Systematic Organic Analysis

Detail of Methods for the Positive Identification of Unknown Organic Compounds[1]

By WILLET F. WHITMORE*

THE chemist is frequently called upon to identify an organic substance. Unless he has had some special training in the methods of organic analysis he is very likely confined to making a few simple chemical tests and basing his conclusions as to the nature of the compound largely on the physical constants of the substance. Even if the substance happens to be a pure compound, any conclusions based almost exclusively on such physical constants as boiling points, melting points, etc. are very likely to be seriously in error. That is to say physical constants without chemical proof will not permit the analyst to answer the question—What is the substance? The proof should be largely chemical.

Kamm, Mulliken and Clarke in this country, Rosenthaler and Staundiger abroad, have been instrumental in collecting data and developing a system of analysis for the identification of an unknown organic substance. While it is still extremely difficult if not impossible to identify the constituents of complex mixtures of organic compounds, it is no longer difficult to identify any single individual provided the compound has been previously prepared and its physical constants determined, and some data of a chemical nature is available. The important thing about an organic compound is its structure, i. e. the manner in which the constituent elements are linked together, hence the problem is not only ascertaining what elements are present in a compound, but determining precisely how these are joined together. If the analyst in his efforts was required to determine constitution by the conventional methods of procedure he would have a very difficult, time-consuming problem every time he started in such an effort. The whole theory and practice in qualitative organic analysis is predicated on the theorem: That a given unknown organic compound is assumed to be identical with a known compound when the two compounds agree absolutely in all of their physical and chemical properties. The basic idea in qualitative organic analysis is to determine to what homologous series a compound belongs and then since the physical constants of the members of an homologous series are different, these may be employed to determine approximately what the substance is. With this information the worker then can consult the literature and will find suggestions for chemical transformations to be applied to the substance, which will give solid derivatives, the physical constants of which will determine exactly the identity of the original substance.

Importance of Homology

THE method of systematic qualitative organic analysis would be impossible if it were not for that very important characteristic of homology. The most practical scheme in the mind of the author for systematic identification of an organic compound is that proposed by Kamm*, and the steps required for the identification of a substance are:

(a) Purification of the compound and determination of its most common physical constants; usually boiling point, melting point, density and occasionally refractive index.

(b) Qualitative analysis for the elements.

(c) Determination of solubility behavior for classification purposes.

(d) Application of class reactions to those types indicated by tests a, b, and c.

(e) Use of the literature on known classes of compounds.

(f) Preparation of derivatives and determination of the physical constants of these derivatives.

The new ideas that these steps present are the classifications scheme and the preparation of derivatives. Classification methods are fairly numerous, but one of the most useful is that making use of the solubility behaviour of the substances in water, in dilute mineral acid, i. e. (HCl), in dilute alkali (NaOH) and cold conc. H_2SO_4. Studies on solubility have brought out some interesting relationships

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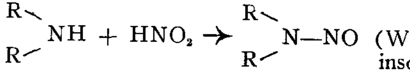
*Qualitative Organic Analysis—Kamm.

and the ideas so divulged have been utilized to classify organic substances. In organic analysis any substance which is alkali soluble is classified as being acidic but this does not necessarily imply that it gives appreciable H^+ ion concentrations in water solution. In the same way a substance which is acid soluble is characterized as being basic, and here again this does not mean that the substance gives appreciable quantities of OH^- ion in water solution. A substance insoluble in both acid and alkali is considered to be neutral. The application of these ideas and others to systematizing organic analysis can best be perceived by an examination of the table on solubility behavior. By means of this table we can classify a substance into one of the groups appearing in this table, and after it has been placed in a definite group then the next step is to determine to which homologous series within a group the compound belongs.

To illustrate these ideas suppose we were dealing with a substance that falls in the soluble category. This establishes the fact that it is a basic type and may be one of the varieties listed in group III. The next question is to ascertain whether it is a primary, secondary, or tertiary amine. This can be determined in several ways. We may use nitrous acid for the purpose, or benzene sulphonyl chloride. With primary amines water soluble diazonium salts are produced when the amine in cold HCl solution is treated with sodium nitrite solution. Secondary amines give under the same conditions water insoluble nitroso-compounds. Tertiary amines in most cases do not react at all with this reagent. Furthermore acid chlorides and anhydrides in general react with primary and secondary amines, but not with tertiary. The advantage of benzenesulphonyl chloride however, over most acid chlorides is that the compound which it forms with primary amines is soluble in alkalis whereas that produced with the secondary amine is insoluble in alkalis. With these two reagents the reactions are as follows: With nitrous acid

1.° R* $NH_2 + HNO_2 + HCl \rightarrow RN = N.\,Cl + 2H_2O$ Water soluble

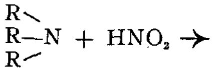
2.°



$$\genfrac{}{}{0pt}{}{R}{R}\!>NH + HNO_2 \rightarrow \genfrac{}{}{0pt}{}{R}{R}\!>N\text{—}NO$$

(Water insoluble)

3.°



$$\begin{matrix}R\diagdown\\ R\text{—}N\\ R\diagup\end{matrix} + HNO_2 \rightarrow$$

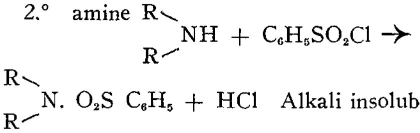
No reaction except with certain aromatic amines.

With benzenesulphonyl chloride:

1.° amine $R.\,NH_2 + Cl.\,O_2S.C_6H_5 \rightarrow$

$R.\,NH.\,O_2S.\,C_6H_5 + HCl$ Alkali soluble compound

2.° amine



$$\genfrac{}{}{0pt}{}{R}{R}\!>NH + C_6H_5SO_2Cl \rightarrow \genfrac{}{}{0pt}{}{R}{R}\!>N.\,O_2S\,C_6H_5 + HCl$$

Alkali insoluble compound

3.° amine No reaction with the reagent.

Suppose now according to the above we have determined that the compound is an amine. Having established the fact that we have— say a primary— amine we now proceed to an examination of the literature with the information that we have a primary amine with certain definite physical constants. Our search will usually reveal but two or at the most three compounds, which have constants checking or approaching those for the substance being examined, one of which must be the unknown substance.

In the case of an amine it might be suggested to make the acetyl or benzoyl derivative for a primary or secondary amine, and for the tertiary amines either a picrate or a quarternary ammonium salt. The solid derivative of the substance so prepared then is purified by recrystallization and its M.P. determined; if the M. P. corresponds to that given in the literature for the substance so prepared then it is absolutely safe to conclude that the original substance has been identified positively. If, for example, you had one of the three toluidines the constants for which are as follows:

	B.P.	M.P. of the acetyl derivative	M.P. of the Benzoyl derivative
ortho-toluidine	199°C	112°C	142°C
para- "	200°	148°	158°
meta- "	203°	65°	125°

positive identification could be obtained by making either the acetyl or benzoyl derivative, recrystallizing, and then determining the M. P. of this derivative. If there is any doubt as to the identity of a compound following this procedure, more than one derivative can be prepared, and also the method of mixed melting points used. In the latter case some substance of supposedly the same composition is added to the unknown and if the M. P. of the mixture remains constant this can be accepted as proof that the unknown material has the same constitution as the addenda.

Oxygenated Compounds

IN GENERAL the most important commonly occurring organic compounds that we meet with are the so called oxygenated types, which are neutral, i. e. insoluble in dil. HCl and in NaOH and of course insoluble in water when there are more than four carbon atoms present in the molecule. The most important compounds in this category are the alcohols, ethers, aldehydes, ketones and esters. It seems to be generally true that these types are soluble in

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*R is used to represent or symbolize an alkyl or aryl group, such as ethyl C_2H_5—, and phenyl C_6H_5— respectively.

cold concentrated sulphuric acid, and most of them can be recovered unchanged from such a solution by pouring the solution into ice water. We can therefore make use of cold concentrated sulphuric acid as a group reagent in assisting us to classify the indifferent compounds of carbon, hydrogen and oxygen; and hence after treatment with dilute acid and dilute alkali we employ this reagent as indicated in the solubility table. In following then the sequence of solubility tests suggested by the table if the unknown substance is soluble in cold conc. sulphuric it may be any one of the types listed in Group V, or it may be a mixed type, i. e. it may possess two or more of the characteristic atomic groupings of this group.

Since the compounds of group V are perhaps of greatest interest to the average chemist, the method of procedure will be indicated for this group. Assume that the solubility behavior indicates an unknown compound in Group V. To determine the homologous series to which the compound belongs in this group, proceed according to the following scheme:

Add to the compound a little phenylhydrazine.

<table>
<tr><td rowspan="3">Positive Reaction indicates aldehydes or ketones or some mixed type containing the C=O group.</td><td colspan="3">NEGATIVE TEST
Esters (anhydrides), alcohols, ethers, unsaturated HC. Apply the saponification test, i.e. Saponify with 25% aqueous KOH.</td></tr>
<tr><td>Positive Reaction Esters and Anhydrides</td><td colspan="2">Negative Reaction. Alcohols, ethers, unsaturated hydrocarboys. Apply the acyl halide test (R. CO. Cl).</td></tr>
<tr><td></td><td>Positive Reaction. Alcohols and other types containing —OH groups.</td><td>Negative Reaction. Ethers and unsaturated hydrocarbons. Add Bromine in CCl_4. Decolorization indicates unsaturated hydrocarbon.</td></tr>
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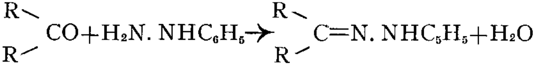
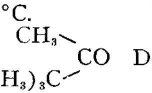
Having succeeded by following the above scheme in ascertaining the family to which the unknown substance belongs we next have to locate the member in a given homologous series. This is done in an approximate manner by determining carefully and accurately two or three physical constants (B. P.—M. P.—Density—Refractive Index). Since the members of an homologous series differ in physical properties, the estimation of the above physical constants enables us to approximate what the substance is. There may, for example, be two or three compounds (seldom more) listed in the literature of the homologous series that the determined constants would satisfy or correspond with. Then it becomes necessary to prepare a derivative to settle absolutely the identity of the substance.

To illustrate the procedure in the case of some of the types in this group, suppose that an unknown substance gives a positive reaction with phenyl hydrazine, i. e. it forms a phenyl hydrazone;

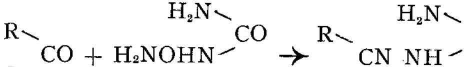


$$\begin{array}{llll} R\diagdown & & R\diagdown & \\ & CO + H_2N.NHC_6H_5 \rightarrow & & C{=}N.NHC_5H_5 + H_2O \\ R\diagup & & R\diagup & \end{array}$$

and that the tests for aldehyde are negative, i. e. no color with decolorized fuchsine, no reduction of Fehling's solution, and no reduction of ammoniacal silver nitrate solution. This shows the substance is a ketone. Two of the physical constants for the substance are B. P. 104°C. and density 0.830 at 0°C. Seeking information from the literature[*] on the subject we find that there are two ketones whose constants are very close to those determined for the substance being examined:

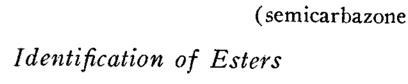
1. Diethyl ketone $(C_2H_5)_2CO$ Density 0°C. 0.834 and B.P. 102°C.
It gives an oxime with M.P. 165°C and a semicarbazone M.P. 139°C.
2. Pinacolone  $\begin{array}{ll} CH_3\diagdown & \\ & CO \\ (CH_3)_3C\diagup & \end{array}$ Density at 10°C. .826 and B.P. 105°C.
Gives an oxime with M.P. 74°C and a semicarbazone M.P. 157°C.

Since no other ketones have physical constants similar to the compounds being analyzed, the substance, in this case, must be one of these two compounds. Hence to settle the question we prepare either the oxime or the semicarbazone of the substance or both, purify and recrystallize and then determine the melting points of the derivatives. The physical constants on the derivatives will determine definitely the identity of the original substance. The reactions for the preparation of the oxime and semicarbazone of diethyl-ketone are:



$$\begin{array}{llll} R\diagdown & & R\diagdown & \\ & CO + H_2NOH \rightarrow & & CNOH\ (oxime) \\ R\diagup & & R\diagup & \end{array}$$

Where R = C_2H_5



$$\begin{array}{llllll} & & H_2N\diagdown & & & H_2N\diagdown \\ R\diagdown & & \quad CO & & R\diagdown & \quad CO \\ & CO + H_2NOHN\diagup & & \rightarrow & \quad CN\ NH\diagup & \\ R\diagup & & & & R\diagup & \end{array}$$

(semicarbazone)

Identification of Esters

SINCE the major constituents of vegetable and animal fats and oils are esters of the trihydric alcohol glycerine, and inasmuch as various esters are being prepared synthetically and used extensively in lacquers, etc. a brief treatment of the procedure in the case of an ester is desirable. In general esters, may produce alcohols and acids which are soluble or insoluble in water and these in turn may be

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[*] Clark, "Handbook of Organic Analysis."
Mulliken, "The Identification of pure organic compounds."
Rosenthaler, "Der Nachweis Organischer Verbindungen."
The original literature may have to be consulted in some cases.

SOLUBILITY TABLE*

Soluble in Water—Groups I & II

I

Soluble in ether

1. Alcohols (low mol. wt.)
2. Aldehydes " "
3. Ketones
4. Acids
5. Other neutral oxygen compounds
6. A few anhydrides
7. A few esters, and amino-phenols
8. Amines (low mol. wt.)
9. Some neutral N comp'ds nitrites, oximes, amides, imides, carbamates

II

Insoluble in ether

1. Polybasic acids, hydroxy acids, etc.
2. Polyhydroxy alcohols, sugars, and certain derivatives
3. Some amides
4. Many sulphonic acids and sulphur compounds
5. Many salts

Insoluble in Water—Groups III, IV & V

Soluble in dilute HCl

III

1. Primary amines
2. Secondary amines
3. Tertiary amines
4. Hydrazine
5. Alkaloids

Soluble in dilute KOH

IV

1. Acids
2. Phenols
3. Some amides, imides, etc.
4. Sulphonamides
5. Primary and 2° nitro comp'ds of the aliphatic series
6. Thio phenols, and sulphonic acids
7. A few enols

Soluble in cold conc. H_2SO_4

Indifferent comp'ds of C, H, & C, H, O

V

1. Alcohols
2. Aldehydes
3. Ketones and quinones
4. Ethers and acetals
5. Esters and lactones
6. Anhydrides
7. Unsaturated hydrocarbons

Insoluble in Water

Insoluble in Water—Groups VI & VII

Insoluble in cold H_2SO_4

VI

Indifferent comp'ds of C, H, & C, H, O

1. Saturated aliphatic hydrocarbons
2. Aromatic hydrocarbons
3. Halogen derivatives of VI_1
4. Halogen derivatives of VI_2

Indifferent compounds containing N and S

VII

1. Nitro comp'ds (tertiary)
2. Amides and negatively substituted amines
3. Nitrites
4. Nitrites, nitrates, azo and hydrazo comp'ds, etc.
5. Sulphones, sulphonyl derivatives of secondary amines
6. Mercaptans, sulphides, sulphates, etc.
7. Miscellaneous

* Qualitative Organic Analysis—*Kamm*

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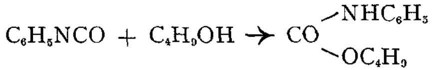
volatile or non-volatile without decomposition. The particular type which one encounters will determine the procedure for the separation of the alcoholic from the acid portion. In the ordinary scheme of procedure the esters are recognized in group V by the fact that they undergo saponification when heated with 20-25% aqueous KOH. Anhydrides also are transformed to the potassium salt of the acid, but in the former case an alcohol is always produced with the K salt of the acid whereas in the latter instance nothing except the potassium salt of the acid is formed. If then a substance has a solubility behavior which places it in Group V and undergoes saponification with 25% KOH, this is fairly conclusive evidence that it is an ester. To illustrate, assume that a compound exhibits this behavior, and that the elementary analysis shows the absence of N, S, and halogens, i. e. an ester of a carboxylic acid. A determination of the physical constants of this substance shows it to have a B.P. of 146°C and a density of .892 at 15°C. Examination of a table of data on esters shows that these constants fit or correspond with the following esters:

	B.P.	Density at 15°C.
ethyl n-valerate	145°	.894
n-butyl propionate	146°	.895
iso-butyl iso-butyrate	147°	.880

To settle the question of identify saponify a sample of the unknown and then distil off the alcohol. This is collected, its physical constants determined and derivatives prepared. If the alcohol so obtained is water-soluble it may be salted out from its aqueous solution by adding K_2CO_3. It is separated from the water layer, dried further if necessary and its physical constants then determined. The physical constants would in many cases be sufficient for the identification of the alcohol, but to make the evidence complete and to provide the chemical proof which is justly required, we make at least one derivative. For alcohols several substances may be prepared such as:

(a) The phenyl urethanes, which are made by heating equal volumes of phenyl isocyanate and the alcohol according to the following reaction: (taking butyl alcohol as an illustration)



$$C_6H_5NCO + C_4H_9OH \rightarrow CO\begin{matrix}\nearrow NHC_6H_5\\ \searrow OC_4H_9\end{matrix}$$

Phenyl urethanes of Butyl alcohol.

(b) The alpha-napthyl urethanes, where alpha-naphthyl isocyanate is employed.

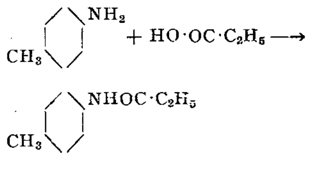
(c) The benzoates, which are usually prepared by the action of benzoyl chloride on the hydroxy type according to the following:

$C_6H_5CO\ Cl + C_4H_9OH \rightarrow C_6H_5CO.\ OC_4H_9$

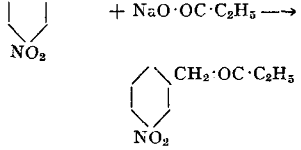
(d) The 1,3,5 dinitro—benzoates which are normally prepared by the action of the acid chloride of 1,3,5 dinitrobenzoic acid on the alcohol in accordance with the equation:

Suppose it was found that the alpha-napthyl urethane and the 1-3-5 dinitro benzoate of the alcohol isolated above had melting points which were respectively 71°C and 64°C. These values correspond to those for the corresponding derivatives of normal butyl alcohol which would seem to confirm the fact that the substance is n-butyl propionate, but in order to make certain of the acid part, we make a derivative of this substance also. Some of the common derivatives for acids and their method of formation are: (taking propionic acid as the example)

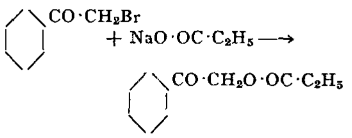
1. The Toluidides



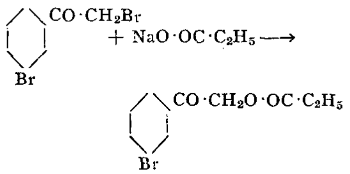
2. The Paranitrobenzyl esters



3. The Phenacyl esters



4. The Para-brom phenacyl esters



In the case of the acid in the above ester if its toluidide melted at 124°C. and its phenylacyl ester at 31°C. the proof for propionic acid would be absolutely complete.

To the uninitiated the suggestion of derivative formation may seem to involve a tremendous amount of work. As a matter of fact, with only a little practice, derivatives can be prepared fairly rapidly and constitute the only proof which is of real significance to the chemist; it is absolutely conclusive. It should be understood that similar methods of characterization such as were illustrated above are available for almost all of the other types listed in the general scheme. In conclusion, it should be pointed out that conclusions based only upon color reactions or colorimetric methods are very hazardous and the more the organic chemist sees of color reactions the less respect he has for them. At the most the evidence which they offer can only be taken as indicative or suggestive and should never be construed as final and complete without some other proof of the nature indicated above.

An investigation of the poisoning effect upon hydrogenation catalysts of various substances has shown that the unsaponifiable matter of cod liver oil causes a marked falling off in the catalyst's activity, while organic phosphorus has little effect. When sulfur in an organic compound is so placed in the molecule as to be in a position to react with the hydrogen, a marked poisoning effect will result. Nitrogeneous material such as isinglass apparently has an effect which is more physical than chemical upon the catalyst. *Chem Trade J.* 84,277-8, 302-3, 351-2, 369-70 (1929). *Chemical Abstracts,* 24,1530 (1930).

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By mixing the sulfonic acids of hydrogenated hydrocarbons having several benzene nuclei with oil in the absence of water and allowing them to stand until the product is soluble in water, preparations with the properties of Turkey red oil may be obtained. Ger. Pat. No. 486,840.