.

Hydrolysis of Condensation Products

General procedure. The condensation products of benzyl carbamate with aldehydes were hydrolyzed by boiling one gram of the derivative with 50 ml. of normal aqueous hydrochloric acid in an atmosphere of nitrogen for the time indicated in Table III. When hydrolysis was complete, a solution of an equimolar amount of 2,4-dinitrophenylhydrazine in a mixture of 10 ml. of concentrated hydrochloric acid and 15 ml. of 95% alcohol was added, and the mixture boiled under reflux for five minutes. After cooling the solution, the 2,4-dinitrophenylhydrazone which separated was filtered off and purified by recrystallization from alcohol. The identity of the hydrazones was established on the basis of their melting points and mixed melting points with authentic samples.

The condensation products with α-keto acids were hydrolyzed by boiling one gram of the derivative with 100 ml. of normal aqueous hydrochloric acid for the time interval indicated in Table III. The lactone of α-carbobenzoxyamino-α-hydroxyglutaric acid was hydrolyzed by merely boiling with water. The hydrolysates were treated with an equimolar amount of 2,4-dinitrophenylhydrazine dissolved in 100–150 ml. of normal aqueous hydrochloric acid. The dinitrophenylhydrazones so obtained were recrystallized from aqueous alcohol and identified by their melting points and mixed melting points with authentic samples.

The data relating to the individual cases are summarized in Table III.

Reduction of the Condensation Products

General procedure. The reduction of the condensation products was accomplished by dissolving or suspending the substances (2–3 g.) in absolute alcohol (50–100 ml.) and shaking with palladium oxide (0.1 g.) in an atmosphere of hydrogen in a Burgess-

TABLE III

HYDROLYSIS OF CONDENSATION PRODUCTS

COMPD. NO.	TIME OF HYDROLYSIS	CARBONYL COMPOUND FORMED	2,4-DINITROPHENYLHYDRAZONE OF CARBONYL COMPOUND		
			Yield, %	M.p. °C.	Ref.
I	15 min.	Isovaleraldehyde	89	124	15
II	15 min.	Benzaldehyde	99	240	16
III	15 min.	Anisaldehyde	99	252	17
IV	15 min.	Piperonal	97	266	17
V	15 min.	Furfural	93	227	18
VI	30 min.	Pyruvic acid	98	217	19
VII	3 hr.	Phenylpyruvic acid	96	192	[a]
VIII	4 hr.	Phenylpyruvic acid	94	192	[a]
IX	5 min.	α-Ketoglutaric acid	100	217	20
X	10 min.	Benzaldehyde	80	239	16

[a] This derivative has not been described previously. It was obtained in the form of fine orange-yellow needles on crystallization from 50% alcohol.
Anal. Calc'd for $C_{15}H_{12}N_4O_6$: N, 16.3. Found: N, 16.4.

TABLE IV

REDUCTION OF CONDENSATION PRODUCTS

COMPD. NO.	SUBSTANCE ISOLATED	M.P., °C.	YIELD, %	DERIVATIVE	M.P., °C.	REF.	NITROGEN %	
							Calc'd	Found
II	Benzylamine hydrochloride	260 decomp.	93	N-Benzylbenzamide	105	21,		
				Benzylurea	148	22, 23		
III	Anisylamine hydrochloride	253 decomp.	89	Anisylamine picrate	190 decomp.		15.3	15.2
IV	Piperonylamine hydrochloride	260 decomp.	90	Piperonylamine picrate	200 decomp.		14.7	14.6
VI	Alanine	280 decomp.	60	Alanine			15.7	15.6
VII	β-Phenylalanine	250 decomp.	62	α-Phenylureido-β-phenylalanine	177 decomp.	24		
				3-Phenyl-5-benzylhydantoin	171			
VIII	β-Phenylalanine	250 decomp.	85	α-Phenylureido-β-phenylalanine	180 decomp.	24		
				3-Phenyl-5-benzylhydantoin	172			

Parr low-pressure hydrogenation apparatus. The reduction of the aldehyde derivatives was complete in two hours, that of the keto acid derivatives in four hours.

The amines formed by hydrogenation of the aldehyde derivatives were isolated

after filtering off the catalyst, by acidifying the alcoholic solution with hydrochloric acid and evaporating to dryness. Recrystallization of the hydrochloride residue from absolute alcohol served to remove the contamination of ammonium chloride. The identity of the hydrochlorides was established by their melting points, and by conversion into suitable derivatives and comparison with samples of known identity as indicated in Table IV.

The amino acids formed by the reduction of the keto acid derivatives usually separated from the alcoholic solution during the hydrogenation. After filtration they were separated from the catalyst by extraction with water. Purification was accomplished by recrystallization from hot water, alone or with the addition of alcohol when necessary. Their identity was established by analysis or by conversion into suitable derivatives and comparison with substances of known identity as indicated in Table IV.

The reduction of the carbobenzoxyamino derivatives of isovaleraldehyde and furfural failed to give the expected primary amines. The nature of the products formed still remains undetermined.

No glutamic acid could be isolated after the reduction of α-carbobenzoxyamino-α-hydroxyglutaryl lactone by the technique just described. After hydrogenation most of the nitrogen was present as ammonia, and excepting a small amount of α-ketoglutaric acid which could be isolated as the 2,4-dinitrophenylhydrazone, no effort was made to determine the fate of the carbon skeleton. Application of the technique successfully used in the conversion of the analogous acetamino derivative to glutamic acid (7) likewise failed to lead to the desired result.

The pertinent data concerning the results of the hydrogenation experiments are summarized in Table IV.

SUMMARY

1. The condensation of benzyl carbamate with a series of aldehydes including isovaleraldehyde, benzaldehyde, anisaldehyde, piperonal, and furfural has been studied. In each case two moles of amide reacted with one mole of the aldehyde.

2. The condensation of benzyl carbamate with *alpha* keto acids leads to a variety of products formed by the interaction of one mole of the keto acid with one or two moles of the amide. With pyruvic acid α,α-dicarbobenzoxyaminopropionic acid is formed. From phenylpyruvic acid, depending on the conditions employed, either α,α-dicarbobenzoxyamino-β-phenylpropionic acid or α-carbobenzoxyaminocinnamic acid is formed. With α-ketoglutaric acid the lactone of α-carbobenzoxyamino-α-hydroxyglutaric acid is formed, while the reaction with benzoylformic acid appears to be abnormal and leads to the formation of carbobenzoxybenzalimine.

3. α,α-Dicarbobenzoxyamino-β-phenylpropionic acid is converted into α-carbobenzoxyaminocinnamic acid by heating. The reverse of this reaction does not take place.

4. A mechanism for the condensation of aldehydes and *alpha* keto acids with benzyl carbamate has been suggested. The reaction involves a primary addition of the amide to the carbonyl group, followed either by

direct replacement of a hydroxyl group by another amide residue, or by elimination of water with the formation of unsaturated intermediates, to which a second mole of amide may add.

5. The hydrolysis of the condensation products with aqueous acid was studied and found to result in the regeneration of the original aldehyde or keto acid and benzyl carbamate.

6. The catalytic hydrogenation of the condensation products of the aldehydes was found to lead to the formation of primary amines, while reduction of the keto acid derivatives leads to alpha amino acids. This constitutes a new method for the synthesis of primary amines from aldehydes, and for the conversion of *alpha* keto acids into *alpha* amino acids.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE STRUCTURE OF THE BISULFITE COMPOUND OF ACETALDEHYDE

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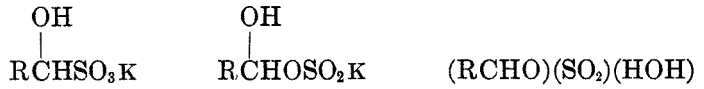
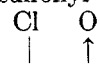
The structure of the compounds resulting from the addition of alkali metal bisulfites to aldehydes and certain ketones has been the subject of much discussion and experimentation. Various investigators have, from time to time, favored either the hydroxysulfonate structure (1, 2, 3) (I), the hydroxysulfite ester formula (4, 5) (II), or a "polymolecule" formula (6, 7) (III). The experiments of Raschig and Prahl (3, 8), Backer and



I II III

Mulder, (9) and the recent work of Lauer and Langkammerer (10) leave no doubt that the bisulfite compound of formaldehyde is best represented by the hydroxysulfonate structure (I). By inference, other bisulfite compounds should possess the same structure. However, in view of the occasional exceptional behavior of formaldehyde as compared to other aldehydes, it was desirable to investigate the structure of the acetaldehyde bisulfite compound in order to add further evidence on the structure of these compounds.

In the present work acetaldehyde (IV) was converted to trithioacetaldehyde (11) (V) by means of hydrogen sulfide in the presence of hydrochloric acid. Treatment of a suspension of trithioacetaldehyde in ice-water with chlorine according to the procedure of Müller and Raudenbusch (12), gave a 75% yield of α-chloroethanesulfonyl chloride (VI). This compound was a liquid which could be distilled *in vacuo*. It possessed all the properties and reactions of a sulfonyl chloride and none of the reactions of the



isomeric structure, $CH_3CHOSCl$. For example, barium hydroxide at 60–70° caused hydrolysis to the barium salt, VII, which upon treatment with potassium sulfate gave the potassium salt (IX). The latter, with

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phosphorus pentachloride, regenerated the α-chloroethanesulfonyl chloride (VI).

Treatment of an ice-cold ether solution of VI with ammonia produced the

CHART I

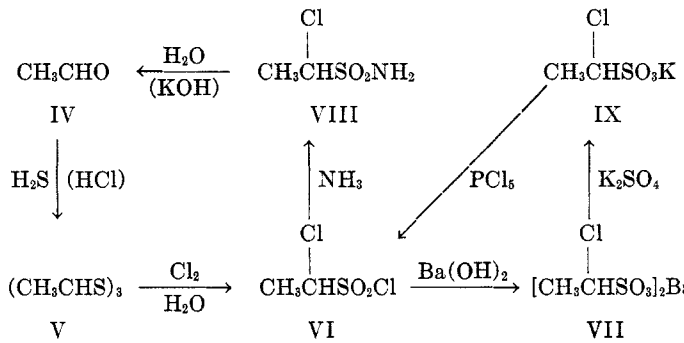
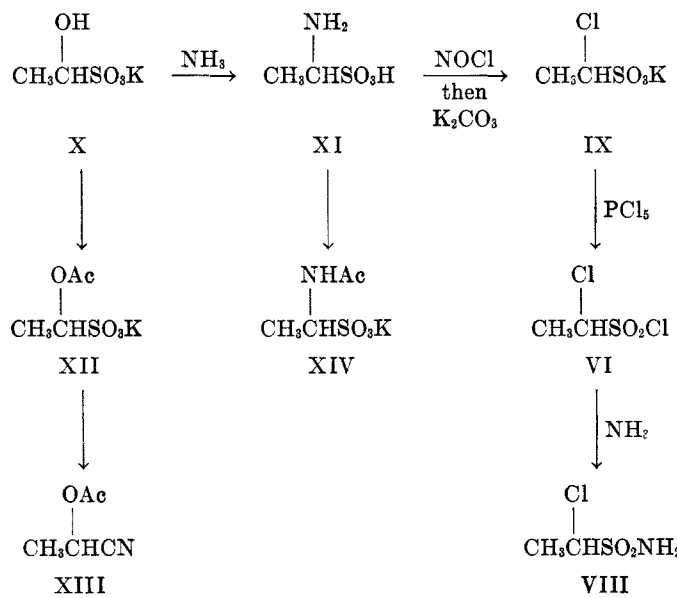


CHART II

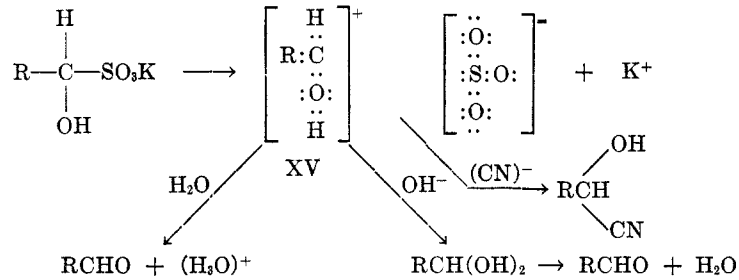


α-chloroethanesulfonamide (12) (VIII). The latter was hydrolyzed by dilute alkali back to acetaldehyde, which was characterized by its methone condensation product. This conversion presumably takes place through the intermediate formation of α-hydroxyethanesulfonamide which in turn

is hydrolyzed into acetaldehyde, ammonia, and sulfurous acid. The chlorine atom in potassium α-chloroethanesulfonate is not sufficiently reactive to permit the formation of the intermediate α-hydroxyethanesulfonate under the conditions used here, although Bunte (13) has demonstrated the production of acetaldehyde from the chloro salt by hydrolysis at an elevated temperature and pressure. Thus, this set of reactions summarized in Chart I, furnishes a series of six compounds derived from acetaldehyde, all of which contain a carbon-sulfur linkage.

Treatment of either the sodium or potassium bisulfite compound (X) of acetaldehyde with concentrated ammonia and subsequent acidification yielded α-aminoethanesulfonic acid (9) (XI) as previously described by Backer and Mulder. Nitrosyl chloride at 0° converted this aminosulfonic acid into the α-chloroethanesulfonic acid, which was neutralized with potassium carbonate and isolated as the potassium salt (IX), identical with that prepared by the reactions in Chart I. This sample of the salt was also converted to the sulfonamide (VIII) by way of the acid chloride (VI), and identity of the sulfonamides established by a mixed melting point determination. It thus seems clear that the acetaldehyde bisulfite compound (X) possesses the hydroxysulfonate structure, since all of these reactions were carried out under mild experimental conditions, and the possibility of rearrangement seems remote.

The chief point in connection with the chemistry of the bisulfite compounds is their instability, *i.e.*, the reaction which leads to their formation is readily reversible and markedly affected by the presence of acids or alkalies. In these α-hydroxy sulfonates the carbon-sulfur linkage is far more labile than in a simple alkyl sulfonic acid. If the initial step in the dissociation of the bisulfite results in the following ions,



then the carbonium ion (XV) may easily stabilize itself by loss of a proton to the solvent, water, and thus regenerate the aldehyde. It could also combine with a hydroxyl ion forming an aldehyde hydrate which could then lose water. Both of these reactions would be sensitive to the *p*H of the solution. In the presence of sodium cyanide, the cyanide anion would combine with the cation (XV) to produce the cyanohydrin.

Acetylation of the hydroxyl group would prevent the loss of a proton mentioned above, and indeed the acetyl derivative (XII) is far more stable than the original acetaldehyde bisulfite compound (X). The sulfonate group in this acetoxy derivative can be replaced by the cyano group by reaction with the cyanide anion leading to α-acetoxypropionitrile (XIII).

EXPERIMENTAL

Potassium α-hydroxyethanesulfonate (X). A saturated solution containing 240 g. of potassium bisulfite was placed in a three-necked flask equipped with a mechanical stirrer and a reflux condenser and immersed in an ice-bath. The acetaldehyde produced by the depolymerization of 110 g. (0.833 mole) of paraldehyde was condensed directly into the bisulfite solution, stirring and cooling being continued throughout the addition. Precipitation of the addition product was effected by the addition of four volumes of 95% ethanol and cooling in an ice-bath. The precipitated material was collected on a suction filter, washed with several portions of cold 70% ethanol, and dried for forty-eight hours in a vacuum desiccator over sulfuric acid. Yield, 219 g.

One gram of the dried material, when dissolved in a small amount of water and acidified with a drop of hydrochloric acid, reduced only two drops of 0.1 *N* iodine solution indicating the practical absence of free sulfite.

Potassium α-acetoxyethanesulfonate (XII). One hundred grams (0.61 mole) of potassium α-hydroxyethanesulfonate, 124 g. (1.22 moles) of acetic anhydride, and 97 g. (1.22 moles) of pyridine were placed in a 500-cc. flask equipped with a stirrer and a reflux condenser. The suspension was stirred and heated with a free flame to gentle boiling. Shortly after refluxing began, the reaction became so vigorous that external cooling was required. In a short time the contents set to a pasty mass and stirring was discontinued. The mixture was cooled, broken up as thoroughly as possible, and transferred to a Büchner funnel by the use of several portions of ether. The washing with ether was continued until the bulk of the acetic anhydride and pyridine was removed. The residue was dissolved in boiling 80% ethanol and treated with two portions of decolorizing carbon. A second recrystallization yielded 46 g. of thick white needles (decomp. at 209–211°, Maquenne block).

An analytical sample was prepared by two further recrystallizations and rendered anhydrous by boiling with toluene.

Anal. Calc'd for $C_4H_7KO_5S$: S, 15.39; K, 18.97.
Found: S, 15.35; K, 18.65.

α-Aminoethanesulfonic acid (XI). Eighty-eight grams (2 moles) of freshly distilled acetaldehyde was added slowly to a cooled solution of 210 g. (2 moles) of sodium bisulfite in 300 cc. of water, the solution being stirred and the temperature kept at 20° or below during the addition. After the addition of 300 cc. of concentrated ammonia, the solution was stirred and heated at 70° for thirty minutes. The cooled solution was acidified by the addition of 150 cc. of concentrated hydrochloric acid and placed in the ice-box overnight. The amino acid was collected on a suction filter and washed with a small portion of ice-water. A yield of 120 g. of white crystals decomposing at 260° was obtained (14).

Potassium α-acetamidoethanesulfonate (XIV). Twenty grams of α-aminoethanesulfonic acid and 11 g. of potassium carbonate were dissolved in 100 cc. of water. Thirty grams of acetic anhydride was added and the solution heated at 70° for thirty minutes. The thick, clear syrup resulting from concentration of the solution on the

steam-bath set to a brittle glass upon cooling but could not be induced to crystallize. This was redissolved in water, placed in a continuous extractor and extracted with ether for several hours. Reevaporation of the aqueous solution yielded a gum which crystallized when rubbed with a spatula. Two recrystallizations from 80% ethanol yielded 18 g. of transparent prisms which decomposed at 180°.

Anal. Calc'd for $C_4H_8O_4KNS$: K, 19.05. Found: K, 19.13.

Potassium α-chloroethanesulfonate (IX). (a) *From α-aminoethanesulfonic acid.* Twenty-five grams of α-aminoethanesulfonic acid was suspended in 100 cc. of concentrated hydrochloric acid. While the suspension was stirred and cooled in an ice-bath a rapid stream of nitrosyl chloride was passed into it. After approximately one hour the gas stream was interrupted and the solution allowed to come to room temperature. When the brown color of the nitrosyl chloride was discharged, the solution was again cooled and the passage of the gas resumed. This process was continued until all of the suspended material had dissolved. The solution was concentrated in a vacuum desiccator over sodium hydroxide until only a trace of chloride remained. Further concentration on the steam-bath produced a viscous brown oil which was diluted with water, neutralized with potassium carbonate, and evaporated to dryness. The residue was dissolved in methanol, treated with charcoal, and allowed to crystallize. A second recrystallization from methanol produced 16 g. of glistening white plates, m.p. 325° (decomp., Maquenne block).

(b) *From α-chloroethanesulfonyl chloride.* The general procedure of Müller and Raudenbusch (12) was followed. Eighteen grams of α-chloroethanesulfonyl chloride (preparation described below) was added to a saturated solution containing 35 g. of barium chloride octahydrate. The chloride dissolved fairly rapidly and the solution became noticeably warm. After the initial reaction had subsided the solution was heated to 60–70° for one hour and filtered while hot. The barium was precipitated by the addition of sulfuric acid, which was in turn removed by shaking the solution with lead carbonate. Removal of the lead by saturating the solution with hydrogen sulfide left a fairly pure solution of the acid which was reconverted to the barium salt by the addition of barium carbonate. This was decolorized with charcoal, filtered, and evaporated to dryness. The residue was recrystallized from aqueous ethanol to obtain 10.6 g. of the crystalline barium salt.

Anal. Calc'd for $C_4H_8BaCl_2O_6S_2+H_2O$: Ba, 31.06. Found: Ba, 30.89.

The barium salt was added to a solution containing the theoretical amount of potassium sulfate, filtered, and evaporated to a small volume. Upon cooling, 8.18 g. of the potassium salt crystallized, m.p. 327° (decomp., Maquenne block).

Anal. Calc'd for $C_2H_4ClKO_3S$: K, 21.41. Found: K, 21.40.

Attempted hydrolysis of potassium α-chloroethanesulfonate. One-half gram of potassium α-chloroethanesulfonate was treated as described below under the hydrolysis of α-chloroethanesulfonamide. Although heating was continued for one hour, no precipitate appeared in the methone solution. A sample of the alkaline salt mixture yielded no precipitate when acidified with nitric acid and treated with silver nitrate solution.

α-Chloroethanesulfonyl chloride (VI). (a). *From potassium chloroethanesulfonate.* To 9.65 g. (0.05 mole) of the potassium α-chloroethanesulfonate obtained from α-aminoethanesulfonic acid was added 10.5 g. (0.05 mole) of phosphorus pentachloride. In a short time the reaction began to take place spontaneously with the liberation of considerable heat and the mixture partially liquefied. The reaction flask was provided with a reflux condenser and heated at 80° for nine hours. The mixture was distilled under reduced pressure. The fraction boiling 80–81° at 22 mm. weighed 4.8 g. and was converted to the amide by the procedure described below.

(b). *From trithioacetaldehyde (12).* Trithioacetaldehyde was prepared by a slight modification of the method of Suyver (11). Eighty-five grams of freshly distilled acetaldehyde was added to 300 cc. of 6 *M* hydrochloric acid. The mixture was shaken in contact with hydrogen sulfide for eight hours. The precipitated solid was removed by filtration and recrystallized from 80% ethanol to yield 75 g. of material melting 77–80°. No attempt was made to separate the α- and β-isomers, since either is reported to serve equally well for the preparation of the sulfonyl chloride (12).

Thirty grams of trithioacetaldehyde was suspended in 600 cc. of water and stirred at ice-bath temperature while a rapid stream of chlorine was passed into the suspension. The addition of chlorine was continued until 122 g. had been absorbed. The chlorosulfonyl chloride was extracted with ether, washed with sodium thiosulfate solution followed by water and dried over magnesium sulfate. After the removal of the ether the chloride was distilled under reduced pressure. The yield was 39 g., b.p. 48–53° at 3 mm.

α-Chloroethanesulfonamide (VIII) (12). Thirty-five grams of α-chloroethanesulfonyl chloride was dissolved in 100 cc. of dry ether. The solution was cooled to 0° and maintained at that temperature while a rapid stream of ammonia was passed into it for a period of thirty minutes. The precipitated ammonium chloride was removed by filtration and washed with two 10-cc. portions of ether. The combined filtrate and washings were evaporated under reduced pressure, and the residual oil allowed to stand overnight in a vacuum desiccator over sulfuric acid. Crystallization was induced by rubbing with a spatula. Two recrystallizations from benzene yielded 21 g. of soft white crystals m.p. 65–66°.

Anal. Calc'd for $C_2H_6ClNO_2S$: S, 22.30. Found: S, 21.89.

Samples of α-chloroethanesulfonyl chloride prepared by each of the methods described above yielded amides melting at the same temperature and showing no depression of melting point when mixed.

Hydrolysis of α-chloroethanesulfonamide. One-half gram of α-chloroethanesulfonamide was placed in a flask containing 20 cc. of 5% potassium hydroxide solution. A moderately rapid stream of nitrogen gas was bubbled through the solution while it was heated to boiling. The emergent gases were passed into a cooled solution composed of 20 cc. of water, 1 g. of sodium acetate, 0.5 cc. of glacial acetic acid, and 5 cc. of 5% alcoholic dimethyldihydroresorcinol. Shortly after the boiling point was reached, the contents of the reaction flask began to darken and a precipitate appeared in the methone solution. The heating was continued until the boiling solution began to foam badly. The precipitate from the methone solution was separated by filtration and recrystallized from water-ethanol. It melted at 137–139° and showed no depression of melting point when mixed with an authentic sample of acetaldehyde dimethone.

Acetoxypropionitrile (XIII). The method used was similar to that used by Lauer and Langkammerer (10) in the preparation of acetoxyacetonitrile. Twenty and six-tenths grams (0.1 mole) of potassium acetoxyethanesulfonate and 4.9 g. (0.1 mole) of sodium cyanide were dissolved in 50 cc. of water and allowed to stand at room temperature for one hour. The colorless liquid which separated on top of the aqueous solution was extracted with ether and the extract dried over sodium sulfate. After removal of the ether, distillation of the oil yielded 5.85 g. of a colorless liquid, b.p. 75–77° at 25 mm. n_D^{20} 1.4027.

SUMMARY

A study has been made of some derivatives of α-chloroethanesulfonyl chloride. Although its potassium salt was resistant to alkaline hydrolysis,

its amide was readily converted into acetaldehyde by heating with dilute alkali.

The presence of a carbon-to-sulfur linkage in potassium acetaldehyde bisulfite has been demonstrated by its conversion through α-aminoethanesulfonic acid, potassium α-chloroethanesulfonate, and α-chloroethanesulfonyl chloride to α-chloroethanesulfonamide.

URBANA, ILL.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF SWARTHMORE COLLEGE]

ETHYLENEDIAMINE. V.[1] THE ACTION OF AROMATIC ACID CHLORIDES ON 4,5-DIHYDROIMIDAZOLES IN AQUEOUS MEDIA

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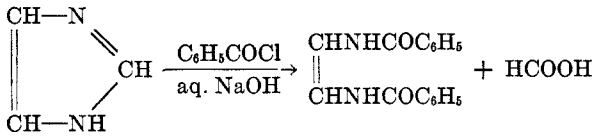
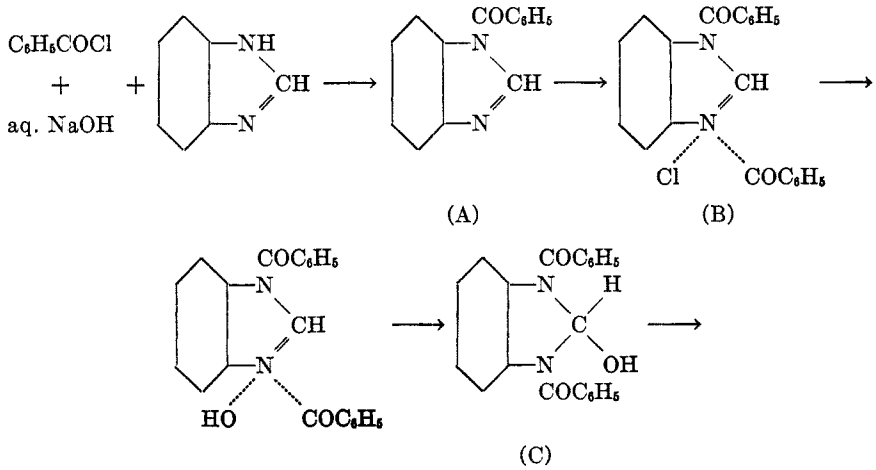
It is known that imidazoles and benzimidazoles of simple structure, although possessing a nitrogenous ring which in general is very stable, readily undergo ring fission when subjected to a Schotten-Baumann reaction even at 0°.

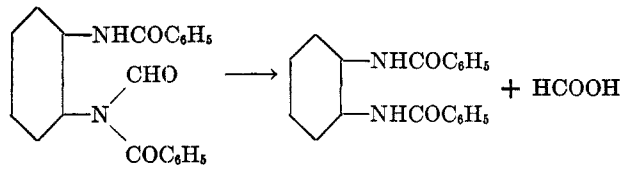


This remarkable vulnerability of a very stable ring has been the subject of many investigations. Gerngross (1) allowed benzoyl chloride to act on benzimidazole under a variety of conditions, and obtained several compounds which he showed to be intermediates and postulated the mechanism shown in formulas A–E.



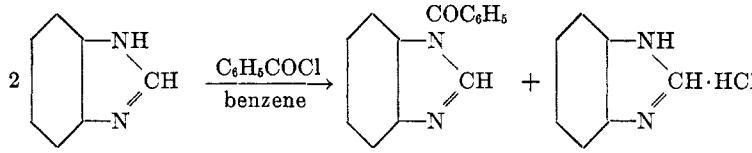
(A) (B) (C)

[1] For the fourth article of this series see *J. Am. Chem. Soc.*, **63**, 852 (1941).

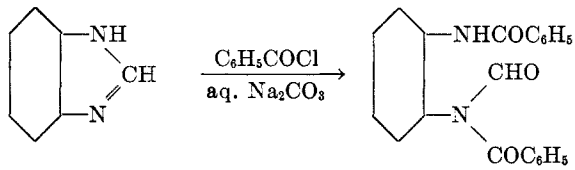


(D) (E)

Benzoylbenzimidazole (A) is obtained by treating benzimidazole in benzene solution with one-half equivalent of benzoyl chloride.



The evidence for the existence of an addition product (B) between benzoylbenzimidazole and benzoyl chloride consisted only in anomalous freezing point depression data; however, if one equivalent of water is added to a mixture of the two, 1,3-dibenzoylbenzimidazolol (C) is produced. This latter compound melts at 135–140°, and in so doing is converted into the isomeric N-benzoyl-N′-benzoylformylorthophenylenediamine (D), which solidifies and then melts at 157°. N-Benzoyl-N′-benzoylformylorthophenylenediamine also arises directly by the action of benzoyl chloride on benzimidazole in carbonate solution.



Finally, the formyl group may be eliminated by heat or alkali to give E.

While the evidence is not altogether concordant, it is generally agreed that the stability towards acylating agents increases in the order imidazoles, benzimidazoles, and naphthimidazoles (*i.e.*, acylation of the secondary nitrogen rather than ring fission is more likely to occur in that order); and that the tendency of the medium to favor fission of the ring rather than simple acylation increases in the order benzene or ether, pyridine, aqueous carbonate, and aqueous caustic. Thus imidazole can be benzoylated in benzene on the secondary nitrogen using one mole of imidazole to absorb the hydrogen chloride formed, but any other technique of acylation results in ring fission. Benzimidazole can be benzoylated in benzene or pyridine, while carbonate or caustic result in ring fission; and naphthimidazole can be benzoylated by the customary Schotten-Baumann method. Imidazoles

are remarkably stable towards alkali, hence the linear amides do not arise by hydrolytic fission of the ring to a monoacyl derivative followed by acylation. Furthermore the diamides isolated were symmetrical and characteristic of the acid chloride, while the 2-carbon was found in

TABLE I

REACTION PRODUCTS AND THEIR DERIVATIVES

NAME	NUMBER ON FLOWSHEET	M.P., °C. CORR.	N, %	
			Calc'd	Found[a]
2-Methyl-4,5-dihydroimidazole[b]	I	103		
2-Phenyl-4,5-dihydroimidazole[b]	I′	102		
Monoacetylethylenediamine	II			
Monobenzoylethylenediamine	II′			
N-Acetyl-N′-benzoylethylenediamine	III; VIII	180[c]	13.59	13.55
sym-Dibenzoylethylenediamine	III′; VII; VIII′	250	[d]	
Monoacetylethylenediamine picrate	IV	175	[d]	
Monobenzoylethylenediamine picrate	IV′	216–221 (decomp.)	17.81	17.95
N-Acetyl-N′-benzenesulfonylethylenediamine	V	104	[d]	
N-Acetylbenzoyl-N′-benzoylethylenediamine	VI	115[e]		
Tribenzoylethylenediamine	VI′	104	7.52	7.60
N-Acetylbenzenesulfonyl-N′-benzenesulfonylethylenediamine	IX	122	7.33	7.33
N-Benzoylbenzenesulfonyl-N′-benzenesulfonylethylenediamine	IX′	162	6.31	6.25
sym-Dibenzenesulfonylethylenediamine	X	171	[d]	

[a] Analytical results are the averages of two Kjeldahl determinations, neither of which differs from the theoretical by more than 0.15%.

[b] Prepared according to Hill and Aspinall, *J. Am. Chem. Soc.*, **61**, 822 (1939).

[c] Literature: 175°; U. S. Patent 1,926,014.

[d] Identified by mixed melting point with an authentic sample.

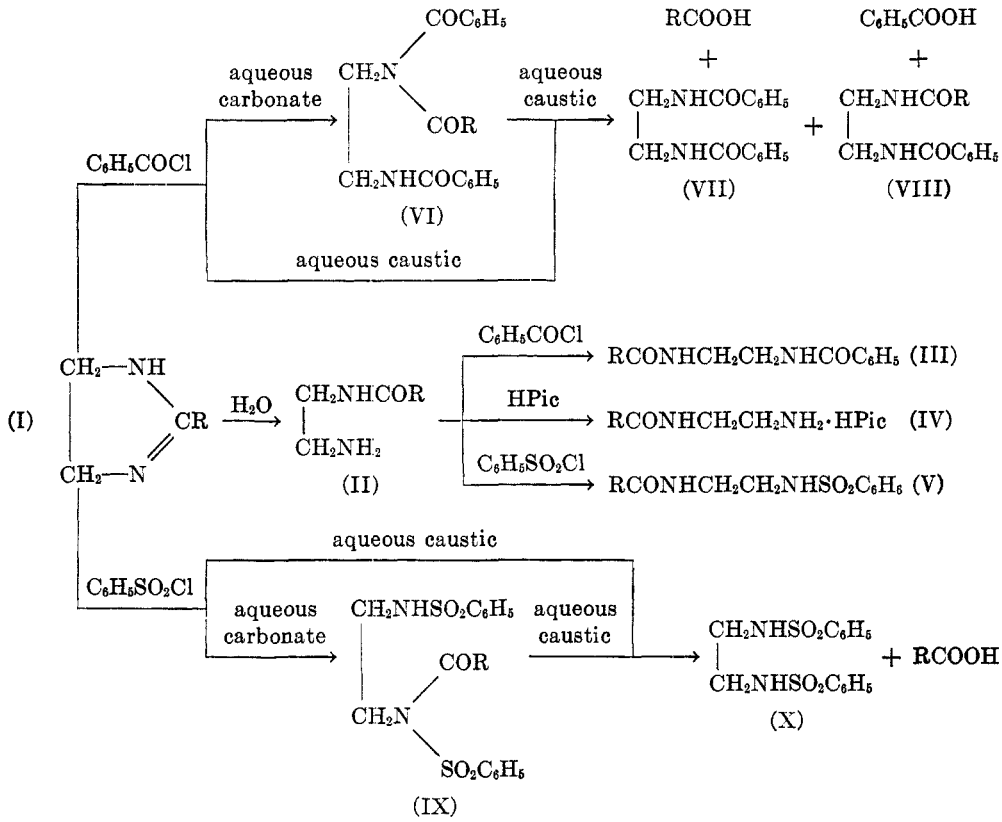
[e] Literature: 114°; *Ber.*, **28**: 3068 (1895).

the filtrate as an acid. It is also known that isovaleryl chloride brings about analogous results, but it has been stated that sulfonyl chlorides do not show this reaction (2).

In contrast to the situation with imidazoles, there is but one reference

to the interaction of a 4,5-dihydroimidazole and an acid chloride (3), which states that 2-methyl-4,5-dihydroimidazole in carbonate solution reacts with benzoyl chloride to yield N-benzoyl-N′-acetylbenzoylethylenediamine which decomposes into dibenzoylethylenediamine and acetic acid when treated with caustic. This reaction, which is strictly analogous to that of an imidazole under the same conditions is quite interesting in view of the many dissimilarities between the two types of compounds.

FLOW-SHEET



Unprimed Roman numerals in the text mean R = CH_3; when primed, R = C_6H_5.

The present investigation consists of a more careful study of the action of benzoyl chloride on 2-substituted 4,5-dihydroimidazoles in aqueous solutions of carbonate and caustic, and the extension of the reaction to include benzenesulfonyl chloride. Contrary to former evidence, when a

triacyl diamine is treated with cold caustic the diacylated nitrogen atom expels some of each one of its two substituents rather than exclusively eliminating the acid characteristic of the 2-substituent. This fact has no practical effect if the 2-substituent is the same as the radical of the acid chloride, but otherwise results in a mixture of products. When a monoacyldisulfonyl diamine is treated with caustic, it quantitatively eliminates the group derived from the 2-substituent. This is due to the much greater stability towards alkali of the N-SO_2R group over the N-COR group.

Although it cannot be stated with certainty that the reactions of 4,5-dihydroimidazoles with benzoyl and benzenesulfonyl chloride in alkaline solution proceed like those of imidazoles, the strict parallel in the two cases in products and reaction conditions heavily favor that belief. It is certain that the diacylated diamine cannot arise from hydrolysis of the dihydroimidazole followed by acylation, because the cyclic compound, although readily hydrolyzed by hot water, is quite stable under the conditions of benzoylation. Furthermore the triacyl diamines, which are shown to be intermediates in the formation of diacyl diamines, could not arise by a simple Schotten-Baumann reaction with monoacylethylenediamine, but must arise from some more complex reaction of benzoyl chloride with the original cyclic compound.

The flow-sheet outlines the work carried out in this investigation.

EXPERIMENTAL

Hydrolysis of a 4,5-dihydroimidazole. A solution of 1.02 g. (0.01 mole) of 2-methyl-4,5-dihydroimidazole (I) in 10 cc. of distilled water is boiled for 10 minutes. One equivalent (2.29 g.) of picric acid in 50% ethanol is added to the resulting solution, and after thorough chilling the quantitative amount (3.9 g.) of pure monoacetylethylenediamine picrate (IV) removed by filtration. That the boiled solution of 2-methyl-4,5-dihydroimidazole contains only monoacetylethylenediamine (II) is further shown by converting it into the theoretical amount of pure N-acetyl-N′-benzoylethylenediamine (III) and N-acetyl-N′-benzenesulfonylethylenediamine (V), using one equivalent of benzoyl chloride and benzene sulfonyl chloride, respectively.

The hydrolysis of an equivalent amount (1.46 g.) of 2-phenyl-4,5-dihydroimidazole (I′) is much slower, being complete only after boiling for one hour in 50% ethanol. The monobenzoylethylenediamine (II′) in solution is identified by converting it quantitatively into its picrate (IV′). (Shorter periods of hydrolysis lead to the formation of a mixture of picrates of monobenzoylethylenediamine and 2-phenyl-4,5-dihydroimidazole). The solution of monobenzoylethylenediamine was also identified by converting it into the quantitative amount of dibenzoylethylenediamine (III′) with one equivalent of benzoyl chloride.

Treatment of a 4,5-dihydroimidazole with benzoyl chloride in carbonate solution. A flask containing 5.1 g. (0.05 mole) of 2-methyl-4,5-dihydroimidazole (I) dissolved in a few cc. of water is immersed in an ice-bath and 0.1 mole of saturated aqueous sodium carbonate solution (10.6 g. Na_2CO_3) and 0.1 mole (14 g.) of benzoyl chloride

alternately added with vigorous shaking during 15 minutes. The N-acetylbenzoyl-N′-benzoylethylenediamine (VI) is filtered, washed with water, and recrystallized from dilute ethanol; yield, 12.4 g. (80%). The results are identical when twice as much dihydroimidazole is used, indicating the impossibility of isolating the N-benzoyldihydroimidazole by this technique.

When carrying out this reaction with the water-insoluble 2-phenyl-4,5-dihydroimidazole, 7.3 g. (0.05 mole) is dissolved at 0° in 25 cc. of ethanol and treated with alternate portions of 21 g. (0.15 mole) of benzoyl chloride and 21 g. (0.15 mole) of potassium carbonate in concentrated aqueous solution. (The excess benzoyl chloride and carbonate are used because of the side reaction with the ethanol; with acetone as a solvent the calculated quantity of benzoyl chloride suffices, but the product is not so easily isolated.) The product is precipitated with excess water and becomes solid after standing in an ice-bath. The crude tribenzoylethylenediamine (VI′) is washed with water and ether (to remove ethyl benzoate) and recrystallized from dilute ethanol. The product thus obtained, (about 17 g., m.p. range about 100–115°) is fractionally recrystallized from dilute ethanol. The first crop melts at 122° and is of unknown constitution, the second melts at 104° and is pure tribenzoylethylenediamine (VI′). Several fractionations may be necessary to obtain the two pure products, which are produced in about equal amounts. Considerable work was done on the 122° compound, but no conclusive evidence for its constitution obtained.

Treatment of a triacyl diamine with aqueous caustic. One-hundredth mole (3.72 g.) of tribenzoylethylenediamine (VI′) is dissolved in a small amount of ethanol and treated at room temperature with 1 g. of potassium hydroxide in 50% ethanol. A precipitate begins to form in a few seconds and after 15 minutes the theoretical amount (2.68 g.) of pure dibenzoylethylenediamine (VIII′) is removed by filtration. The alcohol is evaporated from the filtrate, the aqueous residue acidified, and 1.2 g. (0.01 mole) of pure benzoic acid filtered off. Both products are identified by mixed melting point.

One-hundredth mole (3.1 g.) of N-acetylbenzoyl-N′-benzoylethylenediamine (VI) is dissolved at room temperature in 25 cc. of 60% ethanol and 1 g. of potassium hydroxide in 60% ethanol added. Precipitation begins immediately and is complete in 15 minutes. The solid product weighs 1.55 g. and is identified by mixed melting point as dibenzoylethylenediamine (VII). After evaporation to a small volume, the filtrate yields 0.84 g. of white solid, identified by mixed melting point as N-acetyl-N′-benzoylethylenediamine (VIII). The clear filtrate is acidified with sulfuric acid and 0.5 g. of benzoic acid filtered off. Finally the acidified filtrate is boiled and acetic acid detected in the vapor by its odor and action on litmus. These figures indicate that about 55% of this triacyl diamine becomes dibenzoylethylenediamine and 45% acetylbenzoylethylenediamine. The addition of the ethanol in these experiments is to dissolve the reactants, since the same results are obtained in pure aqueous solutions provided they are boiled or allowed to stand several hours.

Treatment of a 4,5-dihydroimidazole with benzenesulfonyl chloride in aqueous carbonate. An aqueous solution of 5.1 g. (0.05 mole) of 2-methyl-4,5-dihydroimidazole is treated at 0° with alternate portions of 17.7 g. (0.1 mole) of benzenesulfonyl chloride and 106 g. (0.1 mole) of 10% aqueous sodium carbonate. The reaction mixture is allowed to stand for 30 minutes after the addition is complete, and the N-acetylbenzenesulfonyl-N′-benzenesulfonylethylenediamine (IX) filtered, washed with water, and recrystallized from dilute ethanol; yield, 13 g. (70%). It is essential that the reaction does not get too warm or a mixture of IX and X will be formed.

A solution of 7.3 g. (0.05 mole) of 2-phenyl-4,5-dihydroimidazole in 40 cc. of ethanol is treated at room temperature with alternate portions of 26.5 g. (0.15 mole) of benzenesulfonyl chloride and 15.9 g. (0.15 mole) of sodium carbonate in saturated aqueous solution. Excess water is added, the N-benzoylbenzenesulfonyl-N′-benzenesulfonylethylenediamine (IX′) filtered, washed with water, and recrystallized from ethanol; yield, 15 g. (70%).

Treatment of a monoacyldisulfonyl diamine with aqueous caustic. One-hundredth mole (3.82 g.) of N-acetylbenzenesulfonyl-N′-benzenesulfonylethylenediamine (IX) is dissolved at room temperature in 25 cc. of 10% sodium hydroxide. After 15 minutes the clear solution is acidified with sulfuric acid and the theoretical amount of dibenzenesulfonylethylenediamine (X) is removed by filtration, washed with water, recrystallized from ethanol, and identified by mixed melting point. The filtrate is then made alkaline, evaporated to a small volume, re-acidified with sulfuric acid, and the acetic acid distilled out and identified as the isobenzylthiourea salt.

Similar results are obtained if N-benzoylbenzenesulfonyl-N′-benzenesulfonylethylenediamine (IX′) is substituted in the previous experiment, except that the quantitative amount of benzoic acid rather than acetic acid is liberated.

The action of carboxylic and sulfonic acid chlorides on 4,5-dihydroimidazoles in aqueous caustic. 4,5-Dihydroimidazoles react with acid chlorides in caustic media to yield the same products in the same yields as result from the stepwise treatment of the dihydroimidazoles in carbonate followed by caustic.

SUMMARY

2-Substituted 4,5-dihydroimidazoles readily undergo hydrolytic fission in hot water to yield monoacylethylenediamines.

Aromatic carboxylic and sulfonic acid chlorides react with 2-substituted 4,5-dihydroimidazoles in carbonate solution to yield triacyl diamines and monoacyldisulfonyl diamines respectively.

The triacid derivatives, which are new amides of ethylenediamine have been characterized by quantitative degradation to diamides of ethylenediamine.

Aromatic carboxylic and sulfonic acid chlorides react with 2-substituted 4,5-dihydroimidazoles in caustic solution to yield diamides of ethylenediamine.

SWARTHMORE, PA.

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[CONTRIBUTION NO. 33 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

THE ACTION OF FORMALDEHYDE ON *ortho*-CHLOROPHENOL AND 2,4-DICHLOROPHENOL

C. A. BUEHLER, ROBERT L. BROWN, JAMES M. HOLBERT, JOHN G. FULMER, AND GEORGE W. PARKER

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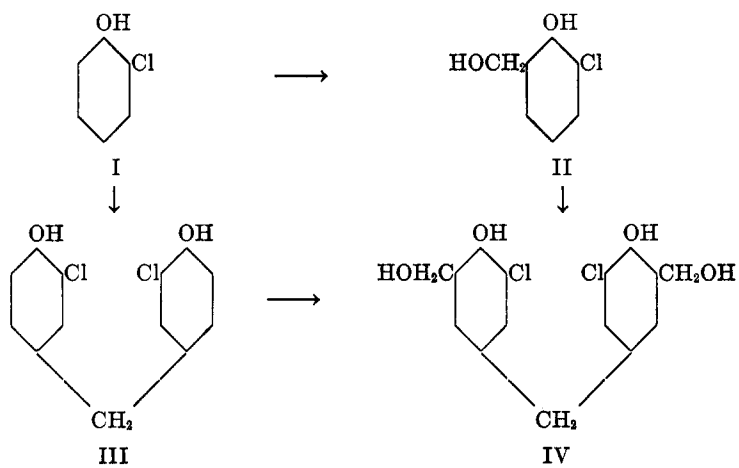
This investigation is one of a series on attempts to isolate and identify the simple condensation products obtained by treating substituted phenols with formaldehyde in acid media. In cases such as *p*-nitrophenol (1) and salicylic acid (2) it has already been shown that in hydrochloric acid the first-formed product, a hydroxybenzyl chloride, may be synthesized in good yield.

In the *o*-chlorophenol-formaldehyde condensation in hydrochloric acid medium, Stoermer and Behn (3) reported an unidentified chlorohydroxybenzyl chloride, m.p. 93°, while a German patent (4) indicated the formation of a benzyl chloride, m.p. 112°. Later another German patent (5) claimed that the higher-melting benzyl chloride was 5-chloro-(or 3-chloro-) 4-hydroxybenzyl chloride. The one other literature reference dealing with *o*-chlorophenol is that of Zinke, Hanus, and Ziegler (6). These investigators, produced the compounds shown below, II and III being obtained directly from the phenol:



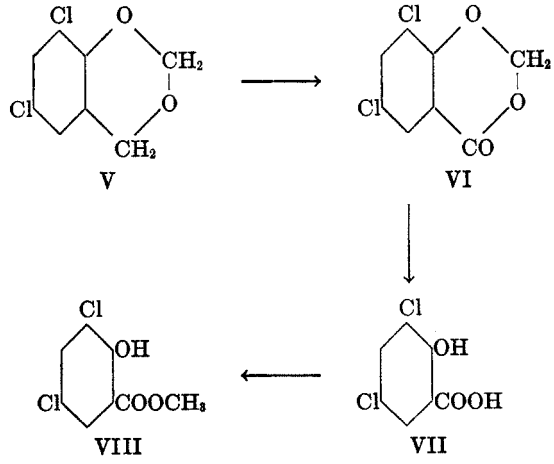
Apparently since I and II are known and IV may be obtained *via* II or III, they concluded that III was 3,3′-dichloro-4,4′-dihydroxydiphenylmethane.

Although the isolation of crystalline products was difficult from the *o*-chlorophenol reaction, two compounds, 3-chloro-4-hydroxybenzyl chloride and 3,3′-dichloro-4,4′-dihydroxydiphenylmethane were obtained. It was extremely difficult to convert the former into known derivatives. Melting at 92–93° in disagreement with the German patent (5) claim, it was shown to have the structure assigned by the identity of its alcohol with that obtained in the reduction of 3-chloro-4-hydroxybenzaldehyde. New evidence in support of the structure of 3,3′-dichloro-4,4′-dihydroxydiphenylmethane was acquired in two ways:

(a) Chlorination gave a tetrachloro derivative whose melting point and analysis agreed with that of 3,3′,5,5′-tetrachloro-4,4′-dihydroxydiphenylmethane.

(b) It was synthesized by the condensation of 3-chloro-4-hydroxybenzyl alcohol and *o*-chlorophenol.

The reaction of 2,4-dichlorophenol was much more favorable to the formation of crystalline products, in all probability because of the limited number of positions available for substitution in the benzene nucleus (7). Although what was regarded as 2,2′-dihydroxy-3,3′,5,5′-tetrachlorodiphenylmethane (8) is the only condensation product of this phenol referred to in the literature, our products in hydrochloric acid medium were 6,8-dichloro-1,3-benzodioxane, V, and 2-hydroxy-3,5-dichlorobenzyl chloride. The structure of this dioxane was established by the method of Borsche and Berkhout (9) by which it was converted through 6,8-dichloro-1,3-benzodioxan-4-one, VI, into the known compounds, 2-hydroxy-3,5-dichlorobenzoic acid, VII, and its methyl ester, VIII:



That the other product was 2-hydroxy-3,5-dichlorobenzyl chloride was shown by its conversion into an alcohol which agreed in melting point with the known 2-hydroxy-3,5-dichlorobenzyl alcohol, and which formed a dioxane with benzaldehyde (10).

EXPERIMENTAL

Products from o-Chlorophenol and Derivatives

1. *3-Chloro-4-hydroxybenzyl chloride.* A mixture of 6 g. of Eastman's C.P. *o*-chlorophenol, 40 cc. of 40% U.S.P. formaldehyde, and 500 cc. of concentrated hydrochloric acid was stirred at room temperature for 10 minutes while hydrogen chloride was bubbled rapidly through the mixture. The temperature was then raised to 45–50° in about 10 minutes and held at that point for 45 minutes. The reaction mixture was filtered rapidly through glass wool to prevent partial solidification and the heavy oil in the filtrate was separated from the aqueous portion. A second filtration was necessary to remove the last traces of oil from the aqueous portion. This oil was then mixed with 400 cc. more of concentrated hydrochloric acid and 30 cc. more of formaldehyde, and the mixture was stirred with hydrogen chloride passing through exactly as before, except that the final stirring at 45–50° was continued for only 30 minutes. In this way a second aqueous portion was obtained. The combined aqueous portions were allowed to stand overnight and the crystals which formed were washed several times with ice-water and dried in the open air. They weighed 2 g. and melted at 91–93°. Further purification by crystallization was exceedingly difficult due to the ease of resin formation. Our best product, m.p. 92–93°, [Stoermer and Behn's (3) unidentified chloride, 93°] was obtained by dissolving the crystals in petroleum ether (b.p. 35–60°), allowing the solution to evaporate at room temperature, and separating mechanically the last crystals which formed.

Anal. Calc'd for $C_7H_6Cl_2O$: Cl, 40.06. Found: Cl, 39.86.

The *alcohol* was obtained by heating, with frequent shaking, 0.5 g. of the chloride and a solution containing a crystal of silver nitrate in 50 cc. of water at 70° for 30 minutes. Upon extracting the cooled filtrate with ether and then allowing the solvent to evaporate, a clear oil was recovered. This product, which soon crystallized, was dissolved in 0.5 cc. of hot alcohol from which solvent it was thrown out by the addition of benzene. The dried, white needles, m.p. 122–123° [Stoermer and Behn's (3) unidentified alcohol, 123°] weighed about 0.05 g.

2. *Synthesis of 3-chloro-4-hydroxybenzyl alcohol.* Through a solution of Eastman's C.P. *p*-hydroxybenzaldehyde, 1.5 g., in 100 cc. of U.S.P. chloroform in an ice-bath, dry chlorine was bubbled at the rate of two to three bubbles per second for about 15 minutes. The evaporation of the chloroform with a stream of air and crystallization of the residue from water gave 1.6 g. 3-chloro-4-hydroxybenzaldehyde, m.p. 132–134°. [Biltz (11) gives 139° for a vacuum-distilled product]. The aldehyde, 1 g., in solution in C.P. ethyl acetate with 1 g. of Raney nickel catalyst was treated with hydrogen at 40 lbs. pressure for about 45 minutes. After filtration and evaporation to dryness in a stream of air, the residue, upon crystallization from benzene, gave 0.6 g. of 3-chloro-4-hydroxybenzyl alcohol, m.p. 127°.

Anal. Calc'd for $C_7H_7ClO_2$: Cl, 22.36. Found: Cl, 22.31, 22.32.

A mixed melting point with the alcohol obtained from 3-chloro-4-hydroxybenzyl chloride showed no appreciable depression.

3. *3,3'-Dichloro-4,4'-dihydroxydiphenylmethane.* To 53 g. of Eastman's C.P. *o*-chlorophenol was added 15 cc. of 40% U.S.P. formaldehyde and 325 g. of 60% sul-

furic acid and the mixture was stirred for 16 hours at 60–65°. Upon pouring into 1 liter of water, the mass solidified, after which the solid was separated and steam distilled to remove any unreacted *o*-chlorophenol. The oil remaining was vacuum distilled in an all-glass apparatus with ground joints, the fraction coming over at 230–240° (25 mm.) being collected. One crystallization from ligroin gave 18 g., m.p. 99–101°. A purer product, m.p. 103–104°, [Zinke, Hanus, and Ziegler (6) give 103°] was obtained by crystallization from water, although this solvent is unsatisfactory due to the limited solubility of the compound in it.

Anal. Calc'd for $C_{13}H_{10}Cl_2O_2$: Cl, 26.36. Found: Cl, 26.50, 26.62.

(a) *3,3',5,5'-Tetrachloro-4,4'-dihydroxydiphenylmethane.* Through a solution of 0.5 g. of the dichlorodihydroxydiphenylmethane in 20 cc. of glacial acetic acid at room temperature, dry chlorine was bubbled for 10 minutes. The needles, 0.45 g., which separated were filtered off and after being washed with water and crystallized from dilute alcohol, gave light brown leaflets, m.p. 184–185°; [Zincke and Birschel (12) give 185–186°].

Anal. Calc'd for $C_{13}H_8Cl_4O_2$: Cl, 41.97. Found: Cl, 41.75.

(b) The dichloro compound, 0.5 g., and acetyl chloride gave 0.45 g. of a *diacetyl derivative*, white needles, m.p. 126.5–127.5°.

Anal. Calc'd for $C_{17}H_{14}Cl_2O_4$: Cl, 20.08. Found: Cl, 20.12, 20.18.

(c) The dichloro compound, 0.5 g., and benzoyl chloride gave 0.45 g. of a *dibenzoyl derivative*, white crystals, m.p. 116–116.5°.

Anal. Calc'd for $C_{27}H_{18}Cl_2O_4$: Cl, 14.86. Found: Cl, 15.07, 15.10.

4. *Synthesis of 3,3'-dichloro-4,4'-dihydroxydiphenylmethane.* This synthesis was accomplished by von Koebner's method (13) as follows: 3-chloro-4-hydroxybenzyl alcohol, 9 g., as synthesized above, was dissolved in 45 g. of *o*-chlorophenol by warming and 1.2 cc. of hydrochloric acid was added. The mixture was set aside for 2 days, at which time it was distilled in the all-glass apparatus, the fraction coming over at 235–240° (25 mm.) being collected. Upon solidification, the distillate was crystallized from water to give 3 g. of a product, m.p. 103–104°. A mixed melting point with 3,3'-dichloro-4,4'-dihydroxydiphenylmethane, m.p. 104–105°, showed no appreciable depression. Chlorination as described previously gave the tetrachloro derivative, m.p. 185.5–187°.

Products from 2,4-Dichlorophenol and Derivatives

1. *6,8-Dichloro-1,3-benzodioxane.* A mixture of 10 g. of Eastman's C.P. 2,4-dichlorophenol, 80 cc. of U.S.P. 40% formaldehyde, 450 cc. of concentrated hydrochloric acid, and 10 cc. of concentrated sulfuric acid was agitated at 35–40° for 2 hours while a rapid stream of hydrogen chloride was bubbled through the solution. Although a solid formed after about 1.75 hours, the reaction mixture was allowed to stand overnight to complete the separation. After filtration and washing with water to remove the acid present, the solid was steam distilled. The white solid, 6.8 g., which came over, was crystallized from methanol, m.p. 109–109.5°.

Anal. Calc'd for $C_8H_6Cl_2O_2$: Cl, 34.59; mol. wt., 205.0.
Found: Cl, 34.86; mol. wt. (crysoscopic, benzene), 194.

(a) *6,8-Dichloro-1,3-benzodioxan-4-one.* The dioxane, 13.5 g., was oxidized by the method of Borsche and Berkhout (9). The crude benzodioxanone, washed with water until free from color, was crystallized from ethanol to give 8 g. of a white compound, m.p. 114°.

Anal. Calc'd for $C_8H_4Cl_2O_3$: Cl, 32.38; mol. wt., 219.0.
Found: Cl, 32.44; mol. wt. (crysoscopic, benzene), 210.

(b) *3,5-Dichlorosalicylic acid.* The dioxanone, 8 g., was boiled in dilute sodium

hydroxide solution and then acidified as recommended by Borsche and Berkhout. The crude product when crystallized from water gave a white solid, 4 g., m.p. 220° [Zincke (14) gives 219°].

(c) For verification the *methyl ester* was prepared by refluxing with methyl alcohol while dry hydrogen chloride was passed through the mixture. Two crystallizations from ethanol gave crystals, 2 g., m.p. 148–149° [Lassar-Cohn and Schultze (15) give 150°].

2. *3,5-Dichloro-2-hydroxybenzyl chloride.* A mixture of 10 g. of crushed Eastman's C.P. 2,4-dichlorophenol and 450 cc. of concentrated hydrochloric acid was stirred at near 50° until the phenol dissolved. Formaldehyde, 10 cc. of U.S.P. 40%, was added dropwise over a period of 20 to 30 minutes and then hydrogen chloride was bubbled rapidly through the stirred solution at 50° for 36 hours. By this time a white solid had formed and the flask was placed in the refrigerator for 12 hours. Filtering through empty Gooch crucibles followed by washing with cold water and drying gave 12 g. of a product, m.p. 81–84°. Crystallization from petroleum ether (b.p. 60–75°) produced long, white needles, m.p. 82–84°.

Anal. Calc'd for $C_7H_5Cl_3O$: Cl, 50.30. Found: Cl, 50.36, 50.36.

(a) *3,5-Dichloro-2-hydroxybenzyl alcohol.* This alcohol was always present in the liquor remaining from the steam distillation of 6,8-dichloro-1,3-benzodioxane. It was best prepared from 3,5-dichloro-2-hydroxybenzyl chloride as follows: Two grams of the chloride in 350 cc. of water was stirred at 50° for 4.5 hours, by which time only a trace of a yellow resinous substance remained undissolved. The clear solution was evaporated down to 100 cc. and, upon chilling, yielded 1.2 g. of white needles, m.p. 80–81°; [Mettler (16) gives 82°].

Anal. Calc'd for $C_7H_6Cl_2O_2$: Cl, 36.74. Found: Cl, 36.58, 36.51.

(b) *6,8-Dichloro-2-phenyl-1,3-benzodioxane.* This dioxane was prepared by the method of Adams (8). A mixture of 9 g. of the alcohol and 0.6 g. of freshly purified benzaldehyde was warmed over a steam-bath for two hours. Cooling gave a dark solid, which when crystallized from ethanol produced 0.7 g. of white, fluffy needles, m.p. 83.5–85.0°. This dioxane gives no color with ferric chloride while the original alcohol produces a deep purple.

Anal. Calc'd for $C_{14}H_{10}Cl_2O_2$: Cl, 25.22. Found: 25.30, 25.40.

SUMMARY

On condensing *o*-chlorophenol with formaldehyde in hydrochloric acid medium, moderate yields of 3-chloro-4-hydroxybenzyl chloride and 3,3′-dichloro-4,4′-dihydroxydiphenylmethane were obtained; under somewhat similar conditions 2,4-dichlorophenol gave good yields of 6,8-dichloro-1,3-benzodioxane and 3,5-dichloro-2-hydroxybenzyl chloride.

KNOXVILLE, TENN.

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[CONTRIBUTION FROM THE GEORGE S. COX MEDICAL RESEARCH INSTITUTE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. VI. NEW METHOD OF PREPARING 6(α)-ACETOXYPROGESTERONE[1]

MAXIMILIAN EHRENSTEIN AND THELMA O. STEVENS

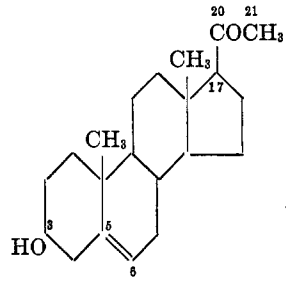
Received October 2, 1941

In an earlier publication (1) a procedure was described for the preparation of certain steroids which are substituted at carbon atom 6 by an acetoxyl group. The arrangement in ring A of these compounds was the same as in the most active hormones of the androstane and pregnane series. Hence carbon atom 3 existed as carbonyl carbon and there was a double bond between carbon atoms 4 and 5. The examples given were the preparation of 6(α)-acetoxyandrostenedione and of 6(α)-acetoxydesoxycorticosterone. It was pointed out that 6(α)-acetoxyprogesterone (VI) previously obtained by Ehrenstein and Stevens (2) according to another procedure should also be accessible by means of the new scheme. The present investigation demonstrates that this is actually the case and that the new method is preferable to the old one.

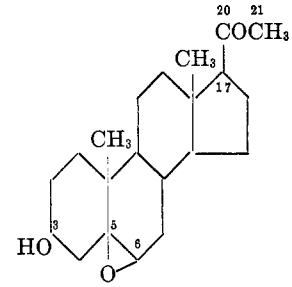
Starting material for this sequence of reactions was 5-pregnene-20-one-3(β)-ol (I). Treatment of this substance with perbenzoic acid yielded mainly (65%) the (5,6)(α)-oxide (II) as was shown by the subsequent reactions. It was pointed out in the earlier paper (1) that (5,6)(α)-oxides furnish with glacial acetic acid 6-acetoxy compounds, whereas (5,6)(β)-oxides yield 5-acetoxy compounds. When pregnane-(5,6)(α)-oxide-20-one-3(β)-ol (II) was treated with glacial acetic acid under proper experimental conditions, only a small quantity of the by-product, pregnane-20-one-3(β),5,6(*trans*)-triol 3,6-diacetate (IV), resulted. The main product (61.3%) of the reaction was pregnane-20-one-3(β),5,6(*trans*)-triol 6-monoacetate (III). Acetylation of this compound with acetic anhydride yielded the above mentioned 3,6-diacetate (IV).

We had previously prepared (2) the 6-monoacetate (III) by partial hydrolysis of the 3,6-diacetate (IV). For the 6-monoacetate (III) the melting point 222–226° was observed. The melting point of the same compound obtained by acetolysis of the (5,6)(α)-oxide (II), however, was

[1] Aided by a grant from the Smith, Kline, and French Laboratories in Philadelphia. Read before the Division of Organic Chemistry at the St. Louis meeting of the American Chemical Society, April 8, 1941.



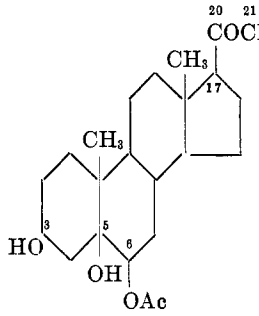
Perbenzoic Acid



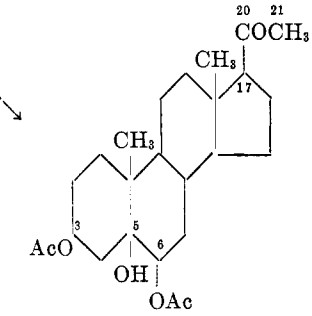
I. 5-Pregnene-20-one-3(β)-ol

II. Pregnane-(5,6)(α)-oxide-20-one-3(β)-ol

glacial CH_3COOH



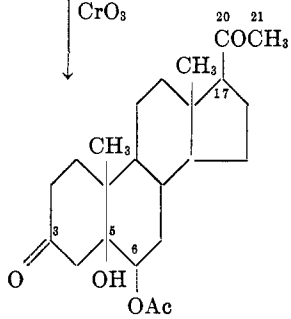
Ac_2O ⟶ ⟵ Partial Saponification



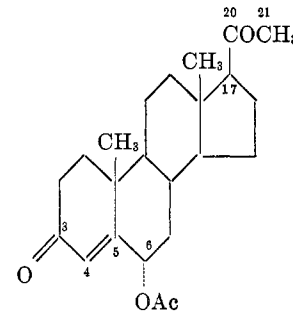
III. Pregnane-20-one-3(β),5,6(*trans*)-triol 6-monoacetate

IV. Pregnane-20-one-3(β),5,6(*irans*)-triol 3,6-diacetate

CrO_3



HCl ⟶



V. Pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate

VI. 4-Pregnene-3,20-dione-6(α)-ol acetate. [6(α)-Acetoxyprogesterone]

247–248.5°. That the substance obtained by the old procedure was not pure was indicated by the fact, mentioned in the previous paper (2), that by oxidation of this material with chromic acid not only pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate (V), but also a certain quantity of pregnane-3,6,20-trione-5-ol was formed. As was pointed out, the latter compound can only have originated from pregnane-20-one-3(β),5,6(*trans*)-triol formed by complete saponification of pregnane-20-one-3(β),5,6(*trans*)-triol 3,6-diacetate (IV). This discrepancy of the melting points induced us to repeat the hydrolysis of the 3,6-diacetate (IV) by means of one mole of potassium hydroxide. The experimental conditions were the same as previously described (2). This time a special effort was made to subject the crude saponification product to a thorough fractionation. Thus it was possible to isolate the 6-monoacetate (III) of the same melting point (246–249°) as obtained by acetolysis of the (5,6)(α)-oxide (II); also the optical rotations were in fairly good agreement. The yield of this pure 6-monoacetate (III) as obtained by partial hydrolysis of the 3,6-diacetate (IV) was only about 42%; a fairly large quantity (34.8%) of the 3,5,6-triol was isolated at the same time. It may be assumed that the remaining mother liquors contain some unchanged 3,6-diacetate. The presence of this second impurity would explain why the analysis of the impure 6-monoacetate happened to give the correct figures. It is obvious that the purification of the 6-monoacetate (III) as obtained by partial hydrolysis of the 3,6-diacetate (IV) is a complicated procedure, and that therefore the preparation of the 6-monoacetate by acetolysis of the (5,6)(α)-oxide (II) is a preferable process.

When the pure pregnane-20-one-3(β),5,6(*trans*)-triol 6-monoacetate (III) was subjected to oxidation with chromic acid, pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate (V) resulted. It was identical in every respect (melting point, optical rotation) with the previously described compound (2). The yield (about 74%) was, however, considerably greater due to the greater purity of the starting material (III).

An unusual observation was made when pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate (V) was subjected to dehydration by dry hydrogen chloride in a solution of chloroform. This reaction had formerly (2) yielded 6(α)-acetoxyprogesterone (VI) in a crystalline form after the crude reaction product had been subjected to chromatographic adsorption. This time we were unable to obtain the 6(α)-acetoxyprogesterone crystalline, although every effort was made to do so. For the details we refer to the experimental part of this publication. It is noteworthy that the melting point of the previously reported compound had changed markedly during the course of a year. It proved to be of no avail when it was used for seeding. There is every evidence that the amorphous modification of

the 6(α)-acetoxyprogesterone as obtained this time is chemically pure. Certain analytical figures are even in better agreement with the theoretical values than those obtained previously with the crystalline form. Also the absorption curve[2] of the purest amorphous modification (maximum at about 233 mμ; molecular extinction coefficient: 16000) is in better agreement with those of analogous compounds (1) than with that of the crystalline modification (2).

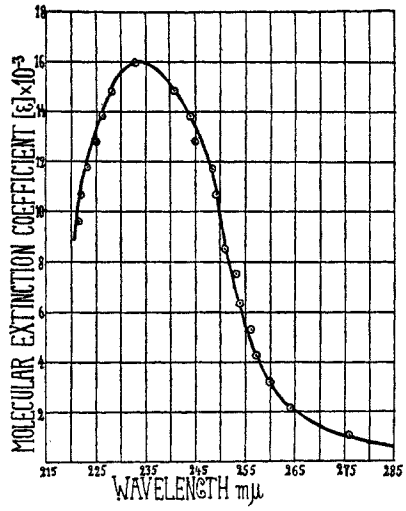


FIG. 1. ABSORPTION CURVE OF AMORPHOUS 6(α)-ACETOXYPROGESTERONE (IN ABSOLUTE ALCOHOL)[2]

As was mentioned in a previous communication (3), hydrolysis of both a (5,6)(α)-oxide and a (5,6)(β)-oxide yielded an identical 5,6-diol. The mother liquors of the above discussed pregnane-(5,6)(α)-oxide-20-one-3(β)-ol (II) obviously contained a mixture of more (5,6)(α)-oxide (II) as well as of (5,6)(β)-oxide. Hydrolysis of this mixture gave a yield of about 75% of a pure compound which was identified as pregnane-20-one-3(β),5,6(*trans*)-triol (4).

When pregnane-(5,6)(α)-oxide-20-one-3(β)-ol (II) was acetylated the corresponding acetate resulted. This substance proved to be identical with the pregnane-(5,6)-oxide-20-one-3(β)-ol acetate which Ehrenstein and Decker (3) had obtained by oxidizing pregnenonol acetate with potassium permanganate in a solution of acetic acid.

[2] We are indebted to Professor George R. Harrison of the Department of Physics of the Massachusetts Institute of Technology for the determination of the ultraviolet absorption spectra.

It should be mentioned here that we had originally planned to oxidize the secondary alcohol group of pregnane-(5,6)(α)-oxide-20-one-3(β)-ol (II). We had hoped to obtain by such treatment pregnane-(5,6)(α)-oxide-3,20-dione. Such a compound might have represented an alternate intermediate in the synthesis of 6-hydroxyprogesterone. When pregnane-(5,6)(α)-oxide-20-one-3(β)-ol (II) was treated in a solution of acetic acid with the equivalent of about one atom of oxygen of either chromic acid or potassium permanganate, a mixture of compounds resulted. From this mixture we were able to isolate in each case the known pregnane-3,6,20-trione-5-ol (4). The mother liquors appeared to consist at least partly of starting material. These observations are in agreement with findings of Ruzicka and Bosshard (5), who treated α-cholesterol oxide with chromic acid (equiv. of 1.5 atoms of oxygen) under mild conditions. Instead of the expected cholestane-(5,6)(α)-oxide-3-one they obtained a yield of 31% of cholestane-3,6-dione-5-ol.

Ehrenstein and Decker (3) found that the treatment of 5,6-unsaturated steroids with an excess of potassium permanganate in a solution of acetic acid yields a mixture of the stereoisomeric 5,6-oxides, a 5-ol-6-one, and possibly also a 5,6-diol. In these reactions the hydroxyl group at carbon 3 was protected by acetylation. Since the findings of Ruzicka and Bosshard (5) and our own have shown that a 3-ol-(5,6)-oxide can be further oxidized to yield a 5-ol-3,6-dione, it can be assumed that the 5,6-oxides are the primary reaction products in the oxidation of 5,6-unsaturated steroids with potassium permanganate in a solution of acetic acid. Since this primary product can be isolated in relatively large amounts from the reaction mixture, provided the hydroxyl group at carbon atom 3 is protected by acetylation, it must be concluded that such an oxide is relatively stable towards the action of potassium permanganate. On the other hand, our failure to obtain any 3-one-(5,6)-oxide by treating the 3-ol-(5,6)-oxide with permanganate seems to indicate that the reactivity of a 5,6-oxide towards permanganate is greatly enhanced if the acetoxyl group at carbon atom 3 is replaced by a carbonyl group.

EXPERIMENTAL

All melting points were determined with the Fisher-Johns melting point apparatus of the Fisher Scientific Company (Pittsburgh, Pa). The readings are sufficiently near the true melting points so that no corrections have been made. All microanalyses were carried out by Mr. William Saschek, Columbia University, New York. The pregnenonol was kindly furnished by Dr. Erwin Schwenk of the Schering Corporation in Bloomfield, N. J.

Pregnane-(5,6) (α)-oxide-20-one-3(β)-ol (II). To a solution of 1000 mg. of pregnenonol in 20 cc. of chloroform was added in the cold-room 9.05 cc. of a chloroform solution containing about 20% excess of perbenzoic acid (524 mg.). This mixture was allowed to stand in the cold-room for 26 hours and thereafter at room tempera-

ture for 22 hours. It was then washed with *N* sodium carbonate solution and with water. After drying the chloroform solution with sodium sulfate, it was evaporated to dryness; the residue was a white crystalline cake, weighing 1071 mg. This material was subjected to purification by chromatographic adsorption, for which it was dissolved in a mixture of 85 cc. of benzene and 175 cc. of petroleum ether. This solution was filtered through a suitably prepared column of 52 g. of aluminum oxide (aluminum oxide anhydrous, standardized for chromatographic adsorption according to Brockmann, E. Merck, Darmstadt). The adsorbed material was eluted by the following solvent combinations: 1, six fractions containing benzene and decreasing amounts of petroleum ether; 2, two fractions consisting of benzene only; 3, four fractions containing benzene and increasing amounts of ether; 4, one fraction consisting of ether only; 5, one fraction containing equal parts of ether and chloroform; 6, one fraction consisting of chloroform only; 7, one fraction containing five parts of chloroform and one part of methanol. The major part of the material was recovered from the fractions containing mixtures of benzene and ether. Appreciable amounts could also be secured from all those fractions which contained chloroform. All these fractions had to be recrystallized many times from various solvents or combinations of solvents. Suitable solvents for this purpose are acetone or mixtures of acetone and either methanol or ether. Finally identical material was secured from all chromatographic fractions except the last one. The melting points were between 180° and 184°. A certain opacity of the molten substance disappeared at about 187°. The total yield of constant-melting material was 510 mg; $[\alpha]_D^{24}$ + 1.0° (20.0 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{21}H_{32}O_3$: C, 75.85; H, 9.71.
Found: C, 75.62, 75.60, 75.61: H, 9.47, 9.43, 9.48.

When the experiment was repeated, no preliminary chromatographic separation was carried out. The crude reaction product was subjected to numerous recrystallizations. The average of the yields of pure α-oxide obtained by several experiments was 65%. The combined mother liquors were utilized for the preparation of pregnane-20-one-3(β),5,6(*trans*)-triol.

Pregnane-20-one-3(β),5,6(trans)-*triol.* The starting material for this experiment was a mixture of the (5,6) (α)-oxide and the (5,6) (β)-oxide of pregnenonol contained in the mother liquors of the preceding experiment. A solution of 2.29 g. of such material in 400 cc. of acetone was diluted by the addition of 115 cc. of water, and then 22.5 cc. of 10% sulfuric acid was added. This mixture was allowed to stand at room temperature for about three days. Then 200 cc. of water was added and the acetone distilled off *in vacuo*. This caused a white precipitate (dry wt. 1.48 g.) to appear. After filtering, the aqueous phase was extracted three times with ethyl acetate and hot chloroform, respectively. After drying with sodium sulfate the ethyl acetate solution was concentrated to a small volume which caused 0.58 g. of crystalline material to separate. The chloroform extract gave only traces of a crystalline residue. Many recrystallizations from acetone only, or from acetone to which a trace of chloroform was added, gave a 75% yield of fairly pure (m.p. above 247°) triol, the major part of which had the melting point 250–253°. There was no depression of the melting point when this latter material was mixed with an authentic sample of pregnane-20-one-3(β), 5,6(*trans*)-triol (4).

Pregnane-(5,6) (α)-*oxide-20-one-3(β)-ol acetate.* A solution of 150 mg. of pregnane-(5,6) (α)-oxide-20-one-3(β)-ol (II) in 3.0 cc. of acetic anhydride was refluxed (metal-bath) for a period of one hour. After cooling to room temperature, water was added and the mixture allowed to stand overnight. The white crystalline precipitate was

separated by filtration (dry weight: 155.0 mg.) and then recrystallized from a mixture of acetone and ether. A single recrystallization sufficed for the recovery of a fair yield of long fine needles with the constant melting point 167–168°. There was no depression of the melting point when this substance was mixed with a sample of the pregnane-(5,6)-oxide-20-one-3(β)-ol acetate described by Ehrenstein and Decker (3).

Acetolysis of pregnane-(5,6) (α)-oxide-20-one-3(β)-ol (II); preparation of pregnane-20-one-3(β),5,6(trans)*-triol 6-monoacetate (III) and of pregnane-20-one-3(β),5,6* (trans)*-triol 3,6-diacetate (IV).* A solution of 1.30 g. of pregnane-(5,6) (α)-oxide-20-one-3(β)-ol (II) in 35 cc. of glacial acetic acid was refluxed (metal-bath, temperature about 120°) for a period of 45 minutes. Immediately thereafter it was poured into water, which caused a white precipitate to appear. After standing in the cold-room for two days the precipitate was separated by filtration (crop 1). The filtrate was neutralized by the addition of solid sodium carbonate, which caused another precipitate to appear (crop 2). After filtration, the filtrate was thoroughly extracted with ether and with chloroform. Both extracts were washed with water, dried over sodium sulfate, and then evaporated to dryness (crops 3 and 4). Summary of yields: crop 1: 1247 mg.; crop 2: 189 mg.; crop 3: 162 mg. Total: 1598 mg. Crop 4 was only a trace of greasy material. In the further separation we were aided by the observation (1) that the 3,6-diacetates of 3(β),5,6(*trans*)-triols are readily soluble in ether whereas the 6-monoacetates are very difficultly soluble. The three crops were separately boiled for a time with ample quantities of ether (about 12 cc. per 100 mg.). After filtering, the ether solutions were gradually concentrated to a smaller volume. The evaporation was interrupted several times and the precipitated material separated by filtration. By this treatment several fractions were obtained which melted at 236–240°. The total of these fractions was 856 mg. Repeated recrystallizations from acetone gave pure pregnane-20-one-3(β),5,6(*trans*)-triol 6-monoacetate (III) of m.p. 247–248.5°; $[\alpha]_D^{23}$ + 8.0° (20 mg. in 2.0 cc. of acetone)

Anal. Calc'd for $C_{23}H_{36}O_5$: C, 70.36; H, 9.25.
Found: C, 70.31, 70.02; H, 8.86, 9.42.

All fractions with melting points lower than about 220° were combined and subjected to chromatographic adsorption. The combined material (620 mg.) was dissolved in 100 cc. of benzene; this solution was filtered through a column of 18 g. of aluminum oxide.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, MG.	APPEARANCE OF RESIDUE
1	100 cc. benzene (original solution)	27.8	Colorless resin
2	100 cc. benzene	165.1	Crystalline
3	60 cc. benzene + 40 cc. ether	168.4	Crystalline
4	40 cc. benzene + 60 cc. ether	8.9	Colorless resin
5	200 cc. ether	13.0	Greasy, yellowish mass
6	75 cc. ether + 25 cc. chloroform	2.8	Colorless resin
7	50 cc. ether + 50 cc. chloroform	4.3	Colorless resin
8	25 cc. ether + 75 cc. chloroform	5.8	Colorless resin
9	150 cc. chloroform	29.4	Colorless resin
10	95 cc. chloroform + 5 cc. methanol	203.3	Largely crystalline
Total		628.8	

The residues of fractions 9 and 10 were washed with ether. From both fractions resulted crystals melting between 225° and 235°. The combined material (146.0 mg.) was boiled with an ample amount of ether and filtered after standing at room temperature (dry weight: 122 mg.). When this crude product was recrystallized from acetone, three crops of crystals melting between 237° and 240°, and totalling 85 mg. were obtained. This material proved to be fairly pure pregnane-20-one-3(β),5,6(*trans*)-triol 6-monoacetate. With the above mentioned 856 mg. the total yield of this compound was 941.4 mg. (61.3% yield).

The residues of fractions 2 and 3 were separately dissolved in a sufficient amount of ether and then concentrated to a smaller volume. From both fractions stout glistening crystals of m.p. 217–219° were obtained; total yield: 183 mg. Somewhat lower-melting material was contained in the mother liquors. There was no depression of the melting point when the crystalline crops of m.p. 217–219° were mixed with an authentic sample of pregnane-20-one-3(β),5,6(*trans*)-triol 3,6-diacetate (IV).

Anal. Calc'd for $C_{25}H_{38}O_6$: C, 69.08; H, 8.82.
Found: C, 69.08; H, 8.59.

Pregnane-20-one-3(β),5,6(trans)-*triol 3,6-diacetate (IV), by acetylating pregnane-20-one-3(β),5,6*(trans)-*triol 6-monoacetate (III) as obtained by acetolysis of pregnane-(5,6) (α)-oxide-20-one-3(β)-ol (II).* A solution of 6 mg. of monoacetate (III) (m.p. 246.5–249°) in 0.2 cc. of acetic anhydride was refluxed for 1.5 hours. After the addition of some water the reaction mixture was allowed to stand. The crystalline precipitate was filtered and dried; wt. 5.3 mg. It was recrystallized from ether and gave crystals of m.p. 216–217.5°.

Anal. Calc'd for $C_{25}H_{38}O_6$: C, 69.08: H, 8.82.
Found: C, 69.11; H, 8.62.

Pregnane-20-one-3(β),5,6(trans)-*triol 6-monoacetate (III) by partial hydrolysis of pregnane-20-one-3(β),5,6*(trans)-*triol 3,6-diacetate (IV).* To a solution of 1.787 g. of pregnane-20-one-3(β),5,6(*trans*)-triol 3,6-diacetate (IV) in 125 cc. of absolute alcohol was added, over a period of two days, in 25 equal fractions, a total of 41.23 cc. of 0.1 *N* solution of potassium hydroxide in absolute alcohol (calc'd for 1 mole KOH: 41.10 cc.). The solution was allowed to stand at room temperature for two more days, and was eventually made neutral to litmus with dilute acetic acid. It was brought to a small volume *in vacuo*, and water was added to the warm concentrate. This caused the separation of crystalline material which was filtered, washed with water, and dried (crop 1; wt. 1.006 g.). The filtrate was concentrated to a small volume *in vacuo*, giving another precipitate (crop 2; dry wt. 0.475 g.). The second crop was recrystallized repeatedly from acetone. A number of fractions, totalling 181.2 mg., resulted, with melting points between 250° and 260°. By mixture melting points this material was identified as pregnane-20-one-3(β),5,6(*trans*)-triol. By proper treatment with ether, the first crop was separated into fractions which were difficultly soluble in ether and into fractions which were readily soluble. The difficultly soluble material was further purified by repeated recrystallizations from acetone; this treatment furnished a number of fractions, totalling 350.4 mg., with melting points between 244° and 248°. This material was found to be identical (mixture melting points) with pregnane-20-one-3(β),5,6(*trans*)-triol 6-monoacetate (III) as obtained by acetolysis of the (5,6) (α)-oxide (II). By proper treatment of the acetone mother liquors, a total of 103.2 mg. of crystalline material was obtained which melted between 251° and 258°, and was identified as a further yield of the free 3,5,6-triol. This raised the former yield of this compound (181.2 mg.) to a total of 284.4 mg. All mother liquors resulting from the 350.4 mg. of pure 6-monoacetate (III) and from the 284.4 mg. of free triol were pooled (dry weight:

810 mg.) and then subjected to chromatographic adsorption. For this purpose the dry material was dissolved in a mixture of 50 cc. of benzene and 200 cc. of chloroform. Part of the material (59.1 mg.) was not soluble in this mixture; by its melting point it was identified as a further crop of the free 3,5,6-triol, increasing the preceding yield (284.4 mg.) of this compound to 343.5 mg. The benzene-chloroform solution, containing 750.9 mg. of dry material, was filtered through a column of 40.0 g. of aluminum oxide.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, MG.	APPEARANCE OF RESIDUE
1	50 cc. benzene + 200 cc. chloroform (original solution)	24.7	dark oil and crystals
2	25 cc. benzene + 100 cc. chloroform	39.5	crystalline
3	50 cc. chloroform + 75 cc. ether	11.5	glass
4	75 cc. chloroform + 25 cc. ether	0.2	—
5	100 cc. chloroform	1.2	dark oil
6	100 cc. chloroform	8.7	crystalline
7	100 cc. chloroform + 0.5 cc. acetone	57.1	crystalline
8	100 cc. chloroform + 1 cc. acetone	65.8	crystalline
9	95 cc. chloroform + 5 cc. acetone	51.8	crystalline
10	75 cc. chloroform + 25 cc. acetone	104.8	crystalline
11	100 cc. chloroform + 1 cc. methanol	61.5	crystalline
12	30 cc. chloroform + 1.5 cc. methanol	71.6	crystalline
13	75 cc. chloroform + 4 cc. methanol	52.0	crystalline
14	50 cc. methanol	129.9	crystalline
15	Thorough extraction of Al_2O_3 with chloroform at room temperature	27.1	crystalline
Total		707.4	

The crystalline residues were separately dissolved in acetone and these solutions were concentrated to a small volume. From fractions 13, 14, and 15 was obtained a total of 158.3 mg. of material which was identified as pregnane-20-one-3 (β),5,6(*trans*)-triol. This brought the total yield of this compound to 501.8 mg. (34.8%). The crystals obtained from fractions 6, 7, 8, 9, 10, and 11 melted between 244° and 248° and were identified as pregnane-20-one-3(β),5,6(*trans*)-triol 6-monoacetate (III). The combined filtrates of these fractions on concentrating furnished further crops of the pure 6-monoacetate. The total of this compound isolated from the chromatogram was 331.2 mg., raising the originally obtained yield (350.4 mg.) to 681.6 mg. This is 42.2% of the theoretical yield. The optical rotation of the 6-monoacetate was determined with a fraction of m.p. 246–249°, $[\alpha]_D^{22.5}$ + 11.8° (20.0 mg. in 2.0 cc. of acetone).

Pregnane-3,20-dione-5,6(trans)-*diol 6-monoacetate* (*V*) *by oxidation of pregnane-20-one-3*(β),*5,6*(trans)-*triol 6-monoacetate* (*III*) *as obtained by acetolysis of the* (*5,6*) (α)-*oxide* (*II*). To a solution of 196 mg. (0.5 millimole) of pregnane-20-one-3 (β),5,6 (*trans*)-triol 6-monoacetate (III) of m.p. 240–242° was added 11.5 cc. (0.575 milligram atoms O) of a solution of 333 mg. of chromium trioxide in 100 cc. of 90% acetic acid. This mixture was allowed to stand overnight at room temperature. After the addition of 10 cc. of alcohol it was brought almost to dryness. Water was added and the

white precipitate was taken up in an ample amount of ether. The ether phase was washed with *N* sodium carbonate and water, and was finally dried with sodium sulfate. After evaporation of the solvent, 192.8 mg. of a dry residue was obtained. By recrystallizing it from 95% alcohol, various crops, melting between 211° and 218° and totalling 143.6 mg. (73.6% yield) were obtained. The purest material crystallized from alcohol in prisms; m.p. 216.5–217.5°. Recrystallization from a mixture of acetone and ether gave either long white needles or very thick plates. It was observed that on standing with solvent for a sufficiently long time the needles frequently changed to thick plates. It appeared that the melting point of the plates (218–221°) was slightly higher than that of the needles (215–218°). There was no depression of the melting point when the pure substance was mixed with an authentic sample of pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate (2); $[\alpha]_D^{24}$ + 20.5° (20 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{23}H_{34}O_5$: C, 70.72; H, 8.78.

Found: C, 70.87, 70.71, 70.80; H, 8.82, 8.89, 8.89.

4-Pregnene-3,20-dione-6(α)-ol acetate [*6(α)-hydroxyprogesterone acetate, 6(α)-acetoxyprogesterone*] (*VI*). Eighty milligrams of pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate (V) was dissolved in 10 cc. of redistilled dry chloroform. A moderate stream of dry hydrogen chloride was passed through this solution for three hours, cooling with ice, temperature not above +2°. The solution was poured into ice-cold *N* sodium carbonate and shaken in a separatory funnel. The chloroform phase was washed twice with water and dried with sodium sulfate overnight. After the removal of the solvent a very slightly yellow resin was obtained, which failed to crystallize when it was treated with various solvents. It was subjected to chromatographic adsorption, for which it was dissolved in 5 cc. of benzene and 20 cc. of petroleum ether, this solution was filtered through a column of 3.0 g. of aluminum oxide.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, MG.
1	5 cc. benzene + 20 cc. petroleum ether (original solution)	0.3
2	2 cc. benzene + 8 cc. petroleum ether	0.2
3	3 cc. benzene + 7 cc. petroleum ether	1.8
4	4 cc. benzene + 6 cc. petroleum ether	9.3
5	6 cc. benzene + 4 cc. petroleum ether	17.3
6	7 cc. benzene + 3 cc. petroleum ether	13.5
7	8 cc. benzene + 2 cc. petroleum ether	9.6
8	10 cc. benzene	7.9
9	10 cc. benzene	4.2
10	8 cc. benzene + 2 cc. ether	5.1
11	5 cc. benzene + 5 cc. ether	2.0
12	3 cc. benzene + 7 cc. ether	0.2
13	30 cc. ether	1.0
14	9.5 cc. ether + 0.5 cc. methanol	3.2
Total		75.6

The residues of all fractions were resinous. They did not crystallize when they were treated with various solvents or combinations of solvents. The whole experiment was repeated three times under exactly the same conditions. The distribution of the

material over the chromatogram in each case was similar to the above scheme. It may be mentioned that also by rechromatographing the main fractions of the chromatogram no crystalline material was obtained. Microanalyses were made of the residues of fractions 5, 6, and 7 respectively of one of the repetitions of the experiment.

Anal. Calc'd for $C_{23}H_{32}O_4$: C, 74.14; H, 8.66.
Found: C, 73.72, 73.65, 73.61; H, 8.95, 8.64, 8.67.

Microanalysis of the residue of fraction 6 of the above experiment yielded the following figures: C, 74.43; H, 8.81.

The residue of fraction 5 of the above experiment was distilled in a high vacuum. The pressure was approximately 5×10^{-6} mm.; the temperature of the oven was gradually raised to 245°. The distillate was a brittle colorless glass. Microanalysis of this material gave: C, 74.34; H, 8.83.

The ultraviolet absorption spectra[2] of the high vacuum distillate of fraction 5 (Fig. 1) as well as that of fraction 6 of the above experiment were determined. They were practically identical.

Optical rotations were determined upon the residue of fraction 7 of another experiment (in absol. alcohol and in acetone) and on the combined residues of fractions 7 and 8 of the above experiment (in acetone), respectively. $[\alpha]_D^{22.5} + 106.7°$ (20 mg. in 2.0 cc of absol. alcohol); $[\alpha]_D^{22.5} + 104.0°$ (20 mg. in 2.0 cc. of acetone); $[\alpha]_D^{22.5} + 101.9°$ (17.5 mg. in 2.0 cc. of acetone).

Oxidation of pregnane-(5,6) (α)-oxide-20-one-3(β)-ol (II) by chromic acid; isolation of pregnane-3,6,20-trione-5-ol. To a solution of 66.4 mg. (0.2 millimole) of pregnane-(5,6) (α)-oxide-20-one-3(β)-ol (II) in 4.0 cc. of glacial acetic acid was added 2.2 cc. (0.22 milligram atoms O) of a solution of 666.7 mg. of chromium trioxide in 100 cc. of 90% acetic acid. This mixture was allowed to stand at room temperature for 3.5 hours. After the addition of some alcohol it was brought almost to dryness *in vacuo*. Water was added to the residue and the resulting white precipitate was filtered and dried; wt. 56.8 mg. Recrystallization from a mixture of chloroform and acetone furnished 15.4 mg. of material melting around 250°. Renewed recrystallization from 95% alcohol yielded 11.4 mg. of crystals melting at 262–264° with decomposition. There was no depression of the melting point when this substance was mixed with an authentic sample of pregnane-3,6,20-trione-5-ol (4). The melting point of the main fraction obtained from the mother liquor (about 27 mg.) was in the region of that of the starting material. There was no depression of the melting point when it was mixed with a sample of the starting material.

Oxidation of pregnane-(5,6) (α)-oxide-20-one-3(β)-ol (II) by potassium permanganate in acetic acid; isolation of pregnane-3,6,20-trione-5-ol. To a solution of 332.3 mg. (1 millimole) of pregnane-(5,6) (α)-oxide-20-one-3(β)-ol (II) in 44 cc. of glacial acetic acid was added at a temperature of 50°, over a period of thirty minutes, 5.67 cc. (1.7 milligram atoms O) of a solution of *N* potassium permanganate (31.5 g. $KMnO_4$ per liter). The reaction mixture was then kept at a temperature of 50° for thirty minutes more. It was cooled to room temperature, diluted with 350 cc. of water, and extracted four times with redistilled ether and once with chloroform. Both phases were freed from acid by washing them first with an excess of 2 *N* sodium carbonate solution and finally with water. After drying over sodium sulfate, both extracts were brought to dryness. Weight of the residue of the ether phase: 308 mg. The residue of the chloroform phase was negligible (5.5 mg.). When the ether residue was recrystallized from acetone, 20.4 mg. of crystals melting between 240° and 245° was obtained. Renewed crystallization from 95% alcohol raised the melting point

to 262–264° (decomp.). There was no depression of the melting point when this substance was mixed with an authentic sample of pregnane-3,6,20-trione-5-ol (4). It was attempted to purify the combined mother liquors by chromatographic adsorption. One fraction of the chromatogram (about 30 mg.) consisted almost entirely of unchanged starting material (mixture melting point). The other fractions apparently still represented mixtures. No further attempt at purification was undertaken.

SUMMARY

1. When pregnenonol (I) is treated with perbenzoic acid the main product is pregnane-(5,6)(α)-oxide-20-one-3(β)-ol (II). Proper treatment of the latter substance with glacial acetic acid furnishes a mixture of pregnane-20-one-3(β),5,6(*trans*)-triol 6-monoacetate (III) and pregnane-20-one-3(β),5,6(*trans*)-triol 3,6-diacetate (IV), in which the former prevails.

2. The previously described preparation of pregnane-20-one-3(β),5,6-(*trans*)-triol 6-monoacetate (III) (2) which consisted of partly saponifying pregnane-20-one-3(β),5,6(*trans*)-triol 3,6-diacetate (IV) was reinvestigated. The new method is preferable to the old one.

3. Transformation of pregnane-20-one-3(β),5,6(*trans*)-triol 6-monoacetate (III) into 6(α)-acetoxyprogesterone [4-pregnene-3,20-dione-6(α)-ol acetate] (VI) by way of pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate was carried out substantially according to the old procedure (2). In contrast with the earlier findings (2) the end-product (VI) did not crystallize. The purity of the amorphous material was established by adequate analytical data.

4. The pregnane-(5,6)-oxide-20-one-3(β)-ol acetate previously described by Ehrenstein and Decker (3) is an α-oxide and should henceforth be named pregnane-(5,6)(α)-oxide-20-one-3(β)-ol acetate.

5. The reaction mechanism of the oxidation of 5,6-unsaturated steroids with permanganate is discussed.

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