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SYNTHESES WITH HEMIMELLITIC ACID
AND RELATED COMPOUNDS

by

David Bruce Randolph Johnston

A Dissertation Submitted to the
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The Requirements for the Degree of
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Major Subject: Organic Chemistry

Approved:

In Charge of Major Work

Head of Major Department

Dean of Graduate College

Iowa State University
Of Science and Technology
Ames, Iowa

1961

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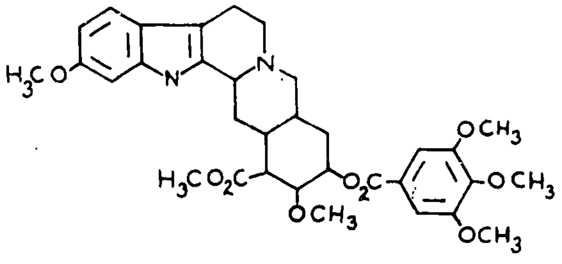
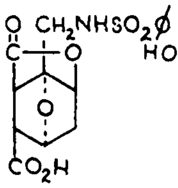
INTRODUCTION

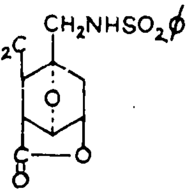
The synthesis of an appropriately substituted cyclohexane which might serve as a key intermediate in a proposed total synthesis of reserpine (I) has been undertaken in These Laboratories by Dr. L. H. Liu and has given encouraging results.* Before the problem can be satisfactorily completed, however, it is imperative to determine to which of two isomeric systems Dr. Liu's intermediates belong. Hence, the structure of one of these intermediates, a compound correctly represented by either IIa or IIb and convertible into a 1,2,3-trisubstituted benzene, is to be elucidated.



I

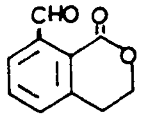


IIa

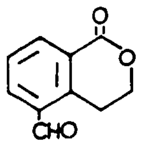


IIb

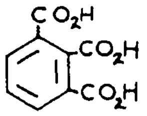
It has been suggested (1) that erythrocentaurin possesses either structure IIIa or IIIb, both of which are 1,2,3-trisubstituted benzenes.



IIIa



IIIb



IV

Since, in principle, systems II and III are both derivable from hemimellitic acid (IV), the chemistry of this acid and related compounds is to be investigated with a view toward synthesizing the Liu and erythrocentaurin systems.

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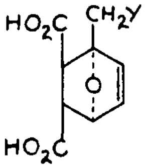
*Dr. L. H. Liu, c/o Professor E. Wenkert, Department of Chemistry, Iowa State University, Ames, Iowa. Postdoctoral investigation of alkaloid syntheses. Private communication. 1958.

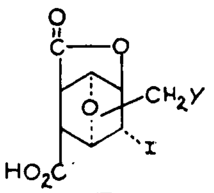
HISTORICAL

Unpublished Work by Dr. L. H. Liu*

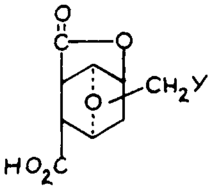
During the period of 1954-1956, work was carried out in These Laboratories by Dr. L. H. Liu aimed at the total synthesis of reserpine-type alkaloids (2). As stated in the introduction, the critical intermediate was an appropriately substituted cyclohexane which would ultimately form ring E of the alkaloid. The approach taken involved the Diels-Alder condensation of a suitably substituted furan with maleic acid (3). This would be expected to yield a racemic mixture of 7-oxabicyclo [2.2.1] heptenedicarboxylic acids, one enantiomer of which is illustrated (V), where Y represents a substituent which would ultimately serve as a handle with which to join the methylene group with a tryptamyl N_b.



V



VI



VII

When the reaction was carried out with Y=NHAc, the intermediate corresponding to V was not isolated. Instead, the reaction mixture was treated with sodium hypoiodite to afford an iodolactone acid. Such a reaction would be expected to afford a γ-lactone and indeed this was verified by the compound's infrared (I.R.) spectrum. However, two isomeric γ-iodolactones are possible, depending upon which carboxyl group undergoes cyclization.

Treatment of the iodolactone VI with hydrogen over palladium on char-

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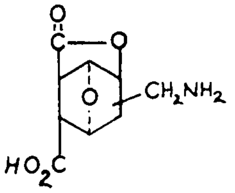
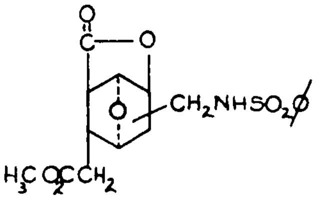
*Dr. L. H. Liu, c/o Professor E. Wenkert, Department of Chemistry, Iowa State University, Ames, Iowa. Postdoctoral investigation of alkaloid syntheses. Private communication. 1958.

col afforded the desiodolactone acid VII. Conversion to the methyl ester with diazomethane followed by equilibration with triethylamine brought about isomerization of the carbomethoxy group to the more stable exo orientation, thus proving epimerization had not taken place during the iodolactone formation.

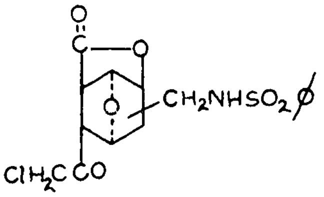
Attempts to homologate the acid were unsuccessful until Y was changed by hydrolysis to the amine VIII, followed by conversion to the sulfonamide IIa. Homologation by the Arndt-Eistert method (4) to the homomethyl ester IX proceeded smoothly.



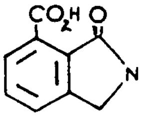
VIII



IX



X



XI

The profound effect of the substituent Y upon the homologation's course was the first suggestion that structure VII, with the free carboxyl close to the methylene group, was correct. In order to prove this, Liu set out to cyclize the carboxyl and methylene substituents.

Because of the possible strain involved, the failure in attempts to cyclize the amino acid VIII could not be invoked to disprove it's structure. Attempts to cyclize homologs of these compounds under irreversible conditions were then made. By treating the diazoketone intermediate in the Arndt-Eistert synthesis with excess HCl, the chloromethyl ketone X was obtained. Attempted cyclization of this compound in basic media, however, gave inconclusive results.

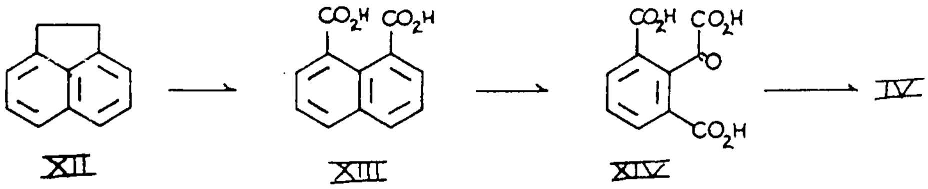
Other attempts to prove the structure by cyclization were equally fruitless. Repeated and varied attempts to hydrolyze, hydrogenolize and oxidize the sulfonamido group failed, usually affording unreacted starting material.

By treating the methyl ester of VII with potassium t-butoxide for a short period of time, the same epimerization observed with triethylamine could be effected. Prolonged treatment, followed by acidification, treatment with diazomethane and chromatography led to an oil which upon subsequent hydrolysis in acid afforded 7-carboxyphthalimidine (XI).

The Chemistry of Hemimellitic Acid

Hemimellitic acid (IV) was first obtained in small quantity and impure form by A. Baeyer (5) as a degradation product from mellitic acid. It was not until the discovery of a practical synthesis (6) that the acid became available in sufficient quantity to permit an investigation of its properties. This study was presented in a paper by Graebe and Leonhardt (7) which contains virtually all of the fundamental chemistry of this compound known until now.

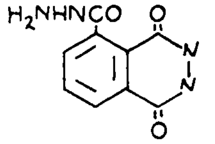
The classical synthesis of hemimellitic acid involves oxidation of acenaphthene (XII) to naphthalic acid (XIII) and subsequent oxidation of



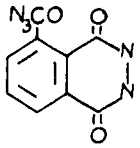
this intermediate, through 6-carboxyphthalonic acid (XIV), to the desired product. An additional laboratory synthesis has become available more recently (8).

The neutral silver, potassium, and barium salts have been prepared and characterized. Graebe also obtained a disilver salt, and calcium (9) as well as iron (10) salts have been reported. Of particular importance is the remarkable insolubility of the monopotassium salt which affords a convenient means of isolation and purification. The stability of this salt is so great, according to Graebe, that it is impossible to obtain pure acid by mere acidification; the salt must be converted to the less soluble barium salt and this in turn treated with sulfuric acid. A more recent paper (11), however, suggests that the elaborate procedure may not be entirely necessary.

Hemimellitic acid reacts with hydrazine (12) to form a phthalhydrazide hydrazide (XV) which can be converted to a phthalhydrazide azide (XVI) and this in turn made to undergo a Curtius rearrangement.



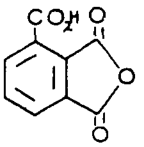
XV

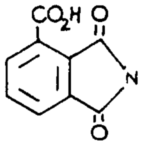


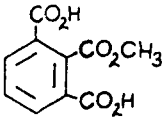
XVI

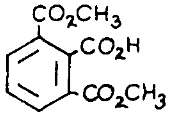
Upon heating, hemimellitic acid melts, losing a molecule of water, to form hemimellitic anhydride (XVII). The potassium salt of the anhydride may be prepared by heating monopotassium hemimellitate. Treatment of molten hemimellitic anhydride at 220° with gaseous ammonia affords the imide acid XVIII. The imide disilver salt has been made and characterized, as well as the calcium salt.

If hemimellitic acid is treated with methanolic HCl, a dimethyl ester is obtained. Hemimellitic anhydride dissolved in methanol affords a monomethyl ester, which will not dehydrate upon heating, and which, upon treatment with methanolic HCl, is converted to the trimethyl ester. Saponification of the trimethyl ester with two equivalents of base yields the original monoester. On the basis of these facts, Graebe proposed structures XIX and XX for the mono- and dimethyl esters, respectively.


XVII


XVIII


XIX


XX

Attempts to obtain the isomeric monomethyl ester through the monopotassium and monosilver salts and methyl iodide were unsuccessful.

Although only the diester XX was obtained by Graebe with methanolic HCl, later workers (13) found the triester was also formed, although in much smaller amounts. It is interesting that these workers found the potassium salt of XX much less soluble in water than the sodium salt.

The triester can be obtained directly by treating the anhydride with methanolic HCl, or the neutral silver salt with methyl iodide. More recently (14) diazomethane has been employed.

Reduction of the trimethyl ester with lithium aluminum hydride (15) affords the corresponding tri-alcohol which readily forms a triacetate.

Graebe also studied the Friedel-Crafts acylation of benzene with hemimellitic anhydride and the hemimellitic anhydride potassium salt, obtaining both isomers in which the anhydride had attacked one benzene molecule. He also obtained both isomers in which the anhydride, having acylated one benzene subsequently acylated a second. By condensation of the anhydride with resorcinol, two isomeric fluoresceins were obtained. Condensation with m-dimethylaminophenol afforded a rhodamine.

Treatment of hemimellitic acid with mercuric acetate leads to replacement of the central carboxyl group with mercury (16). This compound may subsequently afford either isophthalic acid or 2-halogenoisophthalic acids.

The dissociation constants (17), crystallographic data (9), and ultraviolet spectrum (18) of hemimellitic acid have been reported. The acid has been successfully separated from mixtures of acids by paper strip (19, 20) and partition (21) chromatography.

The Raman spectrum (22) and heat of vaporization (14) of the trimethyl ester have also been reported.

The Chemistry of Graebe's Acid

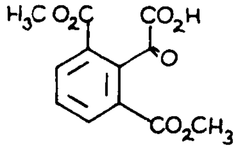
In the course of his investigation on the oxidation of acenaphthene (XII) Graebe (6) isolated 6-carboxyphthalonic acid (XIV). If the reaction mixture is further oxidized, hemimellitic acid (IV) is obtained (7), as already mentioned. In a later paper (23) Graebe and Bossel reported the results of their investigation on the chemistry of 6-carboxyphthalonic acid, which, for simplicity, we shall henceforth refer to as Graebe's acid or G-acid. As in the case of the hemimellitic acid paper (7), this work has remained until now the only comprehensive study of the chemistry of this compound.

Treatment of G-acid with red phosphorous and HI afforded a dicarboxylic acid, characterized by its neutral barium salt. The physical properties distinguished this diacid from its isomer, homophthalic acid, and thus established the presence of a methyl group. Since the methyl group would be expected to have arisen from the glyoxylic ketone, and the dicarboxylic acid could not be converted into an anhydride, the methyl group and hence the glyoxylic group was assigned a position between the two carboxyl groups. The correctness of this assignment is apparent from the distinctly different properties of Graebe's methyl diacid and the known (24) 3-methyl phthalic acid, which readily forms an anhydride.

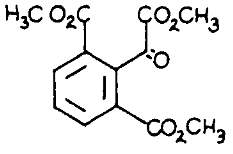
Condensation of G-acid with phenylhydrazine affords a compound which analyzes as a phenylhydrazone.

The neutral barium, calcium, potassium, and silver salts have been prepared and characterized.

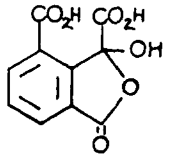
Upon treatment with methanolic HCl, G-acid afforded an acidic diester, while treatment of the neutral silver salt with methyl iodide affords a neutral triester, to which Graebe assigned structures XXI and XXII respectively. Later workers (25, 26) have been unable to obtain either of the esters, even when Graebe's original procedures have been employed. Instead, they obtain under all conditions, including esterification with diazomethane, the same trimethyl ester, melting 10-12 degrees lower than Graebe's compound. On the basis of a difference in the ultraviolet spectra of G-acid in neutral and in basic media, it has been suggested that in the former case, the compound exists in the lactol form XXIII and only in the latter case in the keto form. Similarity in the spectra of the triester and the acid in neutral media has led to the proposal that XXIV cor-



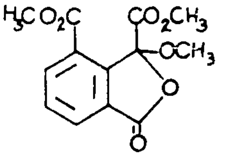
XXI



XXII



XXIII

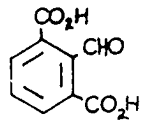


XXIV

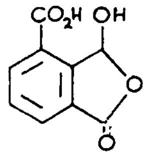
rectly represents the structure of the trimethyl compound obtained in the later work. It was further suggested that the keto-lactol equilibrium was responsible for the diversity of products.

Upon heating, G-acid melts and decomposes with the evolution of CO, CO_2 and H_2O. Three major products are isolable, one of which proves to be hemimellitic acid. The lower melting of the other two products forms a neutral monobarium salt and gives a positive Schiff's test. It also forms a compound with phenylhydrazine which affords a nitrogen analysis consistent with a phenylhydrazone. The pyrolysis product was accordingly assigned structure XXV, but later workers (26) on the basis of ultraviolet spectra, prefer the lactol structure XXVI for the compound.

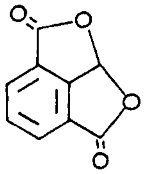
The higher melting pyrolysis product was virtually insoluble in all solvents except aqueous base, in which it formed a reddish solution and from which it could be recovered upon acidification. Since its analysis indicated a formula isomeric with the aldehyde XXVI, less the elements of water, and treatment with phenylhydrazine afforded the aldehyde phenylhydrazone, the compound was assigned the dilactone structure XXVII.



XXV



XXVI



XXVII

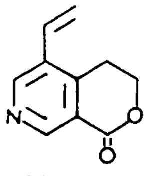
The recovery of XXVII rather than XXVI from basic solution upon acidification, coupled with quite different ultraviolet spectra for the two compounds, has led later workers (26) to reject structure XXVII.

Treatment of basic solutions of either XXVI or XXVII with Raney nickel alloy has afforded 2-methylisophthalic acid (27).

Erythrocentaurin

From Swertia japonicus, Makino, a bitter glycoside has been isolated (28) and named swertiamarin. Enzymic hydrolysis of this material affords a crystalline aglycone known as erythrocentaurin. In 1958, Kubota and Tomita (1) reported the results of their investigation on the constitution of this compound.

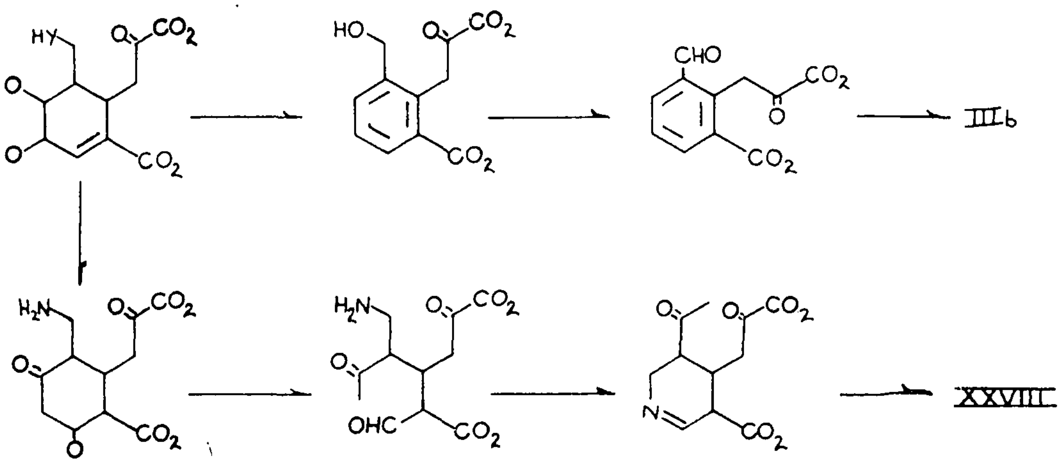
Erythrocentaurin analyzes as $C_{10}H_8O_3$ and exhibits an infrared spectrum with absorption at 5.82 and 5.91μ and an ultraviolet spectrum with λ_{max} 223 and 290mμ, logε 4.30 and 3.13 respectively. The compound gives a positive Tollens test, but is unaffected by Schiff's reagent, hypoiodite, nitromethane and a diazoaromatic compound. It consumes one equivalent of base upon warming in aqueous sodium hydroxide, but is recovered unchanged upon acidification. Condensation was effected with semicarbazide, dimedone and o-phenylenediamine, one mole of each reagent reacting with one mole of compound. Reduction of erythrocentaurin with lithium aluminum hydride affords a crystalline triol which is unaffected by hydriodic acid. Kuhn-Roth oxidation indicates the absence of C-methyl groups and permanganate oxidation affords hemimellitic acid. Oxidation with chromic acid affords a lactonecarboxylic acid. The data is in agreement with either of two structures, IIIa or IIIb. Since gentianine (XXVIII) (29) is also found in the same plant (30) the authors proposed, by analogy, structure



XXVIII

IIb as the correct one. Subsequently, Wenkert and Bringi (31), have arrived at the same structure through biogenetic arguments.

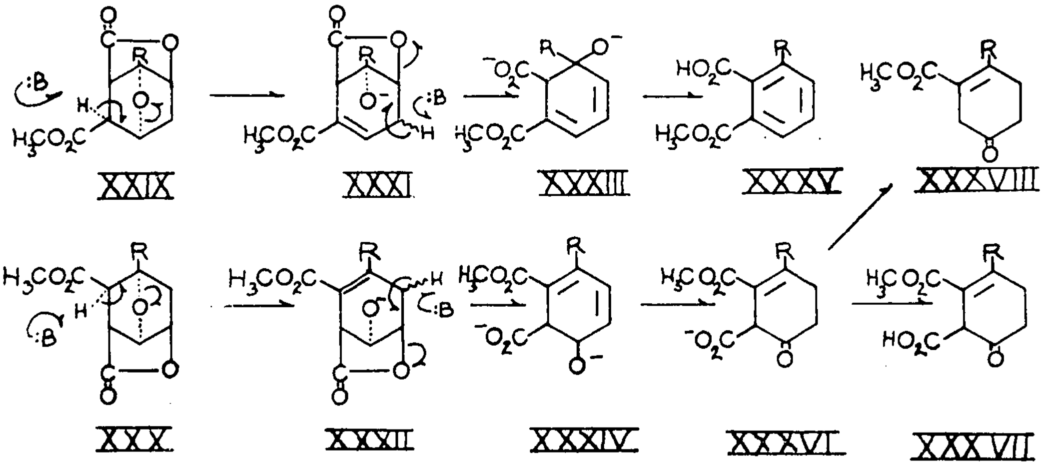
These authors suggest that erythrocentaurin and gentianine both arise from a common intermediate, a hydrated prephenate, through transformations indicated below.



DISCUSSION

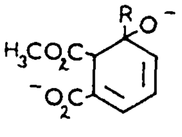
It seemed that Liu's observation of the convertibility of the acetamido lactone ester, XXIX or XXX, into an aromatic compound through base treatment could be taken advantage of in attempting its structure proof. An examination of the reaction mechanism was therefore undertaken to determine whether or not one structure would be favored over the other.

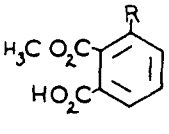
The first step, regardless of which structure is correct, must be the abstraction of a proton α to the ester followed by β-elimination of the ether oxygen to give either XXXI or XXXII ($R=CH_2NHAc$). Abstraction of the proton γ to the ester can now take place, followed by the vinylogous β-elimination of the lactone carboxylate to give XXXIII or XXXIV. Since XXXIII lacks an ε proton it cannot undergo further elimination, and would be stable. On the other hand, XXXIV is vinylogous to a γ-hydroxy-α,β unsaturated ketone, a system known (32) to undergo isomerization to a diketone in basic media, and it would seem likely that if present, XXXIV would isomerize rapidly to XXXVI. It could then either lose CO_2 to give XXXVIII, or remain unchanged until acidification and work-up to give XXXVII. In either case the product is not aromatic, and hence cannot correspond to

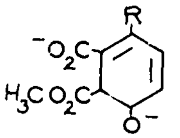


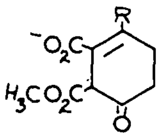
the observed compound.

Although XXXIII would not be able to aromatize to XXXV until after acidification, the possibility of internal ester exchange cannot be overlooked. Ester exchange of XXXIII would lead to XXXIX which, since it possesses a proton α to the ester, could lose that proton and eliminate the β-hydroxyl group to yield XL upon acidification. Since the crude aromatization product is esterified with diazomethane, both XXXV and XL would lead to the same compound and examination of the products could not distinguish mechanisms passing through XXXV or XL.


XXXIX

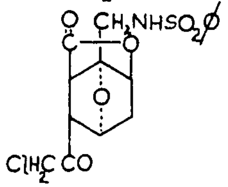

XL


XLI

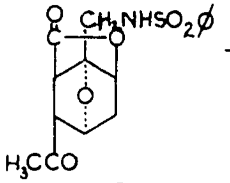

XLII

If transesterification is possible in XXXIII, it must be equally possible in XXXIV and XXXVI. Should XXXIV transesterify to form XLI, a proton is now α to the ester group and may be abstracted. Thus XLI, like XXXIX, may now aromatize in the basic media by β-elimination of the oxygen as hydroxyl. The rate of transesterification, however, would probably be much lower than the rate of isomerization to XXXVI. Although XXXVI could very well transesterify to XLII, β-keto esters do not eliminate the keto oxygen under basic conditions, and upon acidification the ester isomer of XXXVII would be obtained, a conclusion contrary to experimental results. Thus, in order that an aromatic compound result, transesterification of XXXIV to XLI must take place more rapidly than would be expected. Structure XXIX was accordingly considered the most likely representation of Liu's acetamido methylester lactone on the basis of this analysis. Nevertheless, the nature of R had been shown to influence reactions on the carboxyl carbon, an observation more readily explained on the basis of structure XXX, and since the possibility of ester interchange could not be ignored, transformation of the carboxyl to a different functional group was undertaken.

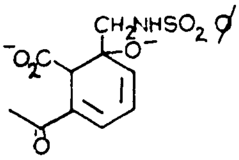
Liu's chloromethyl ketone, XLIII, was chosen as starting material in the hope of reducing it and aromatizing the resultant methyl ketone XLIV with base. From this compound, an intermediate, XLV, would be obtained corresponding to XXXIII in the ester series. Here, however, no interchange is possible, and aromatization must take place after acidification to lead to compound XLVI. Should the methyl ketone not possess structure XLIV, but rather structure XLVII, then an intermediate, XLVIII, corresponding to XXXIV would be expected. Once again, no interchange could occur, and XLVIII would isomerize to XLIX, giving on acidification non-aromatic products. Should XLVIII prove abnormally stable and aromatize upon acidification, or should the aromatization proceed by a different path, compound L, isomeric with XLVI and possibly existing in other tautomeric



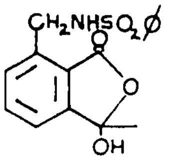
XLIII



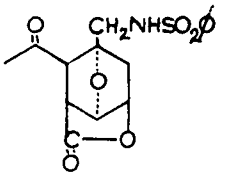
XLIV



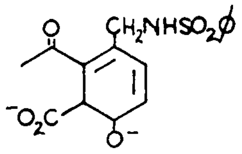
XLV



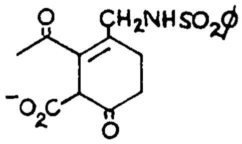
XLVI



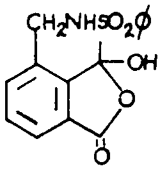
XLVII



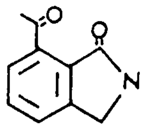
XLVIII



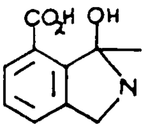
XLIX



L



LI



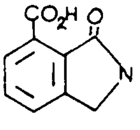
LII

forms, would result upon work-up. Subsequent removal of the sulfonyl group would afford either LI or LII (the latter might appear as one of several other tautomeric forms).

The chloromethyl ketone did indeed undergo reduction affording a crystalline compound exhibiting an infrared spectrum with peaks at 3.04μ (NH), 5.63μ (lactone carbonyl), and 5.77μ (ketone carbonyl) and analyzing correctly for the desired product, but attempts to aromatize the methyl ketone led only to oils. In an attempt to cyclize the adjacent side chains of the aromatic ketone the oils were subjected to refluxing aqueous HCl for 22 hours. Subsequent attempts to obtain a solid product by direct crystallization were unsuccessful. Unexpectedly, the untreated oil upon standing a few days, afforded a small quantity of crystalline material which exhibited an infrared spectrum with peaks at 3.02μ(OH), 3.12μ(NH), and 5.71μ (lactone carbonyl), and which analyzed correctly for either compound XLVI or L. A comparison of the ultraviolet spectrum of this compound with its precursor showed clearly the presence of a new chromophoric system, λ_{max} $284m\mu$ ($\log\epsilon$ 3.2), similar to the absorption of o-acetylbenzoic acid, λ_{max} $275m\mu$($\log\epsilon$ 3.0) (33).

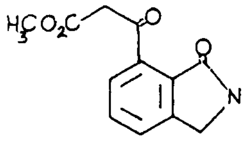
Removal of the sulfonyl group was now undertaken. Treatment of the compound with HBr and phenol (34) yielded only tarry products. Nitrosation with HNO_2 afforded a crude solid product which lacked an NH absorption at 3.0μ in its infrared spectrum and exhibited a new peak at 6.6μ. The latter peak is characteristic of the N-nitroso-N-sulfonamide system as illustrated by a comparison of the spectra of N-cyclohexylbenzenesulfonamide and its nitrosation product, as well as similar pairs of compounds prepared in These Laboratories. The peak also lies within the region quoted (35) for absorption by solutions of monomeric N-nitroso alkylamines. Upon hydrolysis, however, the N-nitroso-benzenesulfonamidomethylacetylbenzoic acid afforded only the original benzenesulfonamidomethylacetylbenzoic acid. Thus it appears that, although the N-nitroso compound does form, the competition between hydrolytic cleavage of the sulfonamido group and simple reversal of the nitrosation process favors the latter reaction. Because of diminishing supplies of the compound, and the inefficiency in converting the small stock of precursor, the degradative approach was abandoned and a synthesis of the degradation product through the key intermediate LI undertaken.

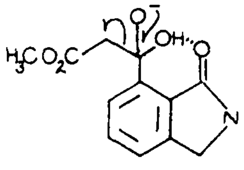
Liu had prepared 7-carboxyphthalimidine (LIII) through the aromatization of XXIX or XXX as already indicated, followed by acid hydrolysis. Enough of the acetamido ester lactone and its precursors had been left by Liu to permit the preparation of a moderate supply of LIII, and to carry out experiments on it designed to synthesize LI.

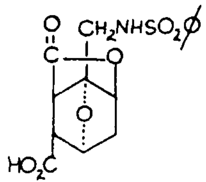


LIII

The first procedure employed was based on the procedure used to convert methyl nicotinate to 3-acetylpyridine (36). Conversion of LIII to its methyl ester with diazomethane proceded smoothly, to yield a crystalline compound with infrared absorption at 2.85μ (NH) and 5.8-5.9μ (ester and phthalimidine carbonyls). Treatment of the ester with solid sodium methoxide and ethyl acetate at 85° under nitrogen for 10 hours, followed by dilution with water and extraction with chloroform, afforded 18% of unreacted ester. Acidification of the aqueous phase and refluxing for several hours afforded only 7-carboxyphthalimidine. These results are best explained by assuming that the desired β-keto ester LIV had been formed and retained in the basic aqueous phase, but that the subsequent hydrolytic attack had occurred preferentially at the site of the ketonic carbonyl group rather than at the ester. This rapid *retro*-Claisen reaction may be attributed to internal solvation by the neighboring phthalimidine carbonyl group, thus lowering the energy of the transition state, LV.


LIV

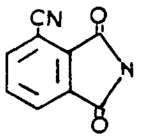

LV


LVI

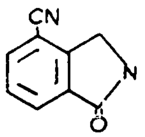
The second approach undertaken was patterned after the successful conversion of acid LVI to methyl ketone. Initially the transformation of LIII to its acid chloride was carried out in tetrahydrofuran with an equivalent of thionyl chloride in order to avoid possible interactions with the phthalimidine system. Prolonged refluxing was required, but a crystalline product was finally obtained which in contrast to LIII, was readily soluble in chloroform. The infrared spectrum of the chloroform solution exhibited a sharp peak at 5.6μ, consistent with an acid chloride, and broad absorption between 5.75 and 5.80μ presumably due to the phthalimidine carbonyl. Treatment of the material with diazomethane followed by exposure to gaseous HCl was expected to form the chloromethyl ketone. The crude product, however, still exhibited an absorption at 5.6μ in its infrared spectrum and hence was retreated with diazomethane and HCl. When the peak persisted, the workup was continued in the hope that the presumably inert acid chloride might undergo esterification. Attempts to obtain a pure product by direct crystallization were fruitless. Reduction of the crude material with zinc and acetic acid, followed by chromatography failed to afford any crystalline products. The infrared spectra of the chromatographic fractions were all similar, and all showed variable amounts of the 5.6μ absorption.

After refluxing for 12.5 hours, a thionyl chloride solution of phthalimidine itself was taken to dryness under reduced pressure, affording a quantitative recovery of starting material. Thus the lactam seemed sufficiently resistant to reaction to permit the formation of the acid chloride directly from LIII without side-reactions. The reaction proceeded smoothly, and after 2 hours afforded a crystalline chloroform-soluble product. Treatment of the solid with methanol failed to yield the expected ester. Instead, a chloroform-soluble gum was obtained which exhibited an infrared spectrum with peaks at 5.6 and 5.75μ. It seemed apparent that some obscure side reactions were taking place, involving or facilitated by the neighboring phthalimidine carbonyl group.

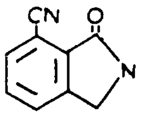
It is known that phthalimide may be reduced to phthalimidine with tin and hydrochloric acid (37). Accordingly, the synthesis of 4-cyanophthalimide (LVII) was undertaken in the hope that zinc and acetic acid would afford one or both of the isomeric phthalimidine nitriles LVIII and LIX. Upon treatment with methyl magnesium iodide, LIX would be expected to



LVII

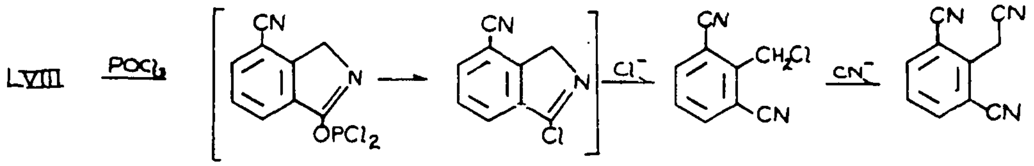


LVIII

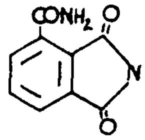


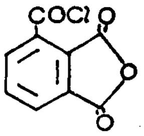
LIX

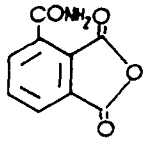
yield LI, and was desired for structure proof of the Liu compound. Nitrile LVIII appeared suitable for synthetic studies of the structure of erythrocentaurin, reactions of the following type being considered:



Although Graebe (1) had synthesized 4-carboxyphthalimide by addition of ammonia to molten hemimellitic anhydride at 210-220°, it was hoped that the imide amide LX would be formed directly by treating the acid chloride


LX


LXI


LXII

anhydride LXI with ammonia. This required intramolecular transacylation of the intermediate amide LXII, formed by ammonia attack either at the site of the acid chloride or at the outer anhydride carbonyl group followed by interaction of the central carboxylate and acid chloride to reform an anhydride, to proceed more slowly than amination by a second ammonia molecule.

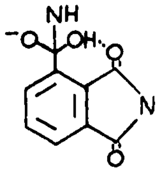
The anhydride was readily formed by fusion of hemimellitic acid at ca.200°. Spectral examination of the product revealed absorption at 5.5 and 5.75μ (anhydride carbonyl), and a broad peak at 6.0μ (carboxyl carbonyl). Treatment of the anhydride for several hours with refluxing thionyl chloride afforded a crystalline product which exhibited an infrared spectrum with peaks at 5.5μ (anhydride carbonyl) and 5.7-5.75μ (anhydride and acid chloride carbonyl) and was assigned structure LXI. A solution of LXI in tetrahydrofuran was added slowly to a rapidly stirred ice-cold aqueous ammonia solution. When the addition was complete the solution was concentrated by boiling and the remaining water removed under reduced pressure.

The product, which was isolated by sublimation, was a material having an infrared spectrum with broad peaks at 3.15-3.32μ(NH), 5.66μ(imide carbonyls), 5.8-6.3μ(imide and carboxylic acid carbonyls), and which analyzed correctly for Graebe's imide acid. It was assumed that the intermediate amide anhydride had undergone intramolecular acylation, and this approach was abandoned.

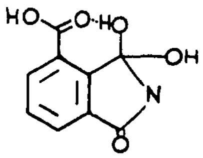
By following Graebe's procedure for imide acid preparation, three products were obtained, one of which proved to be the imide acid previously isolated. A second product had an extremely high melting point, and exhibited an infrared spectrum with peaks at 3.02 and 3.28μ(NH), 5.66 and 5.76μ(imide carbonyls) and 5.93 and 6.04μ(amide carbonyl). It was assigned structure IX, for which it analyzed correctly. The third product upon heating appeared to give off water and resolidify. Recrystallization of the heated material afforded the imide acid. The material exhibited an infrared spectrum with a single sharp peak in the carbonyl region at 5.80μ and a broad and complex band at 6.40-6.70μ, and analyzed as a dihydrate of the imide acid. In view of Graebe's observation that monopotassium hemimellitate was relatively stable in acid media, a hot concentrated aqueous solution of hemimellitic acid was treated with an equimolar solution of ammonium chloride. Upon cooling, the now acidic solution yielded a crystalline precipitate, identical with the unknown compound, which was therefore identified as monoammonium hemimellitate.

Graebe's procedure was modified by carrying out the ammonia addition at 250°, above the melting point of imide acid. Extraction of the solid product with ammonium hydroxide afforded 40-50% of insoluble material which proved to be the desired imide amide IX. Upon acidification of the aqueous extract, after concentration under reduced pressure, the imide acid crystallized. Further concentration afforded additional quantities of imide acid, and the final mother liquors afforded monoammonium hemimellitate. As previously mentioned, the monoammonium salt, upon fusion, affords the imide acid. Treatment of imide acid for several hours in refluxing thionyl chloride, followed by addition of a tetrahydrofuran solution of the crystalline product to a rapidly stirred ice-cold solution of ammonium hydroxide afforded the imide amide IX. Thus by a stepwise procedure, a satisfactory route to IX was available.

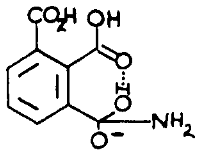
It was found that prolonged boiling of either the imide acid or imide amide in water during recrystallization caused serious losses in the yields of imides obtained. If either the imide amide or the imide acid were boiled for 40-60 minutes in water, an almost complete conversion to monoammonium hemimellitate was observed. This was quite unexpected, since amides, and in particular phthalimide, require catalysis by acid or base in order to effect hydrolysis. The explanation must again lie, as in the case of the retro-Claisen reaction mentioned earlier, in rate enhancement by internal solvation by the neighboring phthalimide carbonyl (LXIII).



LXIII



LXIV



LXV

A similar solvation by the substituent's carbonyl could equally well lower the energy of the transition state in the hydrolysis of the imide (LXIV). Finally the central carbonyl can solvate the intermediate in the hydrolysis of the remaining amide (LXV). Although presented in the opposite order, the hydrolysis of the imide could equally well precede the hydrolysis of the substituted amide.

Treatment of the imide amide IX with refluxing phosphorous oxychloride smoothly converted the compound to 4-cyanophthalimide (LVII) which exhibited infrared absorption at 3.07μ (NH), 4.48μ (nitrile), 5.61 and 5.80μ (imide carbonyls) and analyzed correctly for the desired compound. It was unaffected by either refluxing phosphorous oxychloride-phosphorous pentachloride or fusion with phosphorous pentachloride. Thionyl chloride was ineffective in the conversion of IX to LVII.

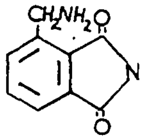
Reduction of the nitrile imide was carried out with zinc and acetic acid for 1.5 hours. The crude product was chromatographed on alumina to afford a trace of a crystalline compound, too small to be characterized followed by incompletely resolved fractions which were steadily eluted from the column. A closer examination of these fractions showed trends in melting points suggesting the presence of three components. Careful fractional crystallization of the purest eluates finally afforded three distinctly different materials which exhibited depressed melting points upon admixture with one another. Although each exhibited a spectrum with absorption at 4.49μ (nitrile) and their 2.5-3.5μ (NH-OH) and 5.5-6.0μ (carbonyl) regions were similar, the "fingerprint" region showed distinct differences which made identification and purification considerably easier. Their melting within 50-60° of one another prevented identification with certainty on the basis of melting point alone. The compounds were conveniently designated as phthalimidines A, B, and C in the order in which they were eluted from the column. Examination of the spectrum of one of the later crude eluates showed it to be predominantly phthalimidine C, but several peaks could not be accounted for. A closer examination of the later eluates led to the isolation of a fourth phthalimidine nitrile, designated as D, which exhibited besides the usual nitrile and phthalimidine carbonyl absorption in its infrared spectrum, absorptions corresponding to the spurious peaks mentioned in the impure phthalimidine C fraction above. Only a small percentage of the total material eluted was obtained as pure phthalimidines. By far the major portion was distributed amongst the intermediate fractions and mother liquors.

Phthalimidines B and C were the major products and upon purification analyzed correctly for the expected phthalimidine nitriles LVIII and LIX. Phthalimidines A and D were not isolated in sufficient quantity to permit purification for analysis. When phthalimidine A was subjected to hydrolysis, a compound was obtained which could not be identified. Since it was not the known 7-carboxyphthalimidine, A could not be the 7-cyanophthalimidine. Similar attempts to obtain hydrolysis products from phthalimidines B and C met with failure. They could not be isolated as crystalline material.

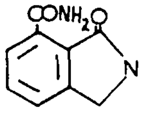
Reduction of LVII was repeated, but the reaction time increased to 3 hours. Chromatography of the products again afforded a complex mixture, but only phthalimidines B and C were isolated. A sixth compound seemed to be present in the later fractions as indicated by its difference in crystal form and melting point from phthalimidine D, but it was not characterized.

The difficulty encountered in the separation of products caused this approach to be abandoned.

Hydrogenation of the nitrile imide LVII was expected to lead to the aminomethyl imide LXVI, which might undergo rearrangement to the phthalimidine amide LXVII. Treatment of LXVII with phosphorous oxychloride would be expected to yield the desired nitrile LIX.

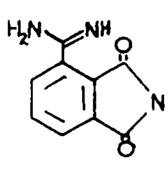


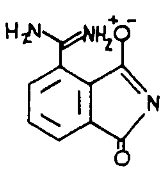
LXVI

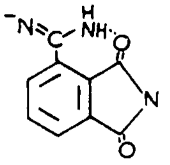


LXVII

Generally hydrogenations of nitriles are run in the presence of ammonia (38) to preclude secondary amine formation by condensation of the primary amines with the intermediate imines. Accordingly, a solution of the imide nitrile LVII in tetrahydrofuran was saturated with ammonia to yield a fine white precipitate, presumed to be either a complex of ammonia and LVII or the ammonium salt of the compound. The suspension was subjected to catalytic hydrogenation in a Parr shaker in the hope that the precipitate would be sufficiently soluble in the medium for nitrile reduction to take place. However, work-up of the reaction mixture led quantitatively to starting material. It was found that upon removal of ammonia by bubbling air through the tetrahydrofuran suspension, the solid dissolved. Examination of the material's infrared spectrum showed a strong similarity in the 5.5-7.0μ region with the spectrum of potassium phthalimide, and suggested that the compound might be the ammonium salt of LVII. It is noteworthy that phthalimide itself, under these conditions, does not form a salt. The spectrum of the above compound, however, exhibited signs, especially in the 3.0-3.4μ region (NH) that the material was actually a mixture of the salt and LVII itself. This was not unreasonable, since the reversal of the reaction by removal of the surrounding ammonia through entrainment suggested that upon prolonged exposure to air or heating, the compound might evolve ammonia and revert to LVII. The compound was accordingly not analyzed. Upon treatment with water the material readily dissolved, and after standing for a short time the solution afforded a highly crystalline precipitate. After isolation and purification, the material exhibited an infrared spectrum in which the 4.5μ nitrile peak was absent, and which also showed absorption at 3.1μ (NH), and 5.9μ (carbonyl). Broad and complex absorption between $6.0-6.6\mu$ was also present. The weak imide carbonyl absorption at 5.6μ was not present. The analytical results were consistent with LVII, to which one molecule of ammonia had been added. The data does not appear to be inconsistant with the assignment of structure LXVIII to the compound, which may prefer to exist in a Zwitterion form such as LXIX. Formation of LXVIII may be explained as due to internal solvation by the phthalimide's adjacent carbonyl (LXX) and thus a lowering of the transition state energy, in much the same way that boiling


LXVIII

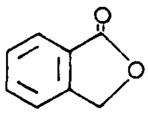

LXIX

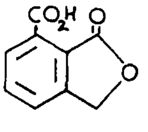

LXX

water can hydrolyze the imide amide IX as mentioned earlier. In this connection it is interesting to note a more recent observation: boiling water will hydrolyze the imide nitrile LVII to monoammonium hemimellitate. It would appear that the imidine formation took place in the presence of water only because the insolubility of the ammonium salt prevented attack at the nitrile. If so, this might also explain the failure which attended all further attempts to reduce the nitrile and obtain LXVII. The intermediate amine might react more slowly intramolecularly, and hence have an opportunity to add, via the above mechanism, to another nitrile. Thus, complex mixtures of di-, tri-, and perhaps polymeric nature could arise.

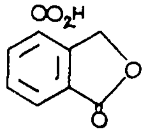
This would be consistent with the observation that under a variety of conditions, hydrogenation afforded only gums and unreacted starting material.

It is known (39) that reduction of phthalic anhydride with zinc and acetic acid affords phthalide (LXXI). A similar reduction of hemimellitic anhydride was undertaken in the hope that it would afford one or both of the two possible isomeric phthalides LXXII and LXXIII. Upon concentration of a methanolic solution of the crude product, a crystalline compound was obtained which upon further purification analyzed correctly for either LXXII or LXXIII and exhibited an infrared spectrum with peaks at 3.85μ (carboxyl OH) and 5.82-6.1μ (phthalide and carboxyl carbonyls). Concentration of the mother liquors afforded additional crops which became progressively richer in a higher melting component whose presence was indicated by its characteristic crystalline form and behavior under polarized light. Fractional crystallization was only moderately successful in separating the two components. Chromatography on silicic acid, however, separated the two, the higher melting compound being eluted with 40-50% ether in Skellysolve B, while the lower melting component, isolated above, was eluted with 60-80% ether in Skellysolve B. Upon purification the higher melting component also analyzed correctly for a phthalide acid, either LXXII or LXXIII, and exhibited an infrared spectrum with peaks at 3.79 and 3.94μ (carboxyl OH), 5.69μ (phthalide carbonyl), and 5.94μ (carboxyl carbonyl). Treatment of the lower melting component with yellow phosphorous in refluxing 57% HI afforded an acid exhibiting an infrared spectrum with


LXXI



LXXII



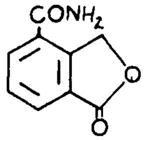
LXXIII

peaks at 3.80 and 3.95μ(carboxyl OH) and a broad peak at 5.9-6.0μ(carboxyl carbonyl). Upon sublimation of the acid a new compound was obtained which exhibited an infrared spectrum with peaks at 5.5 and 5.75μ(anhydride carbonyl), and which analyzed correctly for 3-methylphthalic anhydride. Thus the lower melting phthalide must be assigned structure LXXII. Repeated attempts to carry out a similar reduction of the higher melting isomer were without success, starting material being recovered. Since the orientation of the π-orbitals of the aromatic system is such as to offer only a minimum of overlap with the incipient vacant p-orbital of the intermediate carbonium ion formed by the opening of the hetero-ring, the transition state would not possess the stability of a benzyl cation. Thus a true S_{N_2} displacement of carboxylate by I^- is necessary, and it would appear that the bulky o-carboxyl group affords sufficient shielding of the back side of the methylene group to prevent the displacement.

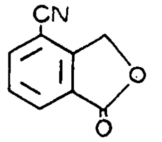
Since 7-carboxyphthalide (LXXII) could be obtained directly by crystallization of the reaction mixture and because it was the first isomer to be fully characterized, an examination of displacement reactions, especially with KCN, were initiated with it rather than with LXXIII. Similar reactions with phthalide are known to take place (40). However, neither the acid nor the ester showed any sign of having undergone reaction with KCN.

Treatment of LXXIII with refluxing thionyl chloride for several hours afforded a crystalline compound which was not characterized. A solution of this compound in tetrahydrofuran was added to an ice-cold solution of ammonium hydroxide. The resulting compound, after purification, exhibited an infrared spectrum with absorption at 2.92 and 3.16μ(NH), 5.81μ

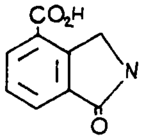
(phthalide carbonyl), and 5.97μ(amide carbonyl), and analyzed correctly for 4-carboxamidophthalide (LXXIV). Treatment of this compound with phosphorous oxychloride afforded a compound exhibiting an infrared spectrum with peaks at 4.5μ(nitrile) and 5.7μ(phthalide carbonyl). Fusion of this compound with KCN afforded only starting material.



LXXIV



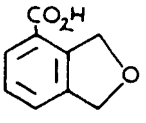
LXXV



LXXVI

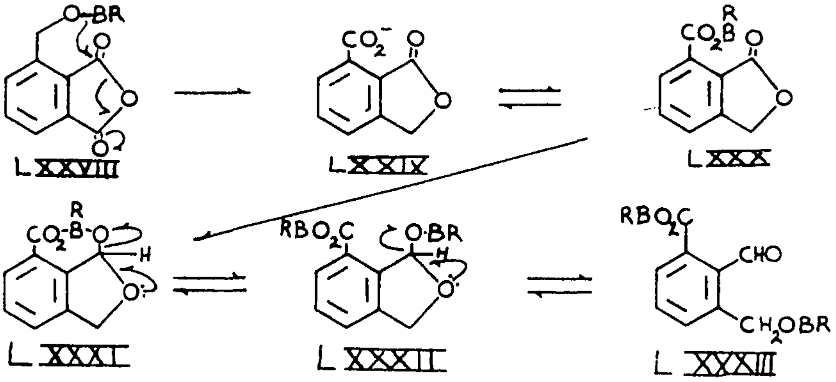
It was of interest to see if LXXIV upon pyrolysis might afford LXXVI, the phthalimidine acid corresponding to the nitrile LVIII. Subsequent conversion to the nitrile might then allow assignment of structures to phthalimidines B and C. Fusion occured at a high temperature and was accompanied by decomposition. Although acidic material was isolated, all attempts to obtain a pure crystalline product failed, and the study was discontinued.

The inefficiency of phthalide production from hemimellitic anhydride by direct reduction led to an investigation of alternate and more specific syntheses. One such procedure involved selective reduction of the acid chloride of hemimellitic anhydride with sodium borohydride. This reagent is known (41) to attack both anhydrides and acid chlorides, but steric considerations suggested that attack on the outside carbonyls would be more rapid than attack on the central carbonyl, and if one equivalent of borohydride were to be added slowly to the anhydride acid chloride, some selectivity could be anticipated. The reaction was run in diglyme (diethyleneglycoldimethyl ether) in which both the borohydride and the anhydride acid chloride are soluble. Upon work-up, a thick oil was obtained, which was dissolved in methanol and concentrated to an oil. Upon standing, the desired phthalide acid LXXII slowly crystallized. Yields were of the order of 30%. Upon careful addition of chloroform, a material precipitated from the viscous mother liquor which, upon purification, proved to be hemimellitic acid. The mother liquors failed to afford any additional compounds directly. Chromatography of the oil on silicic acid afforded, on one occasion, a crystalline acid which exhibited an infrared spectrum with peaks at 3.18 and 3.93μ (carboxyl OH), 5.80 (weak) and 5.94μ (carboxyl carbonyl), and analyzed correctly for 4-carboxy-1,3-dihydroisobenzofuran (LXXVII).



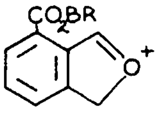
LXXVII

Sodium borohydride has been known to reduce lactones in the presence of neighboring hydroxyl groups (42). On the other hand, esters and lactones which have no vicinal hydroxyl are known to be resistand to borohydride reduction (43). This apparent anomaly may be explained by assuming that the borohydride first reacts with the hydroxyl group. The resulting borate hydride is then in a position to intramolecularly reduce the carbonyl, and would be, effectively, a more powerful reducing agent than a borohydride forced to react intermolecularly. A similar situation exists in the system under consideration. Examination of the spectrum of hemimellitic anhydride acid chloride in diglyme reveals a sharp peak at 5.5μ due to the anhydride carbonyl, and a somewhat more broad but also much stronger peak at 5.1μ which must be due to the second peak of the anhydride carbonyl doublet as well as the acid chloride's carbonyl. If the reduction is now carried out, but no water added, the infrared spectrum of the concentrated reaction mixture still shows a strong sharp peak at 5.5μ and a peak at 5.7μ diminished in intensity relative to the 5.5μ peak as compared with starting material. Traces of other components are indicated by a weak, broad band at 3.1μ and a weak peak at 5.90μ. This can only mean that the anhydride is still present as the predominant carbonyl functional group and that phthalide formation takes place after water is added. Thus, the intermediate leading to phthalide which is present prior to hydrolysis must be LXXVIII. (Since constant exchange can occur, no attempt will be made to specify the nature or number of substituents on the boron atom other than the one shown or explicitly stated.) Should this now choose to slowly rearrange, a <u>small</u> quantity of LXXIX could arise. Displacement by the carboxylate of a group from a borate or

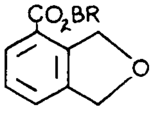


borohydride could lead to the borate carboxylate anhydride LXXX. Should one of the R groups be a hydride, either initially or through subsequent exchange, the combination required to initiate reduction at the phthalide carbonyl would be present, leading to the intermediate LXXXI which would be in equilibrium with the other intermediates LXXXII and LXXXIII. Loss of oxygen to give the oxonium compound LXXXIV could occur intramolecularly through LXXXI or intermolecularly through LXXXII.

Since ether formation does not occur in the lactone reduction examples cited (42) it is apparent that the π-orbitals of the aromatic system must have participated in the cleavage of the C-O bond which gave LXXXIV. Subsequent reduction of the oxonium system with borohydride would afford LXXXV, which upon hydrolysis and work-up would afford the isolated compound LXXVII.

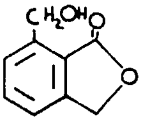


LXXXIV

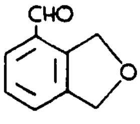


LXXXV

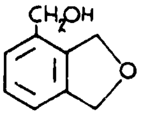
Further proof that proximity of the borate substituent to the phthalide carbonyl is necessary for ether formation was supplied by the following series of reactions. Conversion of the two phthalide acids to the corresponding acid chlorides followed by reduction with sodium borohydride affords the corresponding hydroxymethyl phthalides, which will be discussed in more detail later, along with starting material. In the case of



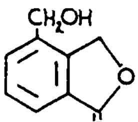
LXXXVI



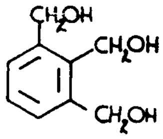
LXXXVIII



LXXXIX



LXXXVII

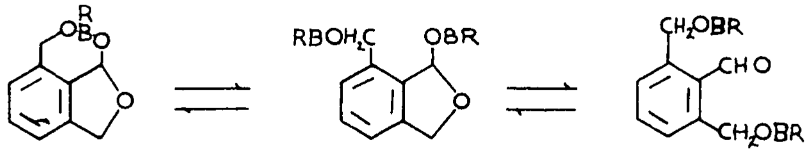


XC

LXXII, in which the substituent and the phthalide carbonyl are adjacent, two additional products are obtained, a large quantity of an oily alcohol, LXXXIX, showing only traces of carbonyl absorption in the infrared, and a trace of a solid, LXXXVIII, showing a single peak at 5.96μ (aromatic aldehyde carbonyl) in its infrared spectrum, with no significant absorption below 3.4μ. Conversion of LXXXIX to LXXXVIII was smoothly effected with MnO_2, the conversion of a benzylic alcohol to an aromatic aldehyde by this procedure being well known (44). The aldehyde LXXXVIII, in turn, could be converted to the previously isolated and analyzed ether acid LXXVII, by treatment with silver oxide; a procedure accompanied by the precipitation of metallic silver. The oxidation thus also constituted a Tollens test, and was consistent with the presence of an aromatic aldehyde.

Hence, the proximity of the borate hydride to the phthalide carbonyl is a prerequisite to ether formation, since in the case of no such proximity only the expected product and unreacted starting material were obtained in over 80% yields.

In the attempted formation of LXXXVI it was also noted that if a somewhat greater portion of borohydride was employed than optimum, substantial quantities of the triol XC were obtained. Apparently an equilibrium similar to LXXXI ⇌ LXXXII ⇌ LXXXIII can also be set up here with XCI. An increase in borohydride concentration would be expected to shift the equilibrium towards XCII and XCIII. Thus the greater concentration of XCIII would promote complete reduction to XC. The chemistry of XC and its synthesis will be presented in more detail later.

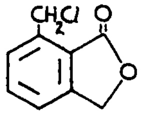


XCI XCII XCIII

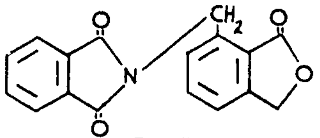
The product obtained from the borohydride reduction of the acid chloride of LXXXII analyzed correctly for LXXXVI and exhibited an infrared spectrum with absorption at 3.01μ (OH), and 5.75μ (phthalide carbonyl). Depending on the sample examined, however, a second set of peaks at 2.93, 5.60, 7.11, 7.97, 8.44, 9.25, 10.24, 12.48 and 12.90μ were often found to accompany the first set, though never replacing it, in spite of the fact that the melting points of all the samples were comparable and no difference could be found in subsequent reactions. It seems reasonable to assume that the two sets of peaks are due to two different crystal forms which occur in varying proportions in different samples.

Treatment of LXXXVI with thionyl chloride for 3 days at room temperature afforded a crystalline product which had no significant absorption below 3.4μ and a phthalide carbonyl peak at 5.71μ in its infrared spectrum. It subsequently analyzed correctly for 7-chloromethylphthalide (XCIV).

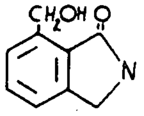
Heating XCIV with potassium phthalimide in dimethylformamide afforded a crystalline product, which absorbed at 5.66 and 5.74μ (phthalimide carbonyls) and 5.86μ (phthalide carbonyl) in the infrared.



XCIV



XCV



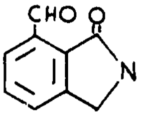
XCVI

The spectrum and analytical results are in complete accord with structure XCV.

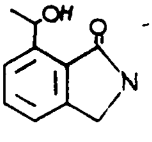
Cleavage of the phthalimide and rearrangement of the resulting aminomethylphthalide was achieved by refluxing XCV in methanol with an excess of hydrazine. From this reaction a crystalline compound was obtained exhibiting an infrared spectrum with absorption at 3.00 and 3.1-3.3μ (NH and OH), and 5.95μ (phthalimidine carbonyl), and analyzing correctly for 7-hydroxymethylphthalimidine (XCVI).

Oxidation of XCVI with a variety of reagents failed to bring about complete conversion to the aldehyde XCVII. The relative insolubility of XCVI in ether made oxidation with MnO_2 unattractive, for prior experience in These Laboratories with more polar solvents, in particular, tetrahydrofuran, had been decidedly unsatisfactory. Experiments using ether-acetone as a solvent for MnO_2 oxidation were only moderately successful, only partial conversion being encountered in spite of prolonged reaction times. The Sarett reagent (45) was finally chosen, although it too afforded only partial conversion. The crude product was chromatographed on alumina which failed to completely resolve the mixture. Eluates rich in product could be fractionally crystallized to afford some additional material. The mother liquors, mixed fractions and pure starting material were combined and cycled through the oxidation-isolation procedure again. The pure crystalline product had an infrared spectrum with peaks at 3.19 and 3.30μ (NH), 5.88 and 5.95μ (aldehyde and phthalimidine carbonyls). In KBr, a peak was observed at 3.5μ consistent with an aldehyde CH. The compound analyzed correctly for the phthalimidine aldehyde and was assigned structure XCVII. Repeated attempts to obtain a positive Tollens test or in other ways to oxidize the compound to the known 7-carboxyphthalimidine were unsuccessful.

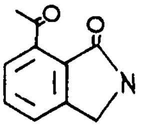
Treatment of XCVII with slightly more than two equivalents of methyl magnesium iodide afforded a semisolid mass which upon chromatography yielded a continuous series of slowly crystallizing oil fractions. Attemps to recrystallize the material from organic solvents failed, but were successful when water was employed. The product, however, was either solvated or tended to occlude water. Unless it was cautiously dried under reduced pressure with progressively stronger heating, it dissolved in its own water even upon gentle warming on the steam bath. After several crystallizations the product exhibited an infrared spectrum with peaks at 2.93μ (OH), 3.15 and 3.30μ (NH), and 5.96μ (phthalimidine carbonyl), and analyzed correctly for the desired methyl carbinol XCVIII.



XCVII



XCVIII

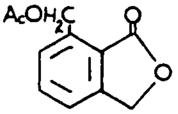


XCIX

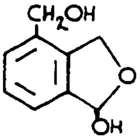
Oxidation of XCVIII to the desired 7-acetylphthalimidine (XCIX) was achieved with chromic acid in 90% aqueous acetic acid. The product was readily separable from XCVIII by crystallization from acetone. Thus, isolation and separation were greatly simplified, even though only partial conversion was effected on each run. Attempts to achieve complete conversion either by prolonging the reaction time or using more than the stoichiometric quantity of chromic acid invariably led to formation of a compound which exhibited an infrared spectrum with absorption at 5.60 and 5.68μ indicating the presence of a phthalimide. Thus it was apparent that oxidation of the phthalimidine's methylene carbon could take place during the course of reaction. The immediate precipitation of the chromium oxide complex upon combination of the chromic acid and methyl carbinol solutions indicated a rapid oxidation was taking place. A procedure was then employed in which stoichiometric quantities of the reactants were rapidly combined, allowed to stand a few minutes, and the reaction then quenched. Under these conditions substantial quantities of starting material were always recovered, but the quantities of phthalimide formed were negligible.

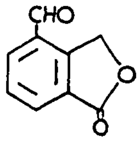
After several preliminary reactions had been run to determine the conditions needed to convert phthalimidine to o-benzenesulfonamidomethylbenzoic acid, a sample of XCIX was heated for several hours with 10% sodium hydroxide. Benzenesulfonylchloride was added and the reaction mixture shaken until homogeneous. The basic solution was extracted repeatedly with chloroform, affording only a trace of material. Acidification of the aqueous solution, followed by extraction with chloroform, afforded a large portion of gum from which a crystalline compound was isolated which had the same melting point and infrared spectrum as the benzenesulfonamidomethylacetylbenzoic acid originally isolated from the aromatization reaction. The melting point was undepressed upon admixture of the two samples. Thus, the compounds obtained by Liu must have undergone iodolactonization with the carboxyl nearest the acetamidomethyl group.

Interest arose in the triol XC as a possible intermediate in a more satisfactory synthesis of the phthalide acid LXXIII. Conversion of hemimellitic acid to its anhydride by fusion followed by dissolution in tetrahydrofuran and slow addition of the solution to a suspension of $LiAlH_4$ in tetrahydrofuran led to the formation of a characteristic deep purple reaction mixture. Upon work-up, the crude product was dissolved in methanol and concentrated. The solution afforded a crystalline compound which upon purification afforded an infrared spectrum with a broad peak at 3.14μ (OH) and no significant absorption in the 5-6μ region and which analyzed correctly as XC. Several additional crops of compound were obtained, after which the mother liquors were acetylated and chromatographed on alumina to give two crystalline products. The first compound, C, had an infrared spectrum with a peak at 5.78μ (acetate and phthalide carbonyl) and analyzed as $C_{11}H_{10}O_4$. The second compound had an infrared spectrum identical with LXXXVI and analyzed as $C_9H_8O_3$. Upon admixture with LXXXVI, the melting point was undepressed. When LXXXVI was acetylated, the product proved identical with C on the basis of infrared spectrum, melting point and mixed melting point.


C

It was previously stated that MnO_2 will oxidize a benzylic alcohol to a carbonyl. It is also reasonable that steric environment would effect the rates at which the alcohols oxidize. Hence, it was expected that if the triol XC was subjected to MnO_2 oxidation, the outside alcohols would oxidize before the central alcohol. If this were to happen, however, the product would immediately form the hemiacetal CI. Since the hemiacetal hydroxyl is a benzylic hydroxyl it may undergo oxidation again to form the phthalide. During the course of these reactions, the other benzyl alcohol would also oxidize, and the product finally isolated would be CII. Oxidation of this would afford the desired phthalide acid.


CI


CII

The reaction, carried out in tetrahydrofuran, was erratic, affording on one occasion a material exhibiting an infrared spectrum with peaks at 5.67μ (phthalide carbonyl) and 5.96μ (aldehyde carbonyl), and which could be oxidized to LXXIII. It was tentatively identified as CII. Several attempts to repeat the successful reaction were made but all failed, and the approach was abandoned. As previously indicated, borohydride reduction of the acid chloride of LXXIII afforded a product assigned structure LXXXVII. This assignment was based on the infrared spectrum of the compound which showed peaks at 2.89μ (OH), and 5.76μ (phthalide carbonyl), and on the fact that the compound analyzed correctly for $C_9H_8O_3$. Treatment of the phthalide alcohol with MnO_2 in ether afforded a new product, identical on the basis of infrared spectrum and melting point with the MnO_2 product from XC. It analyzed correctly for CII and the structure was thus confirmed.

By oxidizing XC in aqueous acetone with a moderate excess of $KMnO_4$ at room temperature, it was found possible to obtain the phthalide acid LXXIII directly in fair yield. This result was observed only in small scale reactions, however. A large run was completely unsuccessful.

Homologation of either LXXII or LXXIII by the Arndt-Eistert procedure followed by reduction with $LiAlH_4$ would be expected to yield the same triol CIII. If the structure of erythrocentaurin is IIIb, the triol obtained upon $LiAlH_4$ reduction (1) must be CIV. If CIII is identical with the authentic triol, then IIIb cannot be the structure for erythrocentaurin. Should it be different from the authentic triol, then IIIb is almost certainly the correct structure.

Homologation of LXXII by the Arndt-Eistert procedure afforded a compound which analyzed correctly for CV and exhibited an infrared spectrum with peaks at 5.73 and 5.81μ (ester and phthalide carbonyl). Upon exposure to $LiAlH_4$ in tetrahydrofuran at room temperature overnight, an oily product was obtained which still exhibited strong carbonyl absorption in the infrared, although an intense hydroxyl band was also present. Further treatment with a large excess of $LiAlH_4$ and prolonged refluxing in tetrahydrofuran failed to remove the carbonyl absorption. Prolonged treatment of the product with refluxing diglyme and a large excess of $LiAlH_4$ was equally unsuccessful. The crude product was chromatographed, but a pure product could not be obtained. Acetylation of the combined eluates afforded an oily product which exhibited an infrared spectrum having no significant absorption below 3.4μ. It too failed to afford solid products, even upon chromatography.

Difficulty in reducing hindered carbonyl groups with $LiAlH_4$ has been encountered before. Reduction of the esters of 3-chlorophthalic acid was found (46) to be more difficult than expected and a large excess of hydride was often found necessary to bring about reduction of the central carbonyl. The isolation of LXXXVI and its acetate from reduction of hemimellitic anhydride with excess $LiAlH_4$, serves to illustrate further incomplete reduction presumably due to steric hindrance. Attention was turned to CVI, since both of its carbonyls are exposed and no steric problems would be expected.

Homologation of LXXIII by the Arndt-Eistert procedure afforded a crystalline product which absorbed at 5.73 and 5.82μ (ester and phthalide carbonyl) in the infrared and analyzed correctly for CVI. Reduction with $LiAlH_4$ yielded an oily product which showed only traces of carbonyl contamination in its infrared spectrum. Benzoylation followed by chromatography afforded a compound which exhibited an infrared spectrum with no significant absorption below 3.4μ and peaks at 5.82 and 5.87μ (benzoate carbonyls). It analyzed correctly for the tribenzoate of CIII. Attempts to hydrolyze the material by prolonged refluxing in basic aqueous-acetone afforded only traces of benzoic acid. Reduction with $LiAlH_4$ afforded an oil which exhibited no significant infrared absorption in the 5.5-6.0μ region. The benzyl alcohol was extracted from the triol with ether, but even on prolonged standing at less than 0°C., the product would not crystallize.

Graebe's acid, 6-carboxyphthalonic acid, possesses the same carbon skeleton as CIV. If the keto group, present as a lactol, could be reduced to a methylene, subsequent reduction would be expected to lead to CIV. This triol would not only be useful in proving the identity of the erythrocentaurin reduction product, but also as the key intermediate in the synthesis of erythrocentaurin itself. Oxidation of the triol with MnO_2 would lead directly to the natural product by reactions of the same type discussed in connection with the conversion of XC to the phthalide aldehyde.

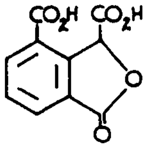
When XIV was exposed to amalgamated zinc-hydrochloric acid, a water insoluble product slowly formed. Upon isolation and purification, the compound exhibited an infrared spectrum with peaks at 3.1-3.3, 3.8 and 4.0μ(carboxyl OH) and a broad complex band at 5.6-6.0μ(phthalide and carboxyl carbonyls), and analyzed correctly for 3,4-dicarboxyphthalide (CVII). Upon melting, the compound decarboxylated and afforded the previously isolated phthalide acid LXXIII. Prolonged exposure of the diacid to amalgamated zinc-hydrochloric acid failed to bring about further reduction.

In order to enhance the ability of the 3-carboxyl to stabilize the transition state in the desired hydrogenolysis of the phthalide's 2-3 bond, CVII was esterified with diazomethane to yield a compound which analyzed correctly for CVIII, and which exhibited infrared absorption at 5.63μ (phthalide carbonyl), and 5.71 and 5.81μ (ester carbonyls). The compound, was treated with amalgamated zinc-methanol-HCl, but only oils or starting material were obtained.

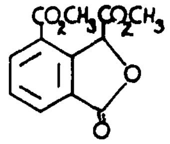
Catalytic hydrogenolyses of CVIII with 10% Pd/C at 1 atmosphere for 40 hours and with Raney nickel at 50 p.s.i.g. for 11 days were unsuccessful.

The diacid CVII was treated with acetic anhydride and warmed, followed by the addition of zinc and acetic acid. It was hoped that the anhydride CIX would afford the desired stabilizing effect in the transition state and facilitate the hydrogenolysis. Since the 3-carbomethoxy group was free to rotate, it could orient itself in such a way that the π-orbitals were coplanar with the phthalide ring and hence in an optimum orientation for participation in the transition state of hydrogenolysis. The restriction offered by the anhydride's 6-membered ring makes such an orientation of the corresponding carbonyl's π-orbitals impossible. However, distortion of the 6-membered ring could permit partial orientation, and this, coupled with the intrinsically greater stabilizing effect of an anhydride relative to a carbomethoxy group, could offset the lack of ideal orientation. The reaction, however, led only to oils.

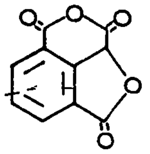
Graebe had originally reported (23) that treatment of XIV with phosphorus and HI had lead to 2-methylisophthalic acid, although it was shown



CVII

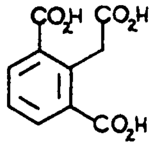


CVIII



CIX

earlier that LXXIII could not be reduced to the same compound by this procedure. Thus it appeared that carboxyl group was important, and that perhaps Graebe's 2-methylisophthalic acid had arisen from decarboxylation of CX.

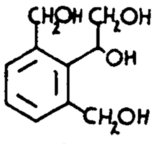


CX

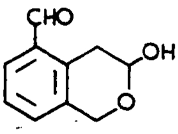
When the diacid CVII was exposed to gentle heating with phosphorous and HI, only starting material was recovered. Stronger heating caused decarboxylation and the phthalide acid LXXIII was obtained. Upon attempting to reproduce Graebe's original results, only starting material and the diacid CVII were obtained.

The cleavage of benzyl ethers can be brought about by treatment with Li in liquid ammonia (47). Similar treatment with two equivalents of Li of the phthalides might lead to the desired hydrogenolysis. The diacid CVII was chosen for study to minimize possible side products. When Li was added to a stirred solution of the acid in liquid ammonia, the solution became orange until enough excess Li had been added for the characteristic blue color to persist. Upon work-up only oils could be obtained, and similar results accompanied attempted reduction of the methyl ester of LXXIII.

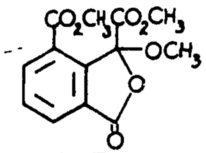
If either the ester of Graebe's acid (CXIII), or CVIII were to be re-



CXI



CXII



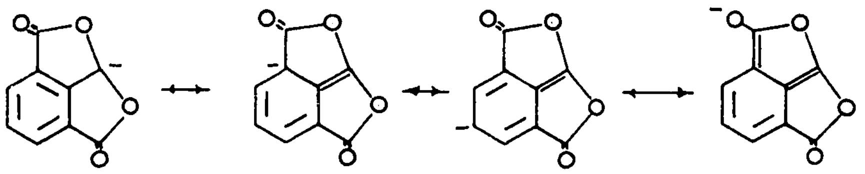
CXIII

duced with $LiAlH_4$ the expected product would be CXI. Treatment of this compound with acid might then lead to dehydration of the α-phenylethanol system, followed by tautomerization of the resulting enol to the aldehyde and formation of a hemiacetal with a neighboring hydroxymethyl group to give CXII. Reduction of this compound should then afford the desired triol CIV.

Graebe's acid was treated with diazomethane to give a product which analyzed correctly for the triester, and exhibited an infrared spectrum with a complex carbonyl region, having peaks at 5.67μ (phthalide carbonyl), 5.81 and 5.87μ (ester carbonyls). In both the ester and the free acid, peaks at 5.67 and 5.65μ respectively are in complete accord with the suggestion by Buu-Hoi (26) that the compounds exist in the pseudoester and lactol forms respectively and are written as such throughout this work. Reduction of the diester CVIII with $LiAlH_4$ gave only oils, but some tendency to crystallize from water was noted. Since this was reasonable for the desired compound, the crude product was treated with acid, acetylated and chromatographed. Only a trace of crystalline material was obtained, and since the reaction had been so unfavorable on the diester, reduction of the triester was not attempted.

Graebe's acid was pyrolyzed and the reaction mixture was worked up by the method of previous workers (27). The water-soluble and sublimable products were chromatographed to give hemimellitic acid, identified by melting point, mixed melting point with authentic hemimellitic acid, and infrared spectrum, and a compound which exhibited an infrared spectrum with peaks at 3.01μ (OH), 3.82μ (carboxyl OH), and a broad peak at 5.82μ (phthalide and carboxyl carbonyls), and which by virtue of its melting point was identified as the aldehyde isolated by Graebe and later workers (23, 26). A third product isolated in slightly greater yield than the aldehyde was identified by melting point, mixed melting point with authentic material, and infrared spectrum as the phthalide acid LXXIII. In the first pyrolytic run dense white fumes were observed issuing from the reaction vessel and a coating of white solid was found on its cooler portions. The second run was carried out in a sublimation apparatus to trap the sublimable material. Since the phthalide LXXIII is readily sublimable, prolonged heating of the reaction mixture in an open vessel might cause its loss and thus account for the failure of earlier workers to discover the compound. Interestingly enough, the sublimate obtained in the second run was primarily the aldehyde. A small percentage of unresolved crystalline material was also obtained along with ca.30% unresolvable oils.

Examination of the so-called dilactone verified its solubility in base with the formation of an orange-red solution, and its reprecipitation upon acidification. There appeared to be some possibility that Graebe's original structure assignment was correct, for removal of the angular proton could be stabilized by a number of resonance forms e.g. CXIV - CXVII.

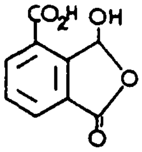


CXIV CXV CXVI CXVII

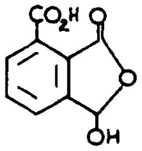
This would not only explain the base solubility and color phenomena associated with the compound, but also would answer Buu-Hoi's objection to Graebe's structure proposal. Buu-Hoi had argued that precipitation of the starting material upon acidification of a basic solution should not occur since the base solubility of the dilactone must be due to its hydrolysis.

The infrared spectrum of the compound exhibited peaks at 3.8 and 4.0μ (carboxyl OH, not as well resolved in figure 14 as in other spectra of the compound), 5.59, 5.73 and 5.93μ. The peaks at 3.8 and 4.0μ are highly suggestive of a carboxylic acid and the peak at 5.59μ suggests a phthalide; indeed the spectrum between 2.5 and 6.5μ is similar to that of the phthalide acid LXXIII. Bellamy (48) states that absorption between 3.7 and 4.0μ may be taken as strong evidence of a dimeric carboxylic acid, provided, of course, corresponding absorption in the carboxylic acid carbonyl region is present. Such absorption has been frequently observed in the course of this investigation and attention is called to all the spectra of carboxylic acids presented in the Spectra Section. Almost always the absorption occurs as two peaks, well illustrated by the spectra of compounds, LXXIII and LXXVII. Although much more poorly defined, a similar absorption appears in the spectrum of Graebe's dilactone, suggesting that the 5.93μ absorption is indeed due to a carboxylic acid. Attempts to purify the dilactone appear to have led to changes in the structure, however, and the spectrum illustrated is of the crude material as isolated by the procedure employed by other workers. Hence, the presence of a carboxyl might be due to a contaminant. Attempts to cyclize Graebe's acid and decarboxylate the product, thus synthesizing the dilactone structure, led on one occasion to a crystalline compound of unknown constitution, which would not decarboxylate and which led in turn to several other unknown products, none of which corresponded to the dilactone. Consideration was given to the cyclization of the Graebe aldehyde, for which structure CXVIII has been proposed (26). Examination of its infrared spectrum showed no absorption in the 5.5-5.75μ region as expected for a hydroxy-phthalide structure of the

CXVIII type. Indeed the infrared spectrum below 6.3μ was quite similar to that presented by the phthalide acid LXXII, even to the extent that the 3.82μ (carboxyl OH) peaks are single in both compounds. Attention should be drawn to the spectrum of Graebe's acid, for in spite of a complex carbonyl absorption, peaks are present at 5.65μ, in the region for the non-intramolecularly hydrogen bonded phthalide carbonyl. Thus, considering only spectral data and Graebe's original analytical figures, one would be inclined to propose CXIX as the structure for the compound. Since it is much easier to account for the originally proposed structure than to account for the new one, it must be concluded that the structure of Graebe's aldehyde has not been rigorously determined. It was therefore not employed in attempting to synthesize the dilactone structure. It is likewise apparent that further study is required before the structure of Graebe's dilactone can be assigned unambiguously.

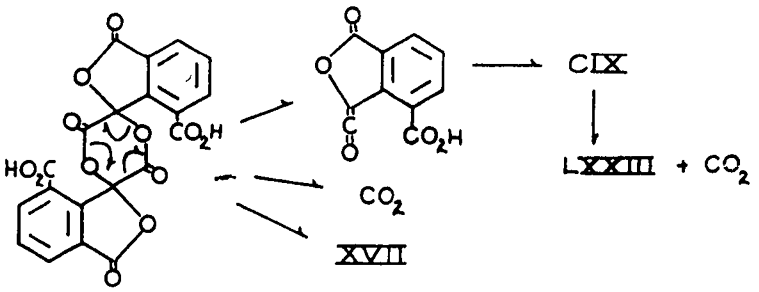


CXVIII



CXIX

The appearance of hemimellitic acid among the pyrolysis products of the Graebe acid appears entirely reasonable, since the decarbonylation of α keto acids is well known (49). The appearance of the phthalide acid LXXIII is less expected, since some form of reduction must take place on the phthalide's C_3. An obvious explanation would center around a Canizzaro reaction between two molecules of the structure proposed by Graebe for the aldehyde, CXVIII. The failure to isolate such an aldehyde from the reaction mixture, assuming that the isolated aldehyde does not have its assigned structure, does not preclude its formation and employment in the formation of isolated products. Although the Canizzaro reaction is generally carried out in strong base, the high temperature of the pyrolysis, coupled with the possibility of anhydride formation between two aldehydo-acids, bringing them into proper position for an intramolecular reaction, could conceivably permit the reaction to take place. An alternate mechanism which avoids the necessity of aldehyde formation or the unusual Canizzaro reaction is founded on the well known condensation of hydroxy acids to form lactides. Should two molecules of Graebe's acid condense in this way CXX would be formed. Loss of CO_2 by the indicated mechanism

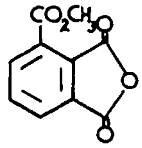


CXX

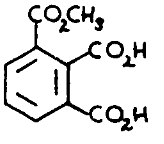
would lead to hemimellitic anhydride and a ketene which would not survive, but would form CIX. Since in the molten acidic media the anhydride could open to form mixed anhydrides, an opportunity would be presented to the freed 3-carboxyl group to undergo decarboxylation, thus giving the phthalide acid LXXIII upon work-up. Since hemimellitic acid is isolated in almost twice the quantity of the phthalide acid and both of the above mechanisms require the 1:1 formation of acid and phthalide, both mechanisms are stoichiometrically possible, the remaining hemimellitic acid being formed by the first-mentioned decarbonylation.

Elderfield (27) had prepared 2-methylisophthalic acid from Graebe's acid by first pyrolyzing the material and then subjecting the pyrolyzate to treatment with sodium hydroxide and Raney nickel alloy, a procedure which has been shown (50) to reduce aromatic aldehydes and alcohols to the corresponding saturated compounds. When the same reduction was attempted on XIV or on CVII, only CVII was obtained. Despite the analytical figures quoted by Elderfield for the dimethyl ester of 2-methylisophthalic acid, the structure assigned to the acid came in doubt. In both the Graebe procedure for HI/P reduction of XIV or for its pyrolysis, the phthalide acid LXXIII was obtained. Yet neither observation had been made previously. Since the melting point of LXXIII was only 10° higher than that reported for the isophthalic acid and the empirical formula differed by only two hydrogens, there appeared to be a slight possibility that the isophthalic acid was actually the phthalide acid. By employing the procedure of Elderfield, the isophthalic acid was obtained. It exhibited an infrared spectrum with peaks at 3.82 and 4.00μ (carboxyl OH), 5.91 and 5.60μ (carboxyl carbonyls), and was otherwise different from the spectrum of LXXIII. Upon admixture the melting points were depressed. Thus the isophthalic acid had been correctly identified.

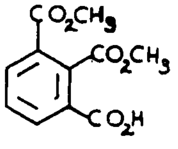
By following Graebe's procedure, a monomethyl ester and a dimethyl ester of hemimellitic acid were prepared. To these Graebe has assigned structures XIX and XX, respectively. The monomethyl ester analyzed correctly for XIX and exhibited an infrared spectrum with peaks at 3.81μ and 3.95μ (carboxyl OH), 5.75μ (ester carbonyl), and 5.87-5.94μ (carboxyl carbonyls). Upon sublimation, hemimellitic anhydride was obtained and identified by comparison with authentic material. This result was consistent with Graebe's formulation, but required a comparison with the isomeric monoester. Treatment of hemimellitic anhydride in tetrahydrofuran with a slight excess of diazomethane, afforded a compound exhibiting an infrared spectrum with peaks at 5.39 and 5.61μ(anhydride carbonyls) and 5.80μ(ester carbonyls) and which analyzed correctly as 4-carbomethoxyphthalic anhydride (CXXI). Upon warming in aqueous acetone a compound was obtained which absorbed at 2.8, 3.30 and 3.95μ(carboxyl OH) and 5.8-5.9μ (ester and carboxyl carbonyls) in the infrared and which analyzed correctly as 3-carbomethoxyphthalic acid CXXII. It differed from XIX in its infrared spectrum and exhibited depression of melting point upon admixture with its isomer. Sublimation of the compound readily yielded CXXI. Thus



CXXI



CXXII



CXXIII

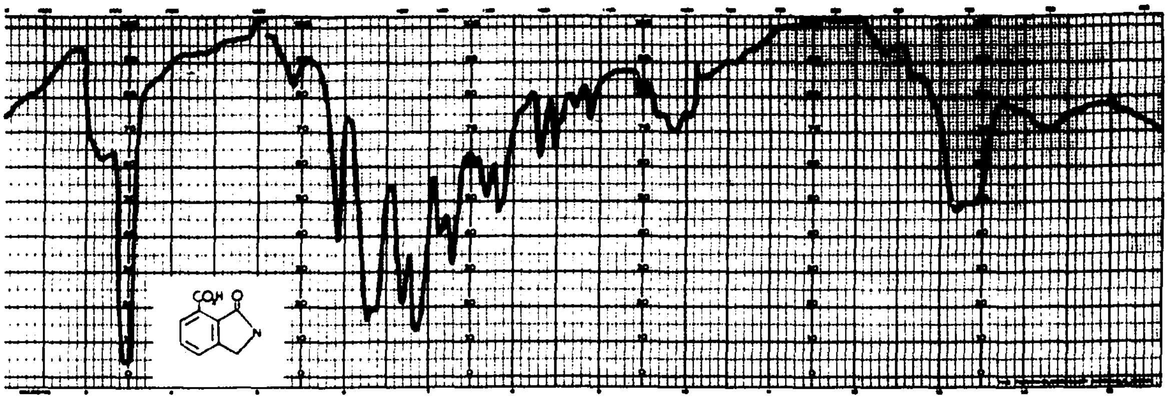
Graebe's original assignment was correct, and the two monoesters are now known and identified.

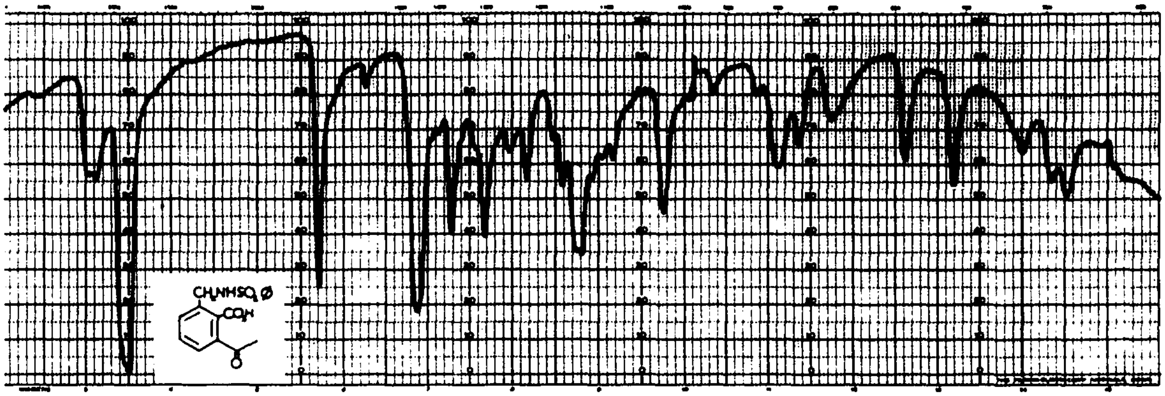
Graebe's dimethyl ester exhibited an infrared spectrum with peaks at 3.7-3.9μ (carboxyl OH), 5.81μ(ester carbonyl) and 5.89μ(carboxyl carbonyl) and analyzed correctly for the assigned structure. Treatment of the anhydride CXXI with methanol afforded a compound which analyzed correctly for a dimethyl ester and which exhibited an infrared spectrum with peaks at 3.7-4.0μ(carboxyl OH), 5.79μ(ester carbonyl), and 5.92μ(carboxyl carbonyls). The spectra and melting points of the two compounds were different, and their melting points were depressed upon admixture. Upon sublimation, both afforded the anhydride CXXI. Treatment of the two diesters separately with thionyl chloride, followed by reduction with sodium borohydride led to mixtures of both phthalide esters in both cases. Although the ester of phthalide LXXII predominated, Graebe's diester afforded 30% while the new diester afforded 45%. In the case of the ester of phthalide LXXIII, Graebe's diester afforded 12% while the new diester afforded 5%. Although it appeared that the esters had undergone extensive isomerization during treatment with $SOCl_2$, the results were consistent with the assignment of structure CXXIII to the new diester and the retention of structure XX assigned by Graebe to his diester.

SPECTRA

The infrared spectra in this section were taken on a Perkin-Elmer 21 infrared spectrophotometer. All samples were emulsions in Nujol.

Figure 1. Infrared spectra


CO2H
O
N


CH2NHSO2Ø
CO2H
O

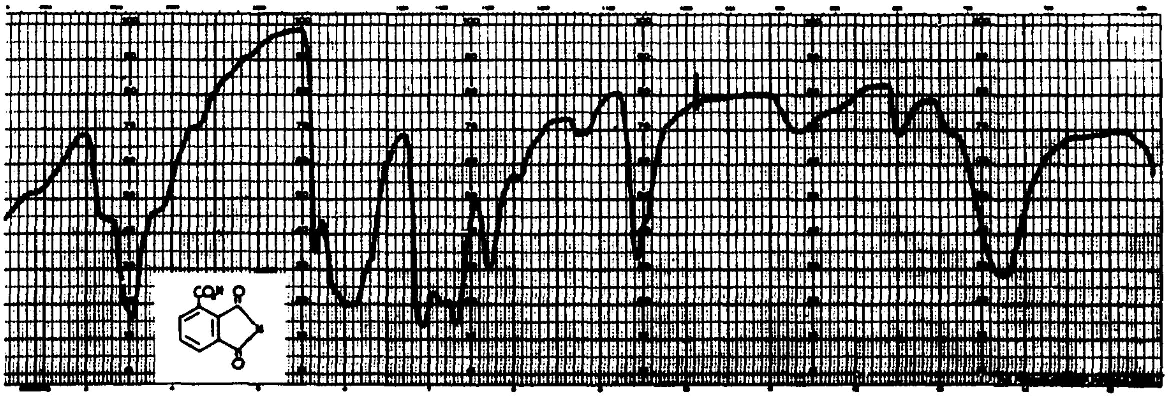
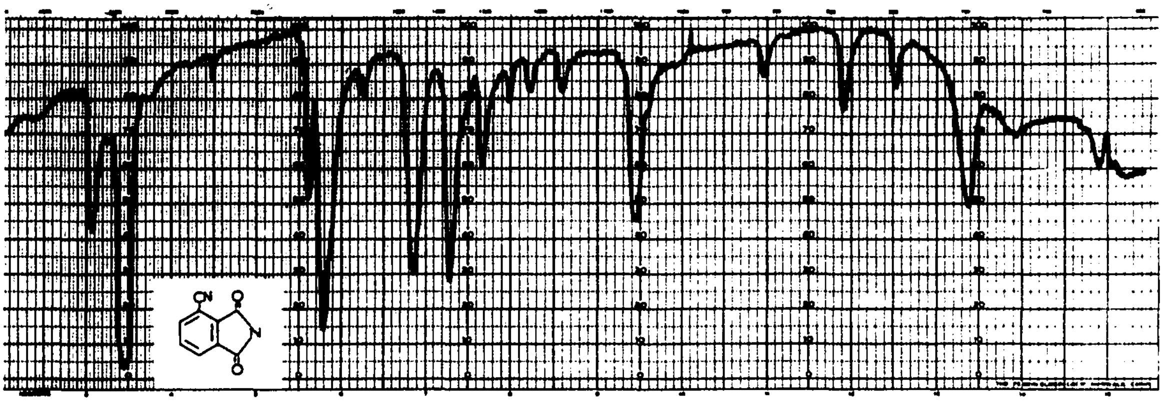

CO2H
O
N
O

Figure 2. Infrared spectra


CONH2
O
N
O


CN
O
N
O

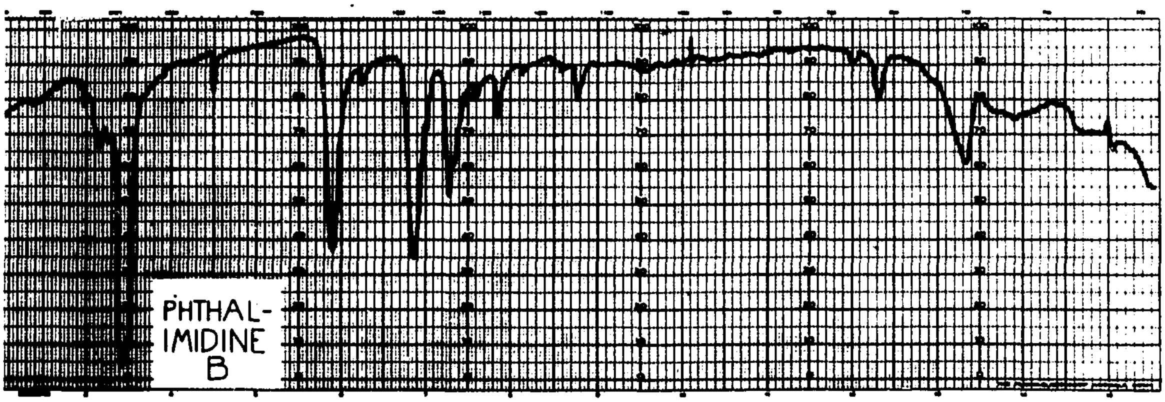
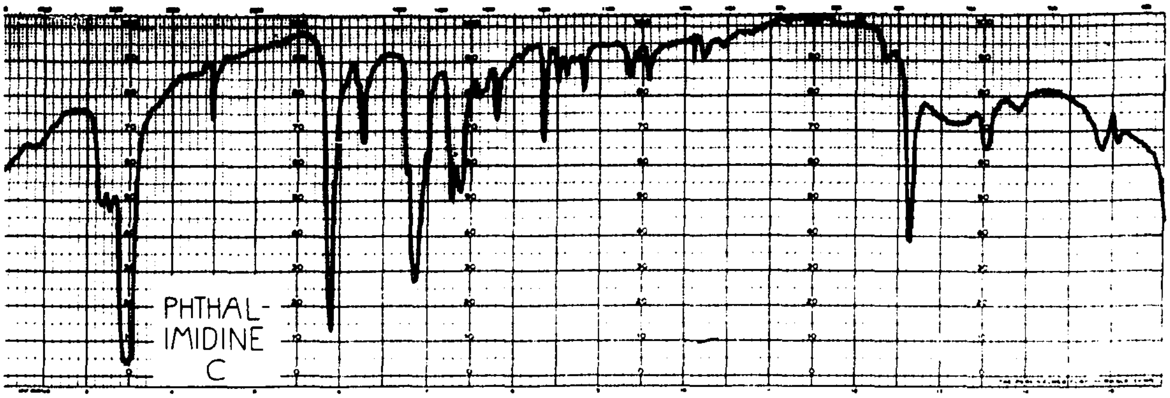
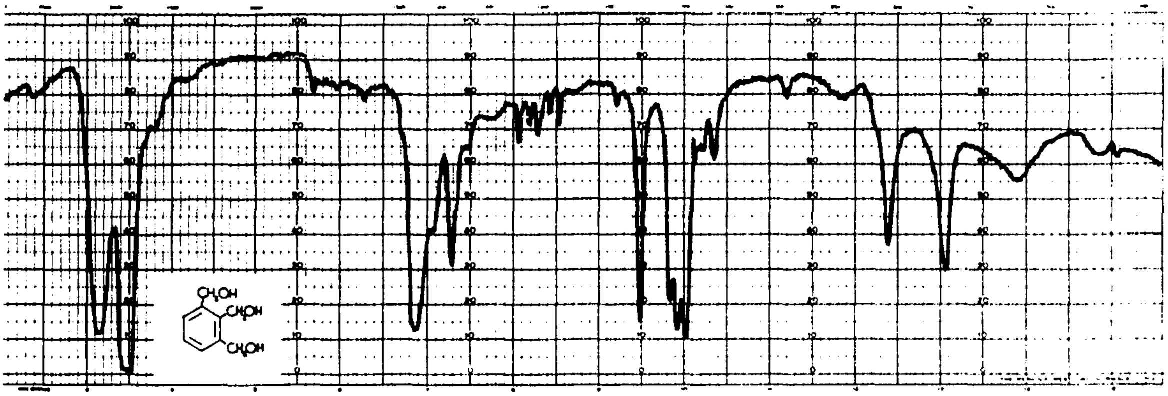

PHTHAL-
IMIDINE
B

Figure 3. Infrared spectra


PHTHAL-
IMIDINE
C


CH2OH
CH2OH
CH2OH

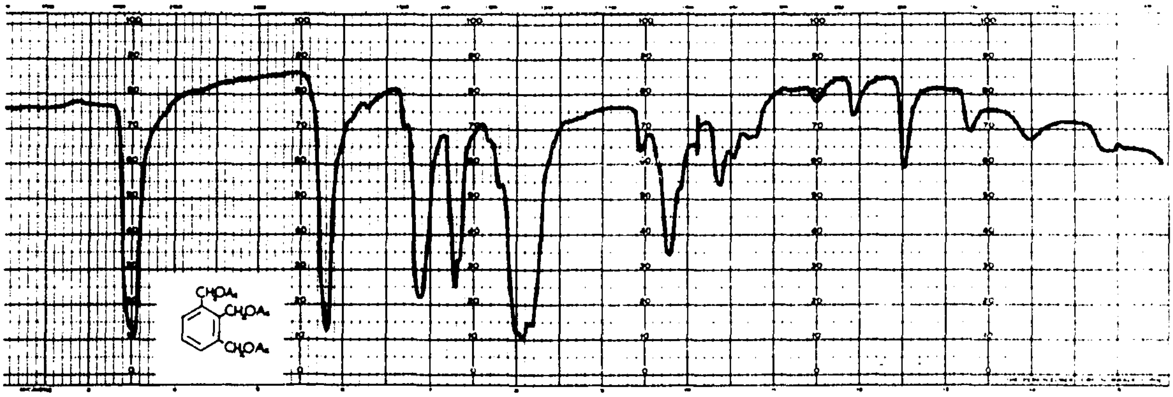
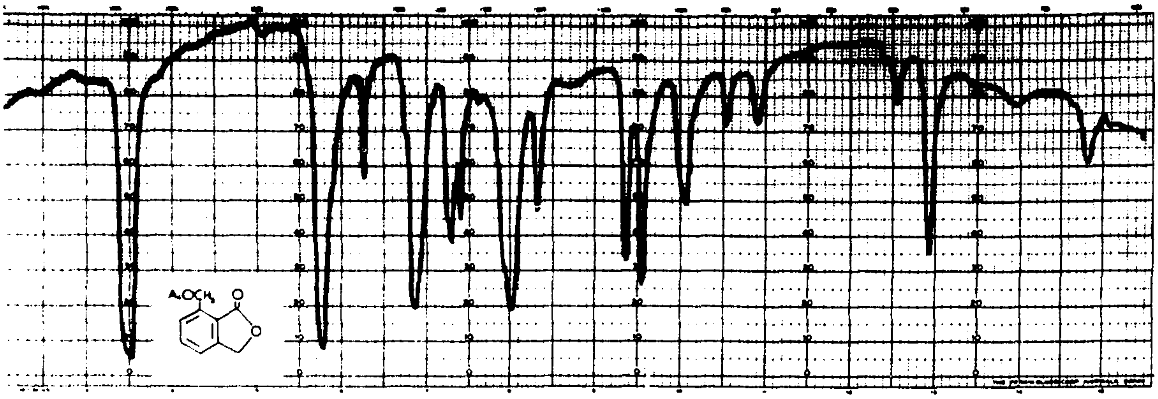
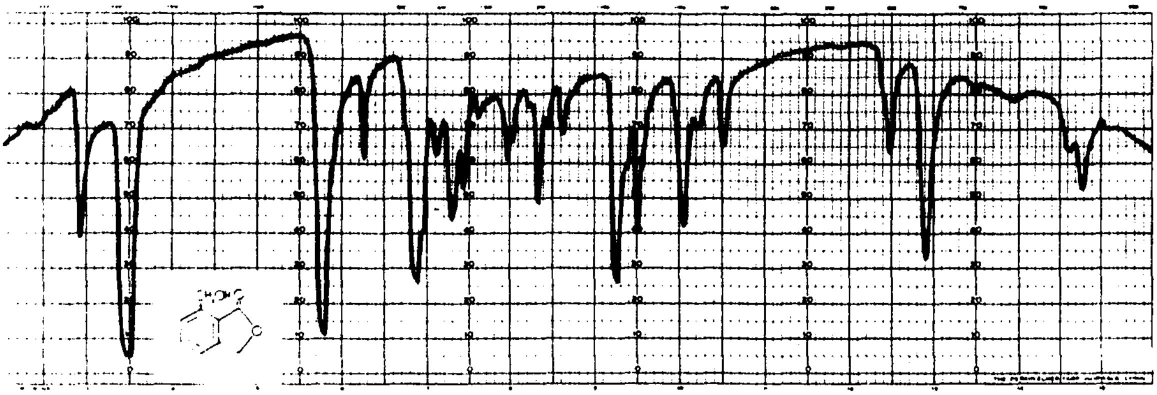

CH2OAc
CH2OAc
CH2OAc

Figure 4. Infrared spectra


AcOCH₂



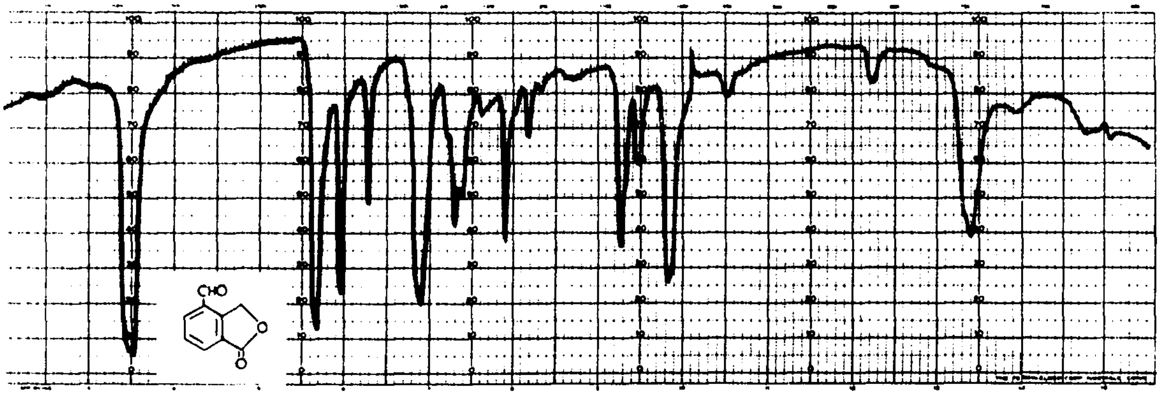
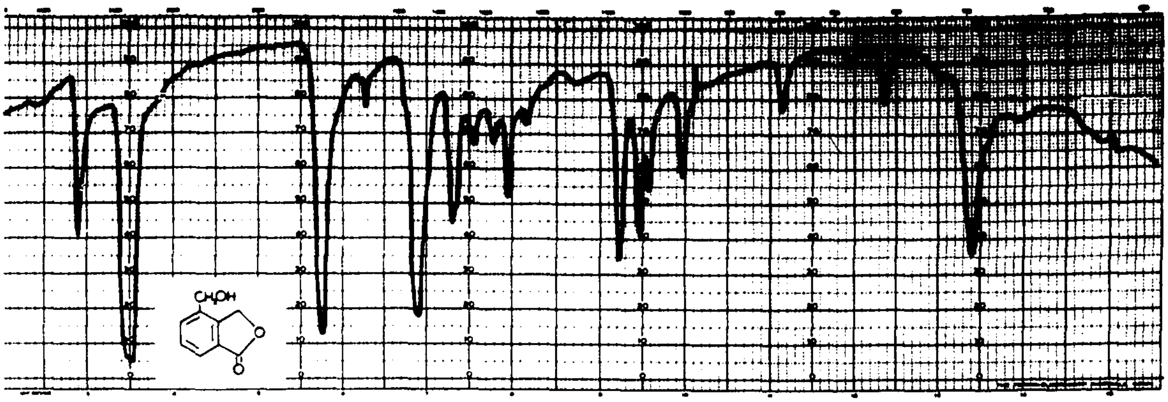
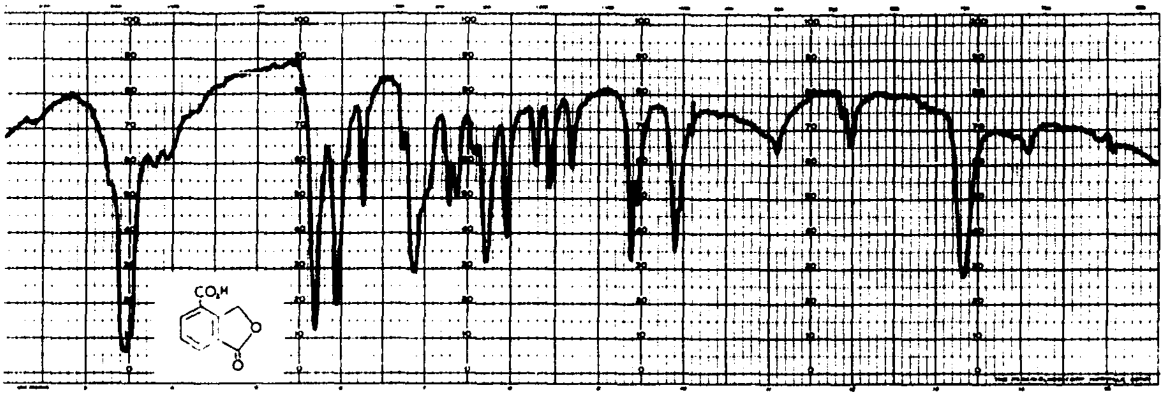

CHO

Figure 5. Infrared spectra


CH_2OH


CO_2H

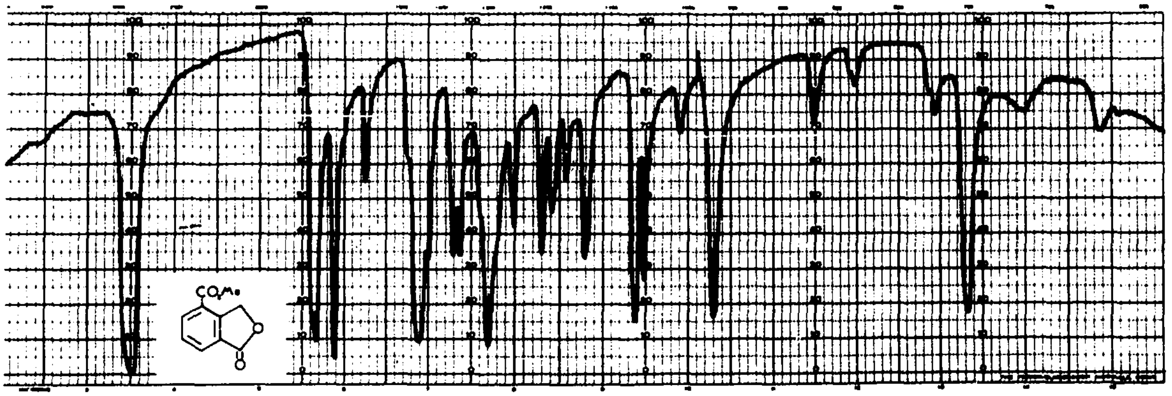
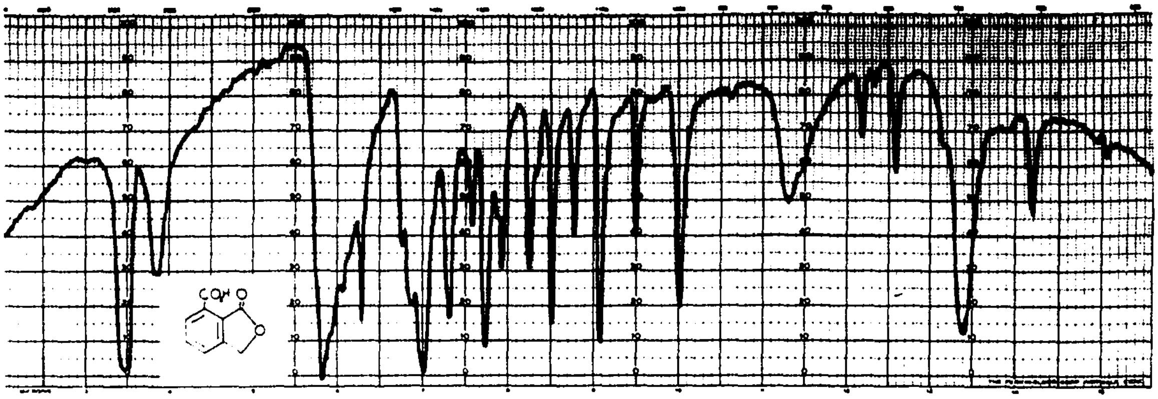
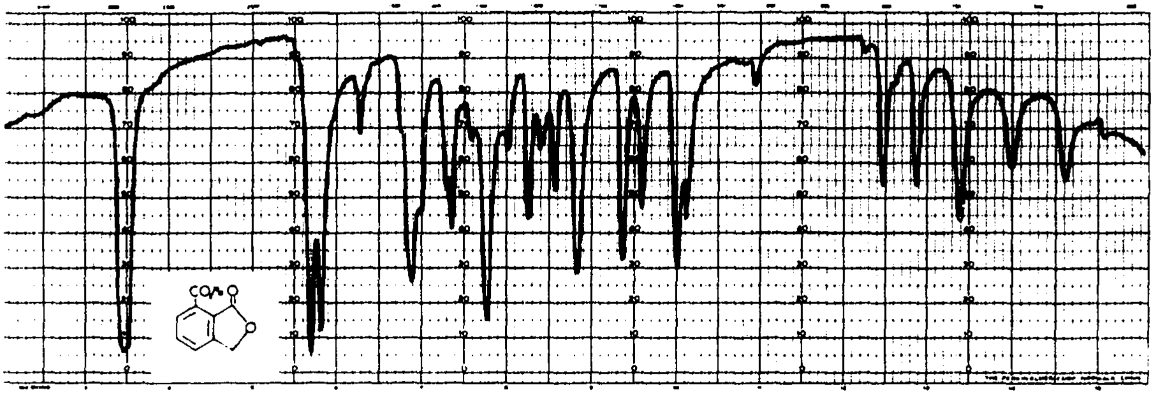

CO_2Me

Figure 6. Infrared spectra


CO2H
O


CO2Me
O

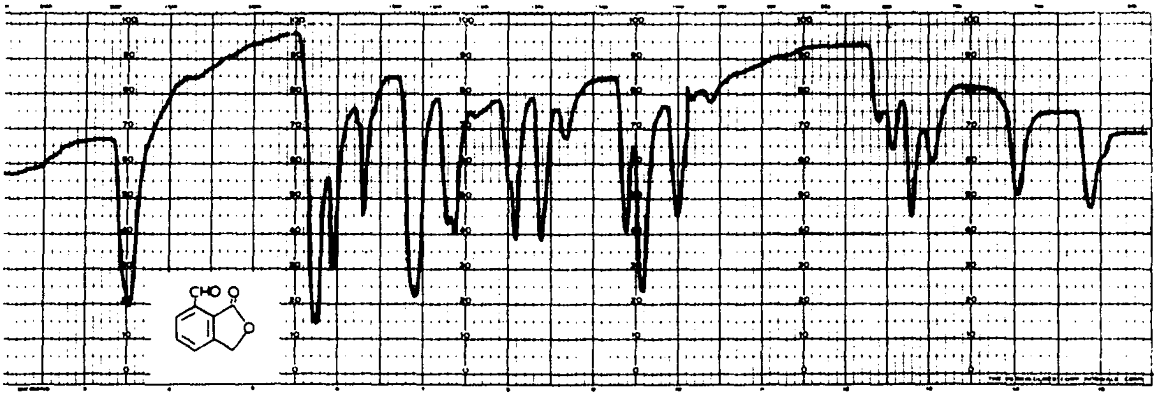
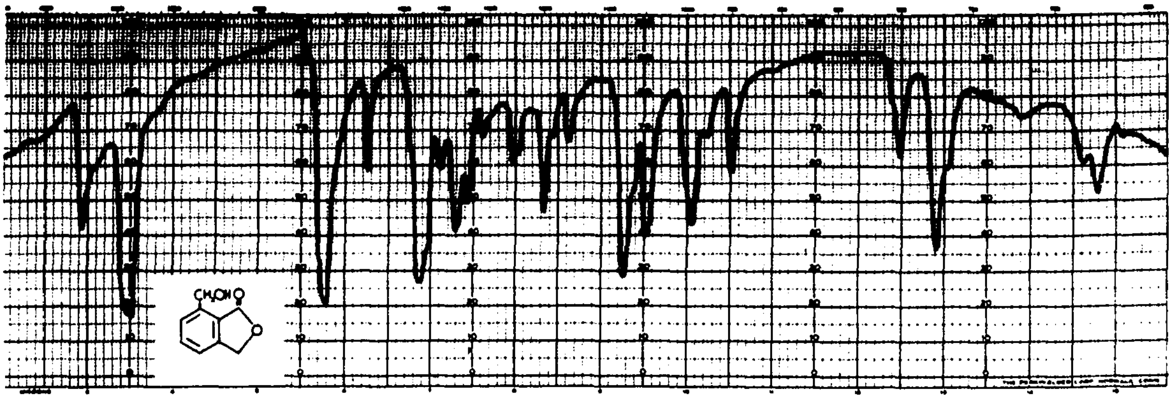
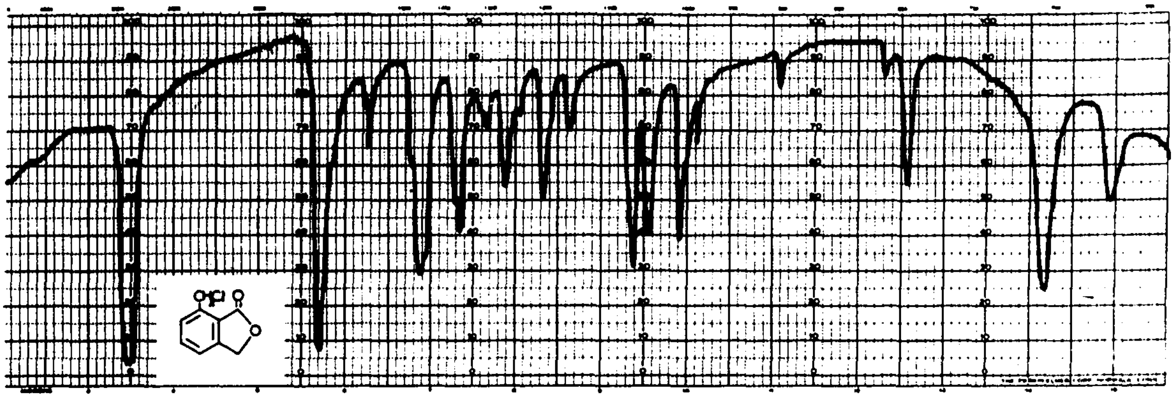

CHO
O

Figure 7. Infrared spectra


CH2OH



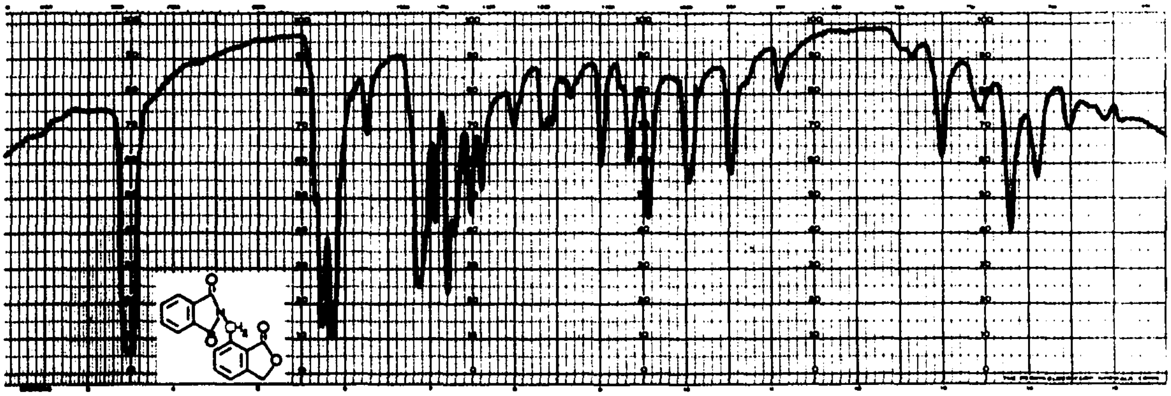
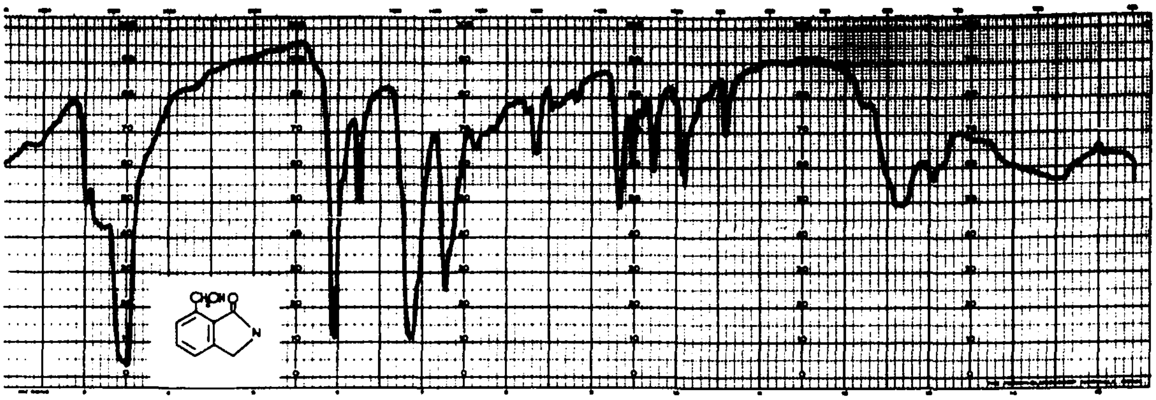
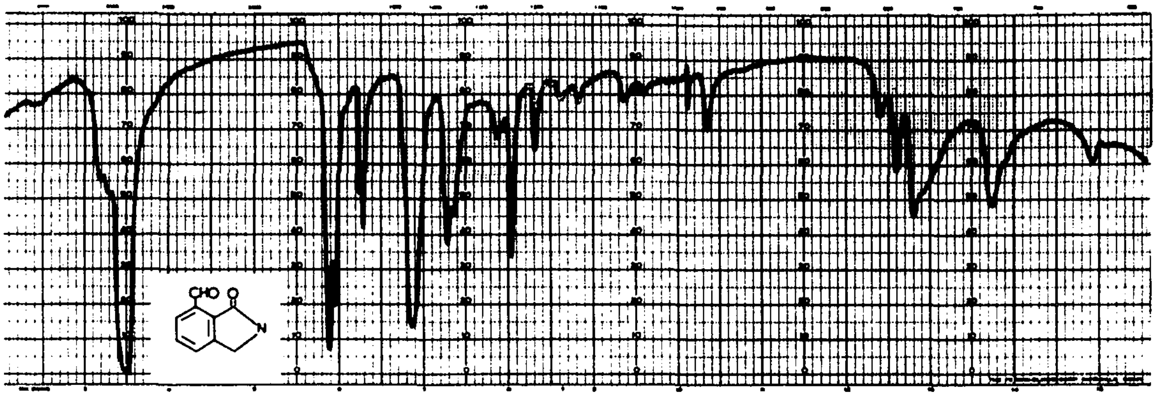


Figure 8. Infrared spectra


CHOH
O
N


CHO
O
N

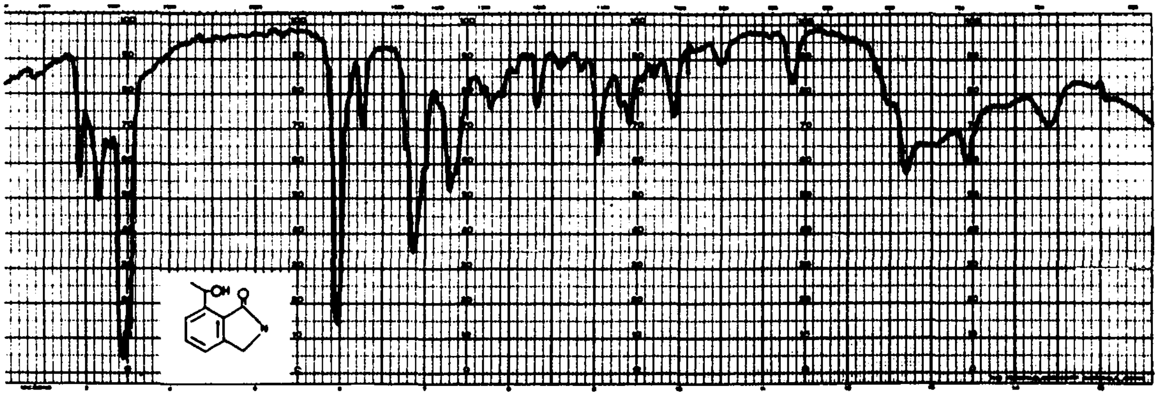
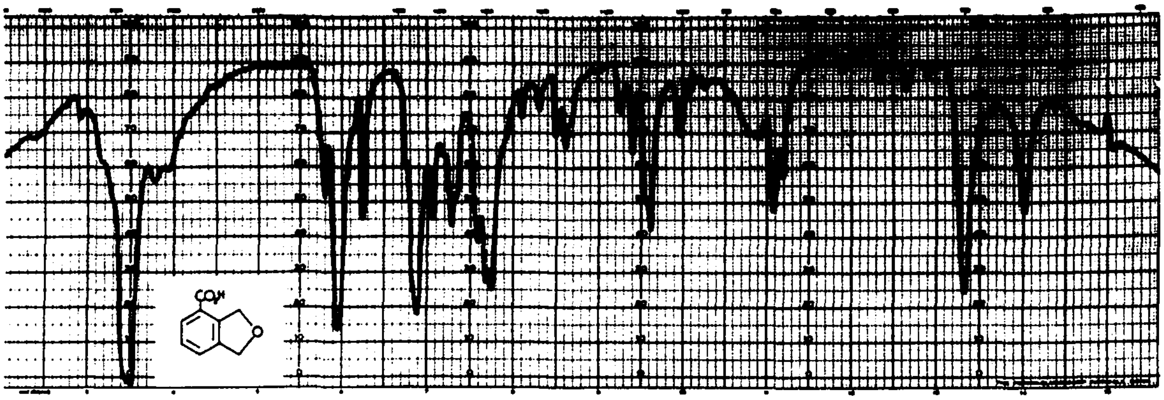
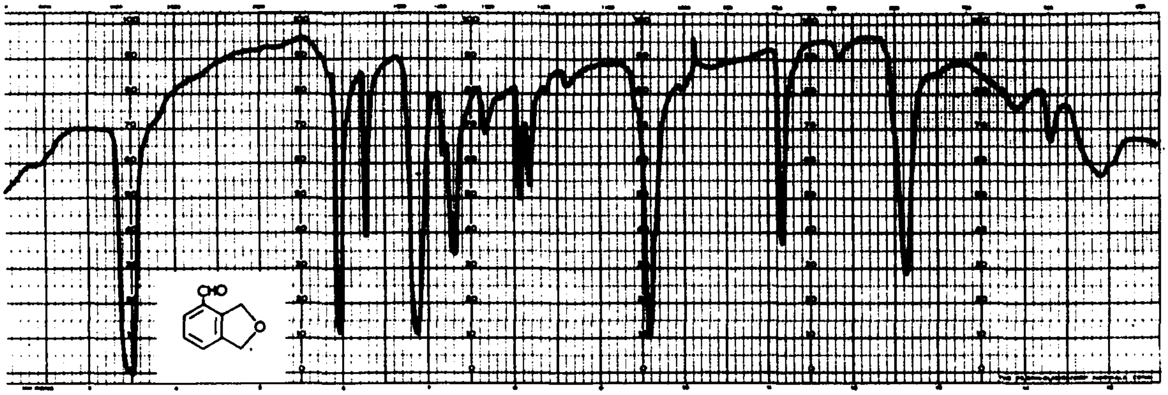

OH
O
N

Figure 9. Infrared spectra


CO₂H


CHO

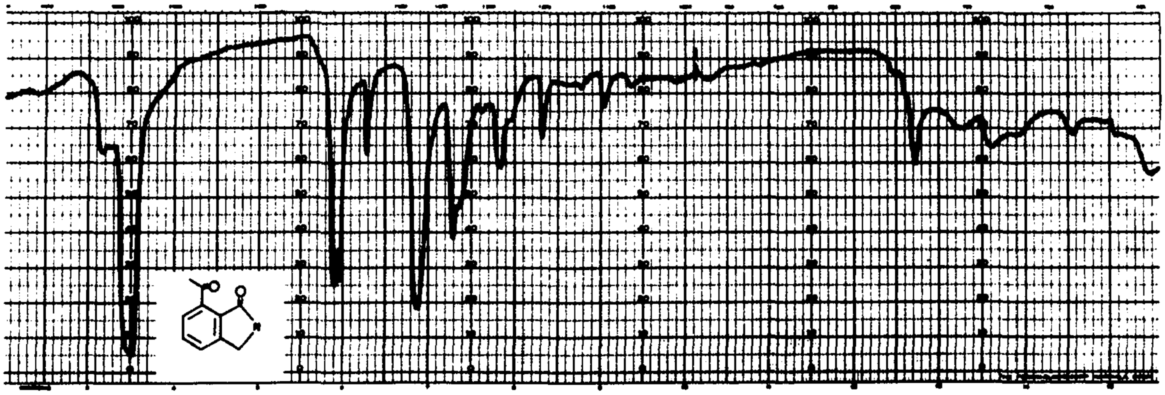
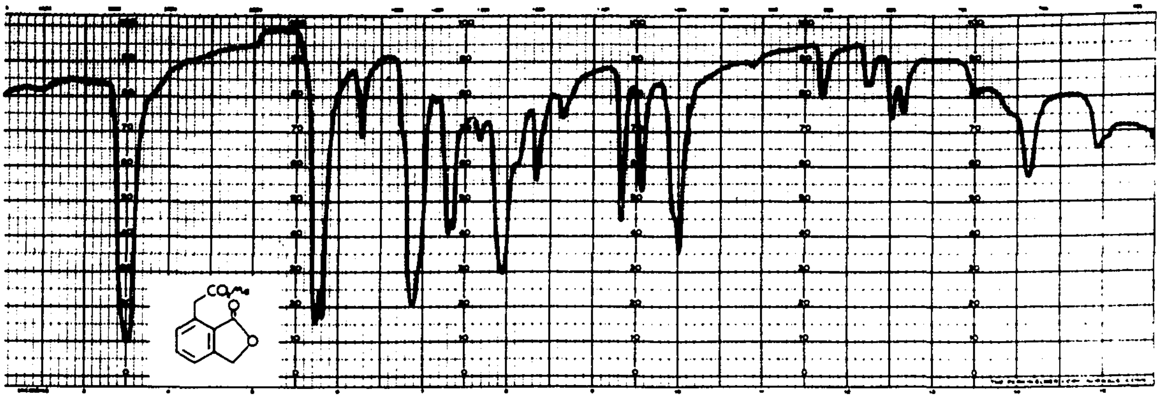
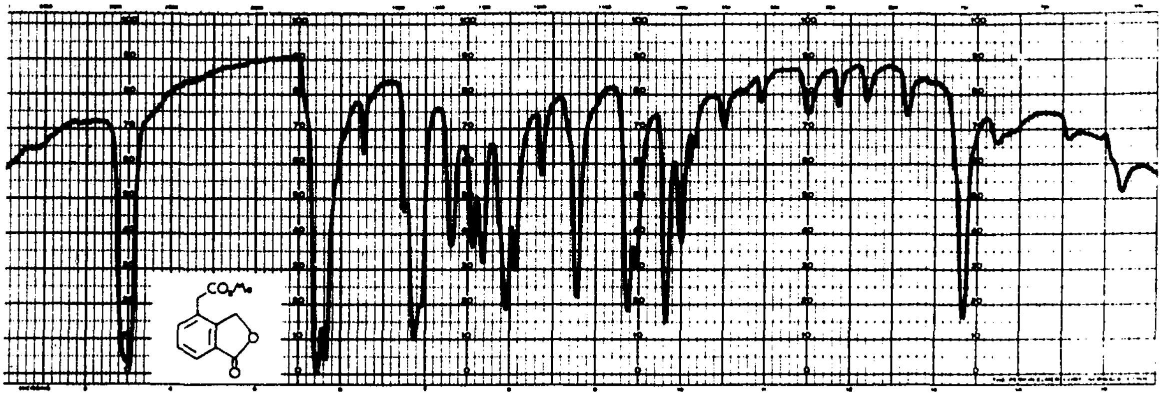


Figure 10. Infrared spectra


CO2Me
O
O


CO2Me
O
O

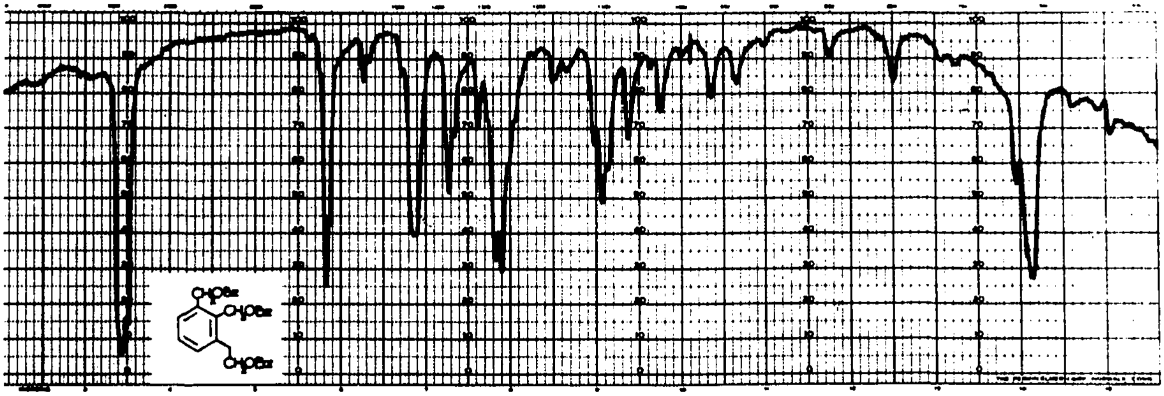
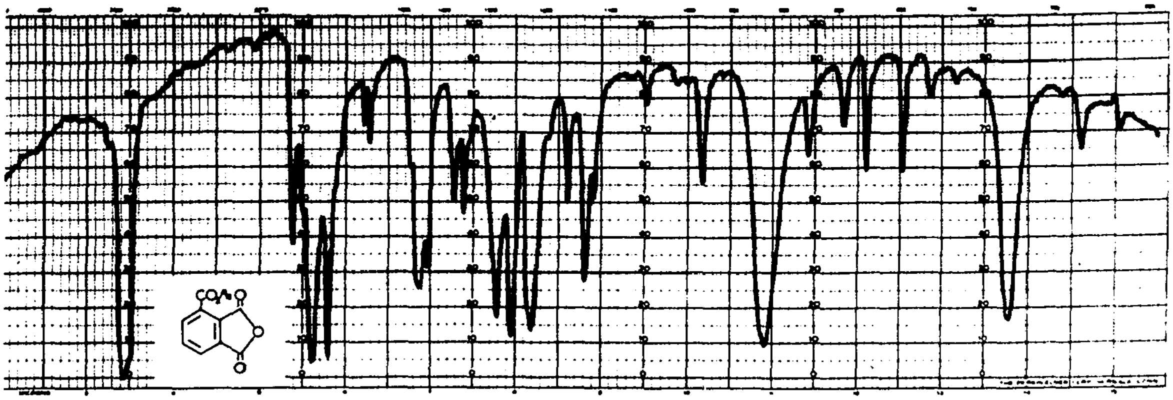
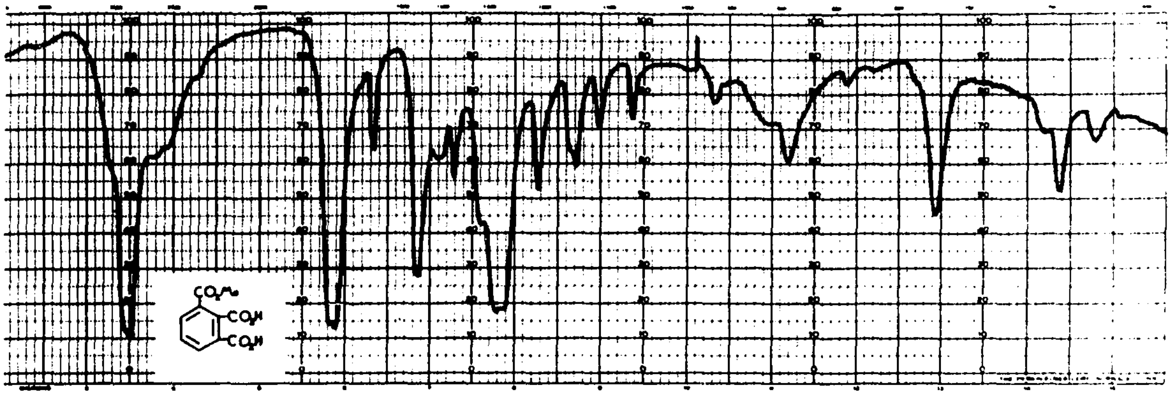

CH2OBz
CH2OBz
CH2OBz

Figure 11. Infrared spectra


CO₂Me


CO₂Me
CO₂H
CO₂H

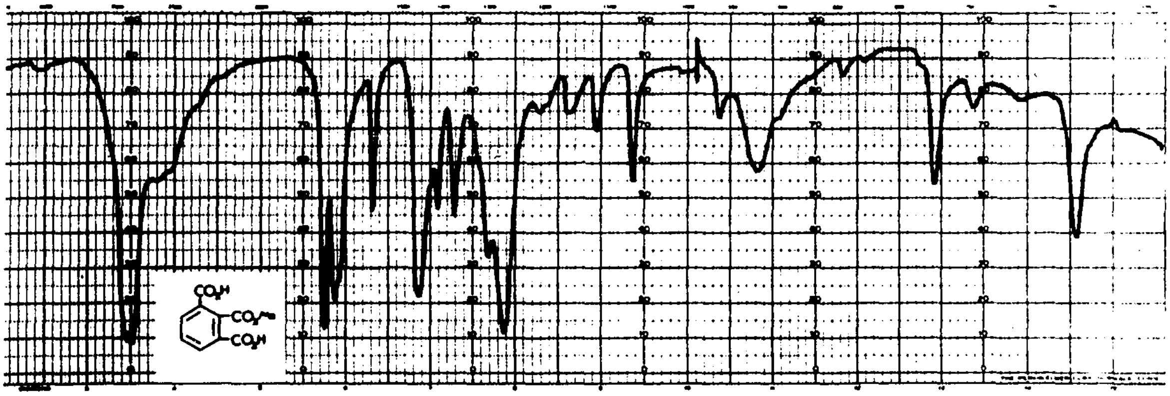
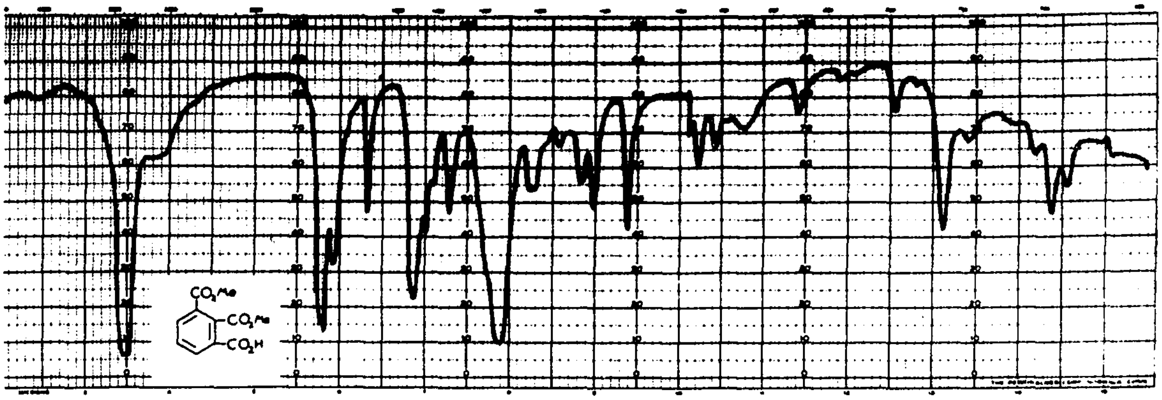
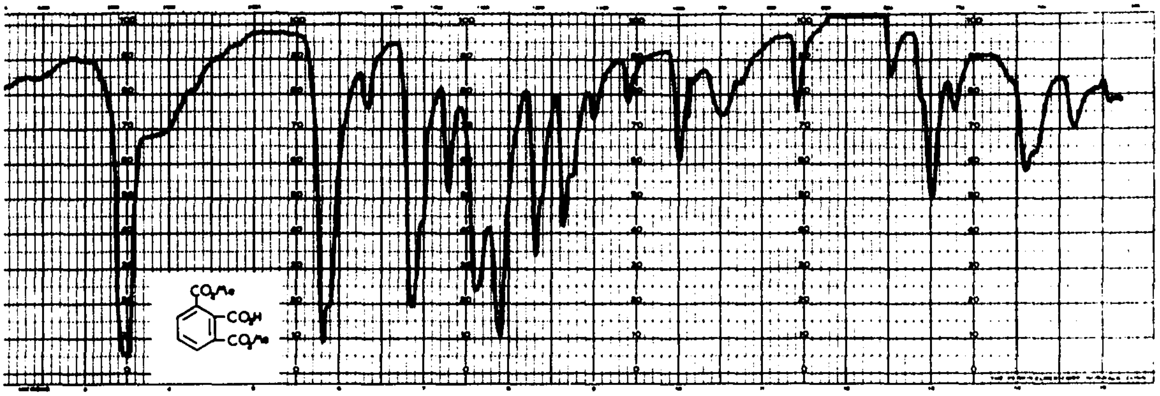

CO₂H
CO₂Me
CO₂H

Figure 12. Infrared spectra


CO_2Me
CO_2Me
CO_2H


CO_2Me
CO_2H
CO_2Me

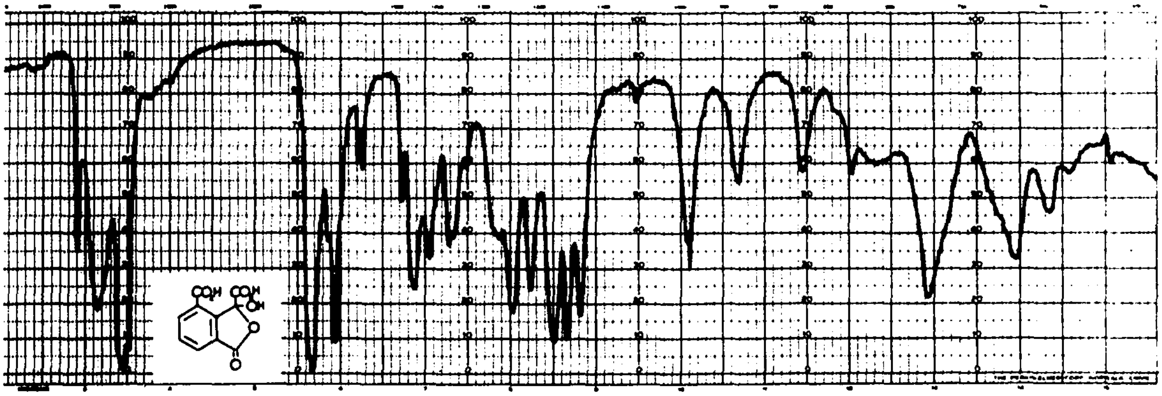
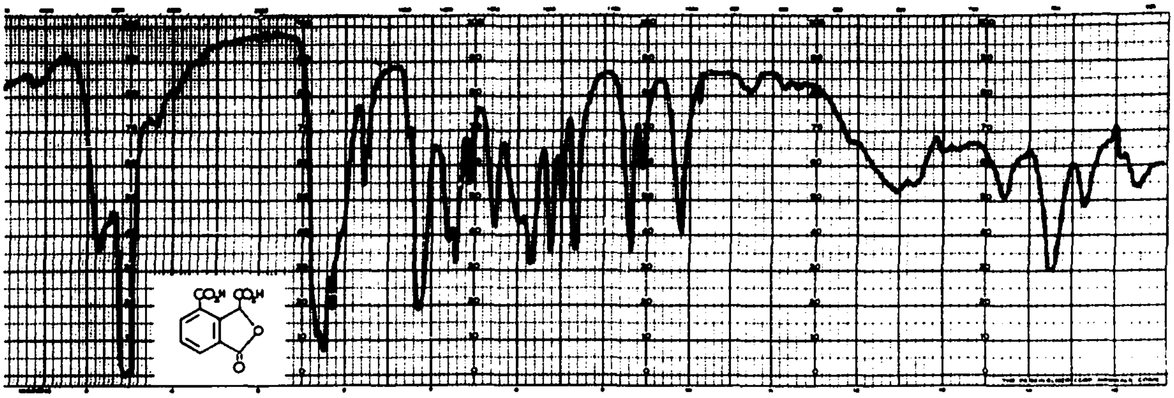
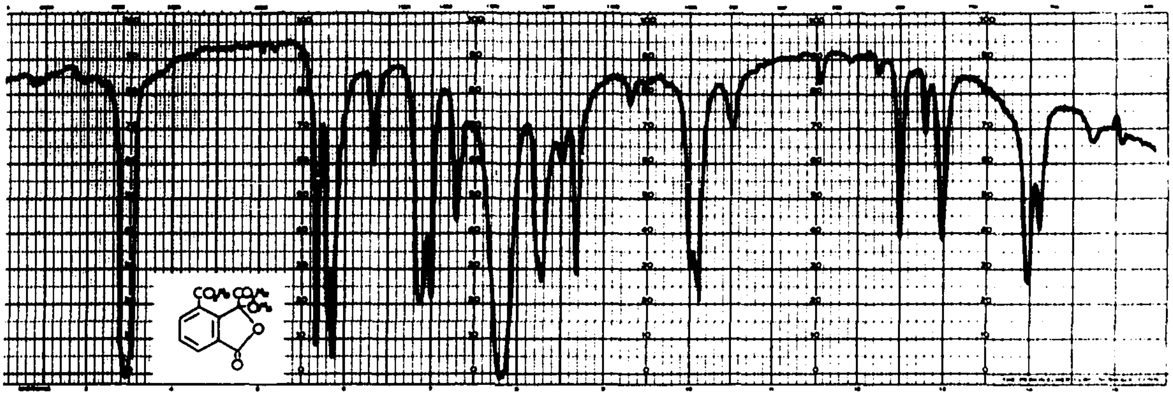

CO_2H
CO_2H
OH
O
O

Figure 13. Infrared spectra


CO2H CO2H


CO2Me CO2Me

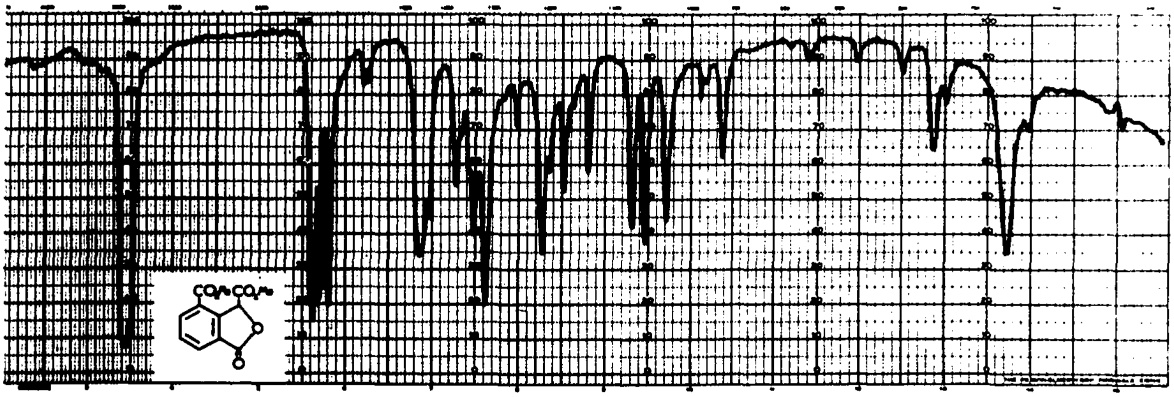
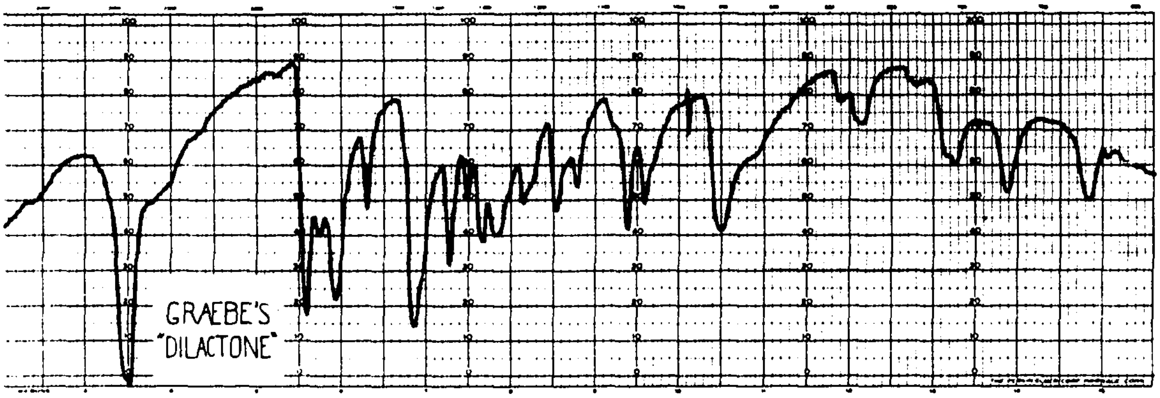
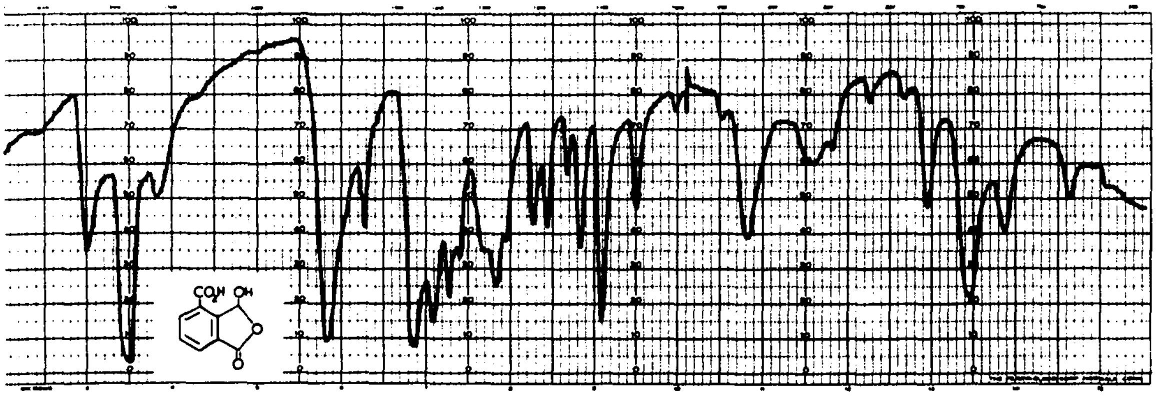
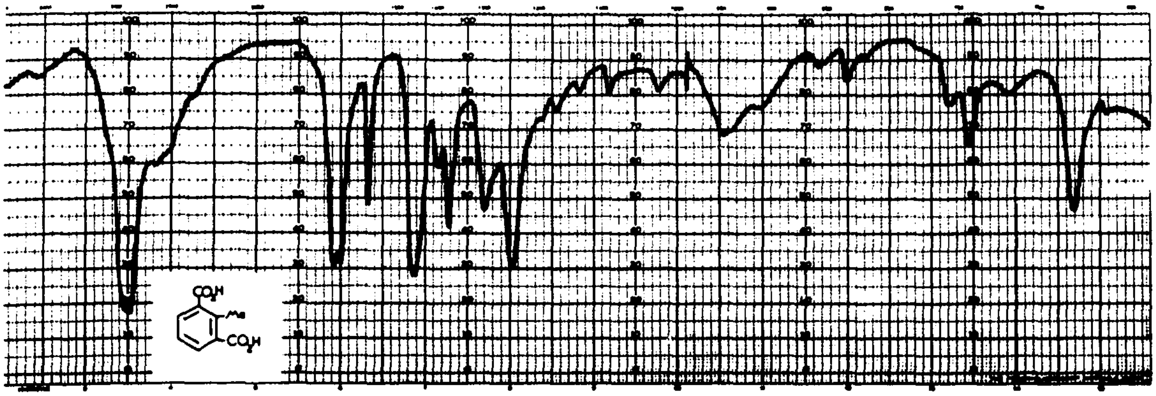

CO2Me CO2Me

Figure 14. Infrared spectra


GRAEBE'S
"DILACTONE"


CO₂H
OH
O
O


CO₂H
Me
CO₂H

EXPERIMENTAL

All melting points are uncorrected. They were taken on a Kofler micro hot stage with a polarizing microscope.

Micro-analyses were carried out by Mr. L. Dorfman of CIBA Pharmaceutical Laboratories, Summit, New Jersey.

"Sk.B" refers to Skellysolve B, a petroleum fraction with a boiling point of 60-70° C.

"Preadsorbed and chromatographed" refers to the following process. The material to be chromatographed was dissolved in a very small volume of a convenient volatile solvent. A few drops of the solution were added to ca. 5% of the adsorbent to be used in the chromatography. Care was taken to avoid wetting the walls of the beaker with solution. The dampened adsorbent was gently stirred and crushed with a spatula to hasten the evaporation of solvent. When the adsorbent was dry, a few more drops of solution were added and the process repeated. After all the solution had been added, the preparation was a free flowing powder. The chromatographic column was then prepared in the usual way and the preadsorbed material added as the last portion of adsorbent prior to the final layer of sand. Elution was carried out in the manner indicated.

Dry diglyme (diethylene glycol dimethyl ether) was prepared by stirring the crude ether (obtained from Eastman Kodak Co.) for several hours with $LiAlH_4$. The material then was distilled under reduced pressure and stored over sodium wire. Note: Distillation of diglyme from $LiAlH_4$ has led to explosions (51). No difficulty was encountered in These Laboratories, but the following precautions were taken:

1. The distillation was carried out behind a safety shield in a hood and safety goggles were used.
2. The distillation was carried out under reduced pressure (aspirator) to avoid undue heating.
3. The heat was supplied by an oil bath so that local hot-spots could not develop.
4. The ether-hydride mixture was stirred vigorously with a magnetic stirrer to prevent bumping and local overheating.
5. The ether-hydride mixture WAS NOT TAKEN TO DRYNESS.

It is advised that this procedure be employed only with recently purchased material or that suitable precautions be taken to avoid the unnecessary risk of having peroxides present.

Adsorbents for Chromatography

Alumina, 80-200 mesh, was allowed to stand with ethyl acetate for 48 hours. It was then washed with water and methanol, and dried at 110° for 24 hours. The same bottle of alumina was used over a 2-3 year period without reactivation.

Silicic acid, 50-200 mesh, was purchased from the G. Frederic Smith Chemical Co., Columbus, Ohio.

1-Benzenesulfonamidomethyl-2-_endo_-hydroxy-5-_endo_-acetyl-6-_endo_-carboxy-7-oxa[2.2.1]bicycloheptane γ-Lactone (XLIV)

By slight modifications of Liu's procedures (see Historical), 1-benzenesulfonamidomethyl-2-_endo_-hydroxy-5-_endo_-chloroacetyl-6-_endo_-carboxy-7-oxa[2.2.1]bicycloheptane γ-lactone (XLIII) was prepared. A mixture of 407 mg. of chloromethyl ketone, 180 mg. of $NaHCO_3$ and 180 mg. of 5% palladium on charcol was suspended in 25 ml. of freshly distilled tetrahydrofuran. The compound was hydrogenated in a Parr hydrogenation apparatus, after flushing the system thoroughly with hydrogen, at 50 p.s.i.g. and room temperature for 24 hours. The reaction mixture was filtered and the filtrate taken to dryness under reduced pressure. The residue was dissolved in methanol, the solution concentrated, and allowed to cool. A crystalline product was obtained, m.p. 182-191°. Concentration of the mother liquors afforded two additional crops of material, to give an overall yield of 304 mg. On one occasion, crystallization from water-methanol afforded material with m.p. 148-152°. Repeated crystallization from methanol yielded an analytical sample, m.p. 188-191° d., which exhibited an infrared spectrum (see Discussion) consistent with the assigned structure.

Anal.

Calculated for $C_{16}H_{17}O_6NS$: C, 54.70; H, 4.88; N, 3.99. Found: C, 54.90; H, 4.87; N, 3.97.

3-Benzenesulfonamidomethyl-
2-carboxyacetophenone (XLVI)

In a three-neck flask equipped with N_2 inlet, reflux condenser, magnetic stirrer and an oil heating bath there was placed 48 mg. of XLIV and 5 ml. of dry t-butanol. The mixture was warmed and stirred under N_2 until a homogeneous thin paste was obtained. To this was quickly added 0.4 ml. of a 1.01 M solution of potassium t-butoxide in t-butanol, with stirring. A yellow coloration rapidly developed and persisted throughout the reaction. The slurry was stirred and heated at 80-90° under N_2 for 3 hours, after which time 0.3 ml. of 3 M HCl was added, with stirring, and refluxing resumed and continued for 4 hours. The reaction mixture was then taken to dryness under reduced pressure, and partitioned between 3 ml. of 3 M HCl and 3 ml. of $CHCl_3$. The aqueous layer was removed and extracted two more times with 3 ml. of $CHCl_3$. The combined organic extracts were treated with $MgSO_4$ and taken to dryness under reduced pressure, yielding 24 mg. of oil. The oil was diluted with a few drops of acetone and preadsorbed and chromatographed on 0.6 g. of silicic acid. The column was eluted with 50 ml. portions of the following eluents: Sk.B, Sk.B-ether 8:2, Sk.B-ether 6:4, Sk.B-ether 4:6, Sk.B-ether 2:8, ether, ether-$CHCl_3$ 8:2, ether-$CHCl_3$ 6:4, ether-$CHCl_3$ 4:6, ether-$CHCl_3$ 2:8, $CHCl_3$. The eluates were evaporated and the residues taken up in $CHCl_3$. When these solutions were allowed to evaporate slowly by standing for several days, crystals formed in the 60% ether in Sk.B and 80% $CHCl_3$ in ether fractions, which were used to seed the intermediate fractions. The crude crystalline product, ca. 4 mg., m.p. 190-197°, was crystallized several times from acetone. The analytical sample had m.p. 201-202°, and exhibited an infrared spectrum (see figure 1) consistent with the assigned structure.

Anal.

Calculated for $C_{16}H_{15}O_5NS$: C, 57.64; H, 4.53. Found: C, 57.57; H, 4.81.

Reaction of Ammonia With Hemimellitic Anhydride (XVII) at 250° C.

Hemimellitic acid (IV), 938 mg., was placed into a large test-tube and heated, at first slowly, with an oil bath until a temperature of 250° was attained. Anhydrous ammonia was bubbled into the melt below its surface through a large bore glass tube, until the mixture set to a dry, hard solid. It was cooled and extracted twice with 5 ml. portions of 10% ammonium hydroxide. The residue was dried by warming under reduced pressure to yield 300 mg. of crude 4-carboxamidophthalimide (LX) m.p. ca. 330° with rapid sublimation. Although generally satisfactory for further reactions, the product could be recrystallized from water. Large excesses of water and prolonged boiling had to be avoided because of the compound's ready autocatalytic hydrolysis. Repeated crystallization from water afforded an analytical sample, m.p. 332-335° (with sublimation), with an infrared spectrum (see figure 2) consistent with the assigned structure.

Anal.

Calculated for $C_9H_6O_3N_2$: C, 56.84; H, 3.18; H, 14.73. Found: C, 56.87; H, 3.45; N, 14.92.

The ammoniacal extracts were combined and concentrated under reduced pressure. Upon acidification, 4-carboxyphthalimide (XVIII) was obtained. The yield depended upon the degree of concentration and the amount of heating employed. Crystallization from water several times afforded an analytical sample, m.p. 240-242°, (Lit. 247°) (7) with an infrared spectrum (see figure 1) consistent with the assigned structure.

Anal.

Calculated for $C_9H_5O_4N$: C, 56.55; H, 2.64. Found: C, 56.43; H, 2.82.

Further concentration of the mother liquors yielded mixtures of 4-carboxyphthalimide (XVIII) and monoammonium hemimellitate. The latter was readily separable from the former because of its greater solubility in hot water, and was isolated and purified. Repeated crystallization from water afforded an analytical sample which upon heating lost water at ca. 180°, melted at ca. 190°, but resolidified and remelted at ca. 235°. The infrared spectrum showed only a single sharp peak at 5.80μ in the carbonyl region, and broad and complex absorption in the 6.4μ region.

Anal.

Calculated for $C_9H_9O_6N$: C, 47.58; H, 3.99; N, 6.17. Found: C, 47.62; H, 4.02; N, 6.01.

Monoammonium hemimellitate was heated and fused at 250°. Crystallization of the fusion residue from water afforded a compound identical in melting point and infrared spectrum with 4-carboxyphthalimide (XVIII). Upon admixture, the melting points were not depressed.

4-Carboxamidophthalimide (IX) from
4-Carboxyphthalimide (XVIII)

A mixture of 378 mg. of 4-carboxyphthalimide (XVIII) and 5 ml. of freshly distilled thionyl chloride was heated at 80-90° for 4 hours. The homogeneous reaction mixture was taken to dryness under reduced pressure and the crystalline residue dissolved in 5 ml. of tetrahydrofuran, freshly distilled from $LiAlH_4$. The solution then was added dropwise to 10 ml. of a rapidly stirred ice-cold solution of ammonium hydroxide. The reaction mixture was allowed to come to room temperature and was concentrated to one third of its volume under reduced pressure with a minimum of heating. The resultant slurry was centrifuged and the precipitate washed once with 1 ml. of ice-cold water to give 284 mg. of crude 4-carboxamidophthalimide

(IX), m.p. 331-333° (with sublimation). The material was identical in melting point and infrared spectrum with the 4-carboxamidophthalimide (IX) obtained above. Upon admixture, their melting points were not depressed.

4-Cyanophthalimide (LVII)

A mixture of 2.43 g. of 4-carboxamidophthalimide (IX) and 30 ml. of freshly distilled phosphorus oxychloride was stirred and heated at 110-120° for 12 hours. The reaction mixture was concentrated under reduced pressure to 10 ml. and, after cooling, treated with 50 ml. of cold water. The two-phase system was rapidly stirred until vigorous hydrolysis took place, whereupon the homogeneous solution was concentrated under reduced pressure and extracted exhaustively with $CHCl_3$. The extracts were combined, treated with $MgSO_4$, and taken to dryness under reduced pressure. The yield of crude nitrile (LVII) was 1.4 g. Repeated crystallization from methanol afforded an analytical sample, m.p. 232-233°, with an infrared spectrum (see figure 2) consistent with the assigned structure.

Anal.

Calculated for $C_9H_4O_2N_2$: C, 62.79; H, 2.34; N, 16.28. Found: C, 62.93; H, 2.47; N, 16.37.

Zinc-Acetic Acid Reduction of
4-Cyanophthalimide (LVII)

Into a large test-tube equipped with a magnetic stirring bar, there was placed 171 mg. of 4-cyanophthalimide (LVII) and 1.4 ml. of acetic acid. The mixture was stirred and heated to gentle refluxing. Over a 45 minute period 315 mg. of zinc dust was added cautiously, and the reaction mixture was then allowed to stir and reflux for an additional 45 minutes.

The reaction mixture was cooled and the supernatent solution decanted, the precipitate washed several times with tetrahydrofuran and the combined liquors and washing taken to dryness under reduced pressure. The residue was extracted several times with tetrahydrofuran, the extract concentrated, and the solution preadsorbed and chromatographed on 6 g. of silicic acid. Since elution did not afford separation, all eluates, Sk.B through ether and $CHCl_3$, were combined and evaporated. A tetrahydrofuran solution of the oil, 138 mg., was preadsorbed and chromatographed on 5 g. alumina. The column was eluted with 125 ml. fractions of eluents. Sk.B afforded nothing, while the first 20% ether in Sk.B afforded a trace of needlelike crystals, too few to characterize. Three further fractions of 20% ether failed to elute any solid material. Two fractions each of 40, 50, 60, 80, and 100% ether in Sk.B afforded only traces of oils, as did the two 20% chloroform-ether fractions. The first 40% chloroform-ether fraction afforded a trace of solid, while a substantial portion of solid was obtained in the second. The six 50% chloroform-ether, two 75% chloroform-ether, two 80% chloroform-ether, two 100% chloroform, two 100% acetone, and methanol fractions all contained large quantities of solids. Crystallization of the first 50% $CHCl_3$-ether fraction from benzene led to a compound, m.p. 202-204° which exhibited an infrared spectrum with peaks at 3.1, 3.2, 4.5 and 5.8μ and was designated phthalimidine A. A solution of 1.6 mg. of phthalimidine A in 0.2 ml. of methanol, 0.6 ml. of water and 1.0 ml. of 3 M HCl was heated on the steam bath for 12 hours, evaporated to dryness and the residue extracted with tetrahydrofuran. Evaporation of the extracts yielded a solid profuct which had an infrared spectrum with peaks at 3.8 and 3.95μ(carboxyl OH), 5.63 and 5.93μ. The spectrum did not correspond to that of any compounds obtained previously. Crystallization of the sixth 50% ether-chloroform fraction afforded a solid with m.p. 247-250°. Upon admixture with phthalimidine A, the melting point of the second compound was depressed. Since it exhibited an infrared spectrum (see figure 2) consistent with a phthalimidine nitrile, it was designated phthalimidine B. Attempts to hydrolyze the compound with base failed to afford crystalline material. Upon recrystallization from acetone, an analytical sample, m.p. 245-248° was obtained.

Anal.

Calculated for $C_9H_6ON_2$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.44; H, 3.96; N, 17.55.

Crystallization of the residue from the second chloroform fraction from acetone afforded a third compound, m.p. 233-235°, which exhibited a depression of melting point upon admixture with phthalimidine B, and an infrared spectrum (see figure 3) consistent with a phthalimidine nitrile. Attempts to hydrolyze the compound with base failed to afford crystalline material. The compound was designated phthalimidine C.

Anal.

Calculated for $C_9H_6ON_2$: C, 68.35; H, 3.82. Found: C, 68.13; H, 3.97.

The methanol fraction contained a small quantity of material which was crystallized only with partial success to give m.p. 215-222°. Upon admixture with phthalimidine C and with 4-cyanophthalimide (LVII), melting point depression was observed. The compound exhibited an infrared spectrum with a broad peak at 2.9-3.3μ (NH and/or OH), 4.5μ (CN) and 5.9μ (phthalimidine carbonyl). The compound was designated as phthalimidine D.

It was not characterized any further.

Zinc-Acetic Acid Reduction of Hemimellitic Anhydride (XVII)

A solution of hemimellitic anhydride (XVII), from fusion of 2 g. of hemimellitic acid (IV), in 15 ml. of acetic acid was heated at reflux while 3 g. of zinc dust was added in small portions over a 45 minute period. A magnetic stirrer was employed to minimize superheating and bumping. Stirring and heating were continued for another hour, after which time the solution was decanted from unreacted zinc and taken to dryness under reduced pressure. The product was dissolved in 50 ml. of methanol, saturated with HCl gas, and the flask stoppered. After standing for 24 hours, the reaction mixture was taken to dryness under reduced pressure and partitioned between $CHCl_3$ and water. The $CHCl_3$ layer was separated from the aqueous layer, washed two more times with water and taken to dryness under reduced pressure. The solid product was dissolved in 20 ml. of methanol to which was added 50 ml. of a 10% aqueous $NaHCO_3$ solution. The reaction mixture was refluxed for 12 hours, acidified with hydrochloric acid, and taken to dryness under reduced pressure. The residue was extracted with tetrahydrofuran and the solution of phthalide acids preadsorbed and chromatographed on 30 g. of silicic acid. The column was eluted with 500 ml. portions of Sk.B, Sk.B-ether 8:2, and Sk.B-ether 7:3, yielding only oils. Generally, 4-carboxyphthalide (LXXIII) was eluted with 40-50% ether in Sk.B, while 7-carboxyphthalide (LXXII) followed with 60-70% ether in Sk.B. The last component frequently trailed and was removed quickly, once its presence in the eluates had been established, by elution with ether. After crystallization, variable quantities of the two components were found, generally 10-15% of theoretical each, with the 7-isomer slightly predominating. Upon repeated crystallization from methanol, the 7-isomer melted at 170-172°, while the 4-isomer melted at 246-247°, with crystal changes at ca. 180° and ca. 220°. In a few instances, the last crystal transformation did not take place and the sample melted at 234-236°. The infrared spectra (see figures 5 and 6) were consistent with the assigned structures.

<u>Anal.</u>

Calculated for $C_9H_6O_4$: C, 60.68; H, 3.40. Found: (7-isomer) C, 60.38; H, 3.45; (4-isomer) C, 60.80; H, 3.49.

Methyl Esters of the Phthalide Acids

The phthalide acid, in tetrahydrofuran, was treated with a solution of diazomethane in ether-tetrahydrofuran 1:1. When the yellow diazomethane color persisted, addition was stopped and the reaction mixture was taken to dryness under reduced pressure. The product was crystallized from methanol. The analytical sample of 7-carbomethoxyphthalide had m.p. 106-108°, while the 4-isomer had m.p. 179-180°. The infrared spectra (see figures 5 and 6) were consistent with the assigned structures.

<u>Anal.</u>

Calculated for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: (7-isomer) C, 62.87; H, 4.31; (4-isomer) C, 62.37; H, 4.26.

3-Methylphthalic Acid from
7-Carboxyphthalide (LXXII)

To 204 mg. of 7-carboxyphthalide (LXXII) was added 0.5 ml. of 58% HI, freshly distilled from phosphorus. After heating to 125-150°, the solution became homogeneous and heating was continued for one hour. To the darkened reaction mixture was added ca. 26 mg. of yellow phosphorus and the heating was continued. After 15 minutes the solution was colorless, while after 3 hours the solution was again opaque. Another 10-15 mg. of yellow phosphorus was added and the solution became light yellow after 15 minutes of heating. After heating for 4 more hours, the solution was still only slightly colored. While still warm, the solution was removed from the reaction vessel with a dropper, care being exercised to exclude particles of phosphorus. The solution was taken to dryness under reduced pressure, and warmed gently to dispel the residual I_2. The solid product was crystallized from methanol and upon heating underwent a crystal change at ca. 140°, and melted at 150-160° with gas evolution. After several recrystallizations, the product, 3-methylphthalic acid, melted at 159-161° (Lit. 157°) (24) and exhibited an infrared spectrum, in Nujol, with absorption at 2.82 and 2.97μ (carboxyl OH) and 6.00μ with a shoulder at 5.95μ (carboxyl carbonyl). Upon sublimation the anhydride was obtained, m.p. 116-117° (Lit. 117-118°) (52) which exhibited an infrared spectrum in Nujol with absorption at 5.52 and 5.74μ (anhydride carbonyls).

Anal.

Calculated for $C_9H_6O_3$: C, 66.67; H, 3.73. Found: C, 66.87; H, 3.94.

4-Carboxamidophthalide (LXXIV)

A mixture of 54 mg. of 4-carboxyphthalide (LXXIII) and 2 ml. of freshly distilled thionyl chloride was heated at 80-90° for 2 hours. The reaction mixture was taken to dryness under reduced pressure and the crystalline product was dissolved in 2-3 ml. of tetrahydrofuran, freshly distilled from $LiAlH_4$. The solution was added dropwise to a vigorously stirred ice-cold solution of ammonium hydroxide. The acid chloride vessel was rinsed with 2 ml. of tetrahydrofuran and the latter added to the ammonium hydroxide solution. A white precipitate formed rapidly. After stirring for 5 minutes the suspension was concentrated under reduced pressure to ca. 3 ml., and filtered. The precipitate was dissolved in methanol, the solution concentrated to 10 ml. and allowed to cool. The first crop of crystals, ca. 43 mg., melted at 290-294° after undergoing a crystal change at 240°. Concentration of the mother liquors afforded an additional 4 mg. of product. Upon repeated crystallization from methanol, an analytical sample was obtained, m.p. 294-296°, with an infrared spectrum consistent with the assigned structure (see Discussion section).

Anal.

Calculated for $C_9H_7O_3N$: C, 61.01; H, 3.98; N, 7.91. Found: C, 60.73; H, 4.15; N, 7.99.

4-Cyanophthalide (LXXV)

A mixture of 47 mg. of 4-carboxamidophthalide (LXXIV) and 3 ml. of freshly distilled phosphorus oxychloride was stirred and heated at 110-120° for 18 hours. The reaction mixture was cooled and carefully treated with water to destroy the excess reagent. The solution was cooled in an ice bath and extracted repeatedly with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated under reduced pressure. Crystallization from methanol afforded a material, m.p. 183-184°, which exhibited an infrared spectrum consistent with the assigned structure (see Discussion section). The material was not analyzed.

Sodium Borohydride Reduction of Hemimellitic Anhydride Acid Chloride (LXI)

A mixture of 147 mg. of hemimellitic anhydride (XVII) and 2 ml. of freshly distilled thionyl chloride was heated and stirred at 80-90° for 3 hours. It was taken to dryness under reduced pressure and the residue dissolved in 2-3 ml. of dry benzene. The solution was warmed, taken to dryness under reduced pressure, and the procedure repeated. The crystalline product was dissolved in 5 ml. of dry diglyme and heated to 105°. A centrifuged solution of 16.2 mg. of sodium borohydride in 12 ml. of dry diglyme was added with stirring over a 1 hour period to the heated acid chloride solution. After stirring for an additional hour the reaction mixture was treated with 10 ml. of water and taken to dryness under reduced pressure. The residue was then dried by azeotropic distillation of benzene, and extracted several times with tetrahydrofuran. The combined extracts were taken to dryness under reduced pressure to yield 185 mg. of oil which was dissolved in methanol. Concentration of the solution to an oil afforded crystals of 7-carboxyphthalide (LXXII) which were isolated by centrifugation and washed twice with small portions of ice-cold methanol. The mother liquors were combined and concentrated, yielding a second crop of 16 mg. The mother liquors were again concentrated and carefully treated with chloroform to yield 42 mg. of a fine white powder which proved to be hemimellitic acid (IV). A trace of additional solid was obtained from the oily mother liquors but was not purified.

A mixture of ca. 1 g. of mother liquors from several runs was chromatographed on ca. 25 g. of silicic acid. The column was eluted with 250 ml. fractions of eluents. Sk.B and the first 20% ether-Sk.B fraction yielded only oils. The second 20% and first 30% ether-Sk.B fractions eluted a new compound which was contaminated with hemimellitic acid. Upon repeated crystallization from acetone, an analytical sample was obtained, m.p. 207-209°. The material reacted vigorously with sodium bicarbonate and had an infrared spectrum (see figure 9) consistent with 4-carboxy-1,3-dihydroisobenzofuran (LXXVII).

Anal.

Calculated for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.94; H, 4.96.

Further elution of the column with three 30% and four 40% ether-Sk.B fractions afforded hemimellitic acid (IV), while five more 40% ether-Sk.B fractions followed by one 50% fraction afforded 7-carboxyphthalide (LXXII). Elution with more polar eluents failed to produce any other crystalline materials.

Preferred Reduction Procedure

Although the above procedure was effective in preliminary studies, it subsequently proved to be irreproducable. The following preferred procedure was developed.

A mixture of 1.57 g. hemimellitic anhydride (XVII) and 25 ml. of freshly distilled thionyl chloride was refluxed for 4 hours. The solution was taken to dryness under reduced pressure, the residue dissolved in 5 ml. of dry benzene and the solution again taken to dryness under reduced pressure. The system was flushed for 10 min. with a gentle stream of dry air, and the residue dissolved in 25 ml. of dry diglyme. The solution was heated to 120° and vigorously stirred while a solution of 5.6 ml. of 1.54 M sodium borohydride (in dry diglyme, stored over sodium wire) in 25 ml. of dry diglyme was added over a 3 minute period. The heated solution was stirred an additional 3 minutes and quickly decomposed with 10 ml. of water, the clear yellowish solution taken to dryness under reduced pressure and dried by the azeotropic distillation of benzene from the reaction vessel. Extraction of the residue with several portions of tetrahydrofuran, evaporation of the combined extracts, dissolution of the residue in methanol and concentration afforded an oil and a crystalline precipitate. The product was isolated by centrifugation and washed several times with ice-cold methanol to yield 460 mg. of material, m.p. 168-172°. Concentration of the mother liquors afforded an additional 222 mg. of 7-carboxyphthalide (LXXII). The mother liquors were generally recycled to obtain a small additional quantity of material.

Sodium Borohydride Reduction of 7-Carboxyphthalide Acid Chloride

A mixture of 544 mg. of 7-carboxyphthalide (LXXII) and 5 ml. of freshly distilled thionyl chloride was refluxed for 4 hours. The solution was taken to dryness under reduced pressure, the crystalline product dissolved in 5 ml. of dry benzene, and the solution again taken to dryness under reduced pressure. The vessel was flushed for 10 minutes with a gentle stream of dry air, after which the residue was dissolved in 10 ml. of dry diglyme and heated to 120°. A solution of 2.1 ml. of 1.54 M sodium borohydride (in dry diglyme, stored over sodium wire) in 10 ml. of dry diglyme was added with vigorous stirring over a 4 minute period to the heated acid chloride solution. The reaction mixture was allowed to stir at 120° for an additional 3 minutes, whereupon 10 ml. of water was added quickly. The solution was concentrated under reduced pressure to ca. $\frac{1}{4}$ of its original volume, 5 ml. of water and an excess of solid sodium bicarbonate was added, and the reaction mixture taken to dryness under reduced pressure. The residue was dried by the azeotropic distillation of benzene from the reaction vessel, and extracted several times with tetrahydrofuran. The residual solids were acidified with 3 M HCl, taken to dryness under reduced pressure, and dried by the azeotropic distillation of benzene from the reaction vessel. The residue was extracted with tetrahydrofuran and upon evaporation of the extract a semisolid mass was obtained. Crystallization of the material yielded 7-carboxyphthalide (LXXII) which could be used along with fresh acid in further reductions.

The tetrahydrofuran extracts obtained previously were combined and evaporated to yield 432 mg. of oily crystals. The crude alcohol from several runs was combined and crystallized from methanol. Repeated crystallization yielded an analytical sample, m.p. 111-113°, with an infrared spectrum (see figure 7) consistent with the assigned structure (LXXXVI).

Anal.

Calculated for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.57; H, 4.86.

Chromatography of the mother liquors on alumina afforded two new compounds. The first, a crystalline solid, was eluted with 20% ether-Sk.B. Recrystallization from ether gave material with m.p. 115-117° and an infrared spectrum (see figure 9) suggesting the presence of only one nonphthalide carbonyl. A small portion was treated with Tollens' reagent, yielding slowly a fine black precipitate of metallic silver. When precipitation seemed complete, the solution was acidified with hydrochloric acid and centrifuged. After removal of the supernatent liquid, the solid was washed several times with tetrahydrofuran and the combined washing and aqueous solution taken to dryness under reduced pressure. A small quantity of semisolid material was obtained which, upon recrystallization from acetone, had a melting point near 205°. Though insufficient for further recrystallization, the melting point was elevated upon admixture with authentic 4-carboxy-1,3-dihydroisobenzofuran (LXXVII), and its infrared spectrum was identical with that of the authentic acid. It was not characterized any further. The reduction product was accordingly assigned structure LXXXVIII.

The second compound was eluted with 20-60% ether-Sk.B. It was a viscous oil which exhibited variable quantities of carbonyl absorption (depending on the sample examined) all of which were weak in comparison to the OH absorption at 2.95μ. Purification attempts revealed the material to be a low melting solid with m.p. $>28°$. Crystallization was not successful. Oxidation of the oil with MnO_2 afforded a solid, which, upon purification, proved to be identical with the aldehyde obtained above. The oil was accordingly assigned structure LXXXIX. Upon prolonged exposure to air, the oil undergoes extensive oxidation to a complex mixture of compounds.

Elution of the column with additional 60% ether afforded additional 7-hydroxymethylphthalide (LXXXVI).

4-Hydroxymethylphthalide (LXXXVII)

A mixture of 129 mg. of 4-carboxyphthalide (LXXIII) and 3 ml. of freshly distilled thionyl chloride was stirred and heated at 80-90° for 4 hours. The homogeneous solution was taken to dryness under reduced pressure and the crystalline residue dissolved in 10 ml. of dry diglyme. A solution of 45 mg. of sodium borohydride in 10 ml. of dry diglyme was prepared, and, after centrifugation, was added to the stirred acid chloride solution at 108°. After stirring and heating for 2 hours, the reaction mixture was treated with 5 ml. of water and taken to dryness under reduced pressure. The residue was extracted several times with tetrahydrofuran, the extract concentrated, preadsorbed and chromatographed on 3 g. of silicic acid. Elution with 100 ml. of Sk.B and 100 ml. of 10% ether in Sk.B afforded traces of oil. Elution with five 50 ml. fractions of 40% ether in Sk.B afforded a second solid. The solid eluted with 40% ether amounted to ca. 40 mg., and was shown to be 4-carboxyphthalide (LXXIII) by melting point, infrared spectrum, and mixed melting point with authentic material. The solid eluted with 20% ether amounted to ca. 58 mg. After repeated crystallization from ether an analytical sample of 4-hydroxymethylphthalide (LXXXVII) was obtained, m.p. 109.5-110.5°, with an infrared spectrum (see figure 5) consistent with the assigned structure.

Anal.

Calculated for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.37; H, 4.84.

7-Formylphthalide

A mixture of 40 mg. of 7-hydroxymethylphthalide (LXXXVI), 125 ml. of ether and 400 mg. of the above MnO_2 was gently refluxed with stirring for

21 hours. The MnO_2 was removed by filtration and washed several times with hot ether. The combined filtrates were taken to dryness under reduced pressure to yield 30 mg. of crystalline solid, m.p. (121) 131-132°. Repeated crystallization from ether afforded an analytical sample, m.p. 131-132°, with an infrared spectrum (see figure 6) consistent with the assigned structure.

Anal.

Calculated for $C_9H_6O_3$: C, 66.67; H, 3.73. Found: C, 66.64; H, 4.03.

4-Formylphthalide (CII)

A mixture of 15 ml. of ether, 17 mg. of 4-hydroxymethylphthalide (LXXXVII) and 133 mg. of MnO_2 (44) (kindly prepared by Houston Brooks) was gently refluxed with stirring for 13.5 hours. The MnO_2 was removed by filtration and washed several times with hot ether. The combined ether solutions were taken to dryness under reduced pressure to yield 149 mg. of crystalline solid which melted at 166-168° with sublimation after a crystal transformation at ca. 120°. Repeated crystallization from ether afforded an analytical sample, m.p. 166-168°, with an infrared spectrum (see figure 4) consistent with the assigned structure.

Anal.

Calculated for $C_9H_6O_3$: C, 66.67; H, 3.73. Found: C, 67.05; H, 3.92.

7-(2-phthalimidomethyl-)phthalide (XCV)

A solution of 40 mg. of 7-hydroxymethylphthalide (LXXXVI) in 0.2 ml. of freshly distilled thionyl chloride was allowed to stand in a loosely stoppered flask for 68 hours at room temperature. The solution was taken to dryness under reduced pressure yielding a crystalline product. Crystallization of a portion of this material from benzene afforded an analytical sample with m.p. 108-110° and with an infrared spectrum (see figure 7) consistent with 7-chloromethylphthalide (XCIV). If the reaction was allowed to stand for only 36 hours, a gummy semicrystalline mixture was obtained, presumably because of incomplete conversion.

Anal.

Calculated for $C_9H_7O_2Cl$: C, 59.19; H, 3.86. Found: C, 59.45; H, 3.93.

The crude chloromethyl compound was dissolved in 2 ml. of freshly distilled dimethylformamide and added to ca. 100 mg. of potassium phthalimide. The reaction mixture was stirred and heated for 2 hours at 105-115°, and the cloudy solution taken to dryness under reduced pressure. The residue was extracted several times with $CHCl_3$ and the combined extracts taken to dryness under reduced pressure, yielding 78 mg. of crude crystalline solid. Repeated crystallization from $CHCl_3$ afforded an analytical sample, m.p. 251-252°, which exhibited an infrared spectrum (see figure 7) consistent with the assigned structure (XCV).

Anal.

Calculated for $C_{17}H_{11}O_4N$: C, 69.62; H, 3.78; N, 4.78. Found: C, 70.05; H, 3.85; N, 4.72.

7-Hydroxymethyl Phthalmidine (XCVI)

A mixture of 350 mg. of 7-(2-phthalmidomethyl-)phthalide (XCV), 10 ml. of methanol and 0.4 ml. of anhydrous hydrazine was heated at 70° with stirring for 3 hours. The resultant slurry was cooled in ice, filtered, and the precipitate washed with a small portion of ice-cold methanol. The combined filtrates were taken to dryness to yield 243 mg. of material. Repeated crystallization afforded 73 mg. of product, m.p. 167-169°. Additional crops of product could be obtained from the mother liquors, water often proving to be a better solvent for crystallization of fractions badly contaminated with the high-melting phthalhydrazide. Recrystallization afforded an analytical sample m.p. 169-170°, with an infrared spectrum (see figure 8) consistent with the assigned structure (XCVI).

Anal.

Calculated for $C_9H_9O_2N$: C, 66.24; H, 5.56. Found: C, 66.15; H, 5.57.

7-Formylphthalimidine (XCVII)

A solution of 102 mg. of 7-hydroxymethylphthalimidine (XCVI) in 2 ml. of pyridine was added quickly and with stirring to a suspension of 105 mg. of CrO_3 in 2 ml. of pyridine. The solution darkened rapidly and the suspension dissolved. After standing for 15 hours at room temperature, the reaction mixture was shaken with 10 ml. of water and extracted five times with 10 ml. portions of $CHCl_3$. The combined extracts were treated with $MgSO_4$, filtered, and the $MgSO_4$ washed with additional $CHCl_3$ and filtered. The combined filtrates were taken to dryness under reduced pressure and the crude product preadsorbed and chromatographed on 3 g. of alumina. The column was eluted with 50 ml. fractions, five of ether eluting a trace of semisolid which was not characterized, and two of 50% $CHCl_3$-ether which eluted a trace of material. Elution with 75% $CHCl_3$-ether gave the major products. The first 7-8 fractions were relatively pure product while 9-15 became progressively richer in starting material. Fractions starting to melt above 170° were fractionally crystallized from methanol yielding material richer in product. Fractions starting to melt above 195-200° were considered pure enough for subsequent reaction. The purified product amounted to ca. 30 mg. The mother liquors and recovered starting material were reused in another oxidation. Upon repeated crystallization from methanol, an analytical sample was obtained, m.p. 211-215°, with an infrared spectrum (see figure 8) consistent with the assigned structure (XCVII).

Anal.

Calculated for $C_9H_7O_2N$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.95; H, 4.38; N, 8.57.

7-(α-hydroxyethyl-)phthalimidine (XCVIII)

To 22 mg. of magnesium and 1 ml. of ether, freshly distilled from $LiAlH_4$, was added 0.6 ml. of methyl iodide. The mixture was stirred under nitrogen until the magnesium had dissolved. A few additional pieces of magnesium were then added and stirring was maintained for an additional 45 minutes. To this mixture there was added 59 mg. of 7-formylphthalimidine (XCVII) in 10 ml. of tetrahydrofuran, freshly distilled from $LiAlH_4$. An immediate evolution of hydrogen took place and the reaction mixture assumed a yellowish color. The suspension was stirred at 80° under nitrogen for 2 hours, whereupon 5 ml. of water was added and the reaction mixture taken to dryness under reduced pressure. The residue was dissolved in 3 M HCl and extracted several times with $CHCl_3$. The $CHCl_3$ extracts were washed with water and the washings extracted with $CHCl_3$. The combined $CHCl_3$ solutions were treated with $MgSO_4$, filtered, and taken to dryness under reduced pressure yielding 76 mg. of crude product. Crystallization from water afforded ca. 25 mg. of plates with m.p. 125-133°. This material was generally employed in the next reaction without further purification. Repeated crystallization of the carbinol from water afforded an analytical sample, m.p. 135-137°, with an infrared spectrum (see figure 8) consistent with the assigned structure (XCVIII).

Anal.

Calculated for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.27. Found: C, 67.67; H, 6.27.

7-Acetylphthalimidine (XCIX).

A solution of 1.8 mg. of CrO_3 in 0.2 ml. acetic acid and 0.02 ml. of water was added to a solution of 5 mg. of 7-(α-hydroxyethyl-)phthalimidine (XCVIII) in 0.1 ml. of acetic acid. The reaction mixture was allowed to stand at room temperature for 90 minutes, after which 3 ml. of water was added and the reaction mixture extracted 4 times with 2 ml. portions of chloroform. The combined extracts were washed once with 1 ml. of water, and the washing in turn, extracted once with 1 ml. of $CHCl_3$. The combined $CHCl_3$ solutions were treated with $MgSO_4$ and taken to dryness under reduced pressure to yield 5.9 mg. of crude solid. Crystallization from acetone afforded two crops of ketone amounting to 2.3 mg. The mother liquors were recycled through the oxidation.

A procedure developed later and found to afford less side product was essentially the one described, with the exception of the reaction being carried out only for 15 minutes. Although somewhat less product was obtained at first, recycling led to a slightly improved efficiency in overall conversion.

Repeated crystallization of the product from acetone gave an analytical sample with m.p. 204-205°, which was depressed upon admixture with 7-formylphthalimidine (XCVII) and exhibited an infrared spectrum (see figure 9) consistent with the assigned structure (XCIX).

Anal.

Calculated for $C_{10}H_9O_2N$: C, 68.56; H, 5.18. Found: C, 68.60; H, 5.33.

Benzenesulfonylation of 7-Acetylphthalimidine (XCIX).

A mixture of 5.2 mg. of 7-acetylphthalimidine (XCIX) and 0.5 ml. of 10% aqueous sodium hydroxide was heated at 120° for 2 hours. The yellowish solution was cooled, 0.05 ml. of benzenesulfonyl chloride added and the mixture shaken for 15 minutes. The basic homogeneous solution was extracted several times with $CHCl_3$, the combined $CHCl_3$ extracts were washed with water, and the washings extracted with $CHCl_3$. The combined $CHCl_3$ solutions were taken to dryness under reduced pressure after treatment with $MgSO_4$. Only a trace of oil was obtained. The aqueous solutions were combined, acidified and extracted several times with $CHCl_3$. The extracts were washed with water and the water washings extracted with $CHCl_3$. The combined $CHCl_3$ solutions were treated with $MgSO_4$ and taken to dryness under reduced pressure to yield a semisolid mass. The material was washed carefully with a small portion of ice-cold $CHCl_3$ to yield crystals, m.p. 192-197°. Upon crystallization from acetone the melting point was raised to 198-200°, and was undepressed upon admixture with XLVI obtained from the aromatization of XLIV. The infrared spectra of the two materials were also identical.

Lithium Aluminum Hydride Reduction of Hemimellitic Anhydride (XVII)

A solution of 2.29 g. of hemimellitic anhydride (XVII) in 50 ml. of tetrahydrofuran, freshly distilled from $LiAlH_4$, was added with stirring over a 15 minute period to an ice-cold slurry of 2.3 g. of $LiAlH_4$ in 50 ml. of tetrahydrofuran, also freshly distilled from $LiAlH_4$. The maroon reaction mixture was allowed to warm to room temperature, and stirring was maintained for 15 hours. The reaction mixture was cooled in an ice bath and the excess $LiAlH_4$ destroyed by the cautious dropwise addition (with stirring) of 5 ml. of water. The suspension was then filtered through Celite and the filter cake washed with additional tetrahydrofuran. The combined filtrates were taken to dryness under reduced pressure yielding 1.45 g. of oil, which was dissolved in methanol. The solution was concentrated and, upon cooling, crystals of 1,2,3-trihydroxymethylbenzene (XC), m.p. 135-136°, precipitated. Concentration of the mother liquors afforded an additional crop of triol. Yield: 809 mg. Upon repeated crystallization from methanol, an analytical sample was obtained, m.p. 134-135° (Lit. 134-136°) (15) which exhibited an infrared spectrum (see figure 3) consistent with the assigned structure.

<u>Anal</u>.

Calculated for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.03; H, 7.18.

Acetylation of 1,2,3-Trihydroxymethylbenzene (XC)

A solution of 10 mg. of triol (XC) in 0.5 ml. of pyridine and 0.5 ml. of acetic anhydride was heated on the steam bath for 30 minutes. The solution was taken to dryness under reduced pressure, taken up in 0.5 ml. of methanol, warmed, and again taken to dryness under reduced pressure. This procedure was repeated several times, and the product then was taken up in a few drops of methanol with heating. Upon cooling and scratching the solution, crystals formed which were subsequently recrystallized from methanol to yield the triacetate of XC, m.p. 55-56° (Lit. 58°) (15) with an infrared spectrum (see figure 3) consistent with the assigned structure. The material was not analyzed.

Acetylation of 1,2,3-Trihydroxymethylbenzene (XC) Mother Liquors

The mother liquors from the isolation of the triol (XC) were concentrated to an oil and dissolved in 12 ml. of pyridine and 12 ml. of acetic anhydride. After heating on the steam bath for 30 minutes, the reaction mixture was taken to dryness under reduced pressure, dissolved in dilute hydrochloric acid and extracted several times with $CHCl_3$. The combined $CHCl_3$ extracts were concentrated and extracted several times with dilute sodium bicarbonate solution. The chloroform solution was then treated with $MgSO_4$ and taken to dryness under reduced pressure, yielding 379 mg. of a semicrystalline mass which was chromatographed on 15 g. of alumina. Elution with 100 ml. of Sk.B and 100 ml. of 10% ether in Sk.B afforded only traces of oil. Elution with five 50 ml. portions of 20% ether in Sk.B afforded a low melting solid, while elution with four 50 ml. portions of

40% ether in Sk.B, followed by 60% and 100% ether in Sk.B, afforded a second solid. After 3 crystallizations from ether the first solid had m.p. 102-104°, which was depressed upon admixture with authentic triacetate. It was subsequently identified as 7-acetoxymethylphthalide (C) by its melting point and infrared spectrum (see figure 4). Its melting point was not depressed upon admixture with authentic material.

Anal.

Calculated for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.11; H, 4.87.

The second solid after 3 crystallizations from ether had m.p. 112-113° which was depressed upon admixture with the monoacetate above. Its infrared spectrum (see figure 4) indicated the presence of a free OH group. It was found to be identical with 7-hydroxymethylphthalide (LXXXVI).

Anal.

Calculated for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.92; H, 4.89.

Permanganate Oxidation of
1,2,3-Trihydroxymethylbenzene (XC)

A solution of 74 mg. of the triol (XC) in 20 ml. of acetone was treated with 525 mg. of potassium permanganate dissolved in ca. 10 ml. of water, and allowed to stand at room temperature for 32 hours. After destroying the excess permanganate with methanol, the resulting manganese dioxide was removed by filtration and washed with warm acetone. The combined acetone solutions were taken to dryness under reduced pressure and the residue (68 mg.) chromatographed on 180 mg. of silicic acid. Elution with 20-30% ether in Sk.B afforded 51 mg. of crude 4-carboxyphthalide (LXXIII) identified by melting point, mixed melting point with authentic material, and infrared spectrum.

Methyl 7-Phthalidylacetate (CV)

Into a flask equipped with reflux condenser, $CaSO_4$ tube, oil heating bath and magnetic stirrer there were placed 64.1 mg. of LXXII and 2 ml. of freshly distilled thionyl chloride. The reaction mixture was stirred and heated at reflux for 3 hours, after which time the homogeneous solution was taken to dryness under reduced pressure. Dry benzene was added, the slurry warmed and then taken to dryness under reduced pressure. The process was repeated, the residue dissolved in 3 ml. of tetrahydrofuran, freshly distilled from $LiAlH_4$, and added slowly to a rapidly stirred ice-cold dry solution of diazomethane in ca. 6 ml. of ether-tetrahydrofuran 1:1. Upon evaporation under reduced pressure, a yellowish residue was obtained which was dissolved in 2-3 ml. of absolute methanol and heated at reflux. A slurry of Ag_2O, prepared from 50 mg. of $AgNO_3$, in absolute methanol, was added to the boiling solution over 1 hour at 15 minute intervals. The reaction mixture was allowed to reflux over night, and then was filtered. The filtrate was concentrated and upon cooling and scratching crystals formed. Concentration of the mother liquors afforded two additional crops which brought the crude yield to ca. 48 mg. Crystallization from ether yielded material, m.p. 90-92°. The melting point was depressed upon admixture with 7-carbomethoxyphthalide. Further recrystallization afforded an analytical sample, m.p. 94-96°, with an infrared spectrum (see figure 10) consistent with the assigned structure.

Anal.

Calculated for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.82; H, 4.96.

Methyl 4-Phthalidylacetate (CVI)

A mixture of 92 mg. of 4-carboxyphthalide (LXXIII) and 5 ml. of freshly distilled thionyl chloride was heated at 80-90° with magnetic stirring for 4 hours. The homogeneous solution was taken to dryness under reduced pressure, suspended and warmed in ca. 5 ml. of dry benzene, and again taken to dryness under reduced pressure. This process was repeated and the resultant crystalline solid dissolved in 5-10 ml. of tetrahydrofuran, freshly distilled from $LiAlH_4$. The solution was added slowly to a vigorously stirred, ice-cold, dry solution of diazomethane in 15-20 ml. of ether-tetrahydrofuran 1:1. The solvents and excess diazomethane were removed under reduced pressure, and the residue stirred and heated with 5-10 ml. of absolute methanol. To the refluxing solution was added a slurry of Ag_2O, prepared from 100 mg. of $AgNO_3$, in 5-10 ml. of absolute methanol over a one hour period. The reaction mixture was allowed to reflux for an additional hour, cooled, filtered, and the filtrate taken to dryness under under reduced pressure. The residue was dissolved in slightly more than the minimum volume of tetrahydrofuran, preadsorbed, and chromatographed on 3 g. of alumina. The column was eluted with two 25 ml. portions of Sk.B, four 25 ml. portions of 10% ether in Sk.B, seventeen 25 ml. portions of 20% ether in Sk.B, and two 25 ml. portions of ether. The 10% ether and first two 20% ether fractions contained 4-carbomethoxyphthalide. The 3rd and 4th 20% ether fractions contained the major portion of material which rapidly diminished through the 8th 20% ether fraction. Later eluates showed progressively more higher melting material and were not investigated. Upon crystallization of the 3rd through 8th 20% ether eluates, 49 mg. of homoester (CVI) was obtained. Another 10-20 mg. of less pure material remained in the mother liquors. After several crystallizations from methanol, an analytical sample was obtained, m.p. 94-95°, with an infrared spectrum (see figure 10) consistent with the desired structure.

Anal.

Calculated for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.96; H, 5.24.

Reduction of Methyl 4-Phthalidylacetate (CVI)

A solution of 332 mg. of CVI in 10 ml. of tetrahydrofuran, freshly distilled from $LiAlH_4$, was added under N_2 to a stirred ice-cold slurry of 350 mg. of $LiAlH_4$ in 10 ml. of tetrahydrofuran, also freshly distilled from $LiAlH_4$. The reaction mixture took on a yellowish coloration which slowly faded as the mixture was allowed to warm to room temperature and then was stirred under N_2 for 12 hours. The excess hydride was decomposed by the cautious, dropwise addition of water to the cooled and stirred reaction mixture. After 2-3 ml. had been added the reaction mixture was allowed to stir 15 minutes, and the flocculent hydroxide removed by centrifugation. The precipitate was washed twice with 5 ml. portions of tetrahydrofuran, and the combined tetrahydrofuran solutions were taken to dryness under reduced pressure. The oily product, 242 mg., exhibited no significant absorption in its infrared spectrum between 5.5 and 6.0μ. Attempts to obtain crystalline material by direct crystallization were unsuccessful. The product was dissolved in 5 ml. or pyridine and treated with 1 ml. of benzoyl chloride. After warming on the steam bath for 10 minutes, the reaction mixture was poured into 25 ml. of water and again warmed on the steam bath for 10 minutes. After cooling, the reaction mixture was made basic with $NaHCO_3$ and extracted several times with $CHCl_3$. The $CHCl_3$ extracts were combined, washed once with water, and twice with 3 M HCl, followed by another washing with water. The organic solution was then treated with $MgSO_4$ and taken to dryness under reduced pressure yielding 1.53 g. of thick oil. The infrared spectrum of the product showed it to be predominantly benzoic anhydride, with additional peaks at 8.0 and 9.1μ. It was dissolved in 5 ml. of pyridine and heated on the steam bath. Enough water was added to cause cloudiness, and heating was continued for 10 minutes. After cooling the reaction mixture was worked up as before to yield ca. .9 g. of oil. The infrared spectrum of the material clearly showed a diminution in the 5.65μ (anhydride carbonyl) peak relative to the 5.80μ (anhydride and benzoate carbonyl) peak. The pyridine hydrolysis was repeated for an additional 35 minutes, the product (ca. 500 mg.) exhibiting an almost complete absence of the 5.65μ peak. The material was chromatographed on 15 g. of alumina, and eluted with two 250 ml. portions of Sk.B, two 250 ml. portions of 10% ether in Sk.B, and twenty 250 ml. portions of 20% ether in Sk.B. Fractions 4-13 of 20% ether eluates contained a thick colorless oil which very slowly crystallized to yield ca. .4 g. of the tribenzoate of CIII. Crystallization from acetone or methanol afforded an analytical sample, m.p. 97-99°, with an infrared spectrum (see figure 10) consistent with the assigned structure.

Anal.

Calculated for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30. Found: C, 75.52; H, 5.40.

6-Carboxyphthalonic Acid (XXIII)

The procedure developed by Graebe (23) was employed. From 15.6 g. of naphthalic anhydride 5.9 g. of crystalline product was obtained after extensive crystallization of the crude oxidation products. Repeated crystallization from water afforded an analytical sample, m.p. 235-237°d. (Lit. 238°) (23) with an infrared spectrum (see figure 12) consistent with the assigned structure.

Anal.

Calculated for $C_{10}H_6O_7$: C, 50.43; H, 2.54. Found: C, 50.19; H, 2.67.

3,4-Dicarboxyphthalide (CVII)

A mixture of 22 mg. of $HgCl_2$ and 332 mg. of zinc dust was stirred with 5 ml. of water and treated with 1 ml. of 3 M HCl. After stirring for 15 minutes, the aqueous layer was decanted and the amalgamated zinc washed free of mercury and zinc salts with several portions of water. A solution of 151 mg. of 6-carboxyphthalonic acid (XXIII) in 1 ml. of water was poured onto the amalgam and stirred while 0.5 ml. of concentrated HCl was added. After a few minutes the clear solution had become quite milky and a precipitate soon became apparent. The constant H_2 evolution caused the solids to form a frothy foam which slowly filled the reaction vessel. Occasional stirring broke up the foam. After 45-60 minutes, the suspension was transferred to a centrifuge tube and centrifuged. The resultant precipitate was washed twice with ice-cold water to remove inorganic salts, and then dissolved in acetone. The acetone solution was centrifuged to remove particles of zinc amalgam. The acetone was evaporated to yield 131 mg. of crude 3,4-dicarboxyphthalide (CVII). Repeated crystallization from water afforded an analytical sample which, upon heating decomposed at 210-215° with the evolution of CO_2 and resolidified, melting finally at 233-236°. The product of decarboxylation was shown by melting point, mixed melting point, and infrared spectrum to be identical with 4-carboxyphthalide (LXXIII) which could be obtained by merely subliming the diacid above 220°. The infrared spectrum of the diacid (see figure 13) was consistent with the assigned structure.

<u>Anal.</u>

Calculated for $C_{10}H_6O_6$: C, 54.06; H, 2.72. Found: C, 53.83; H, 2.88.

Upon treatment of 3,4-dicarboxyphthalide (CVII) in tetrahydrofuran with an excess of diazomethane in ether-tetrahydrofuran and evaporation to dryness under reduced pressure a crystalline product was obtained. Repeated crystallization from methanol yielded an analytical sample with m.p. 113-116°, and an infrared spectrum (see figure 13) consistent with the assigned structure.

<u>Anal.</u>

Calculated for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03. Found: C, 57.76; H, 4.21.

By a similar procedure the trimethyl ester of 6-carboxyphthalonic acid (XXIII) could be prepared. It had a m.p. 145-147°(Lit. 146°) (26) and an infrared spectrum (see figure 13) consistent with the assigned structure.

Anal.

Calculated for $C_{13}H_{12}O_7$: C, 55.72; H, 4.32. Found: C, 55.71; H, 4.40.

Pyrolysis of 6-Carboxyphthalonic Acid (XXIII)

A small sublimation apparatus was charged with 1.06 g. of 6-carboxyphthalonic acid (XXIII). The vessel was introduced into an oil bath previously heated to >250°. The temperature dropped and was held at 250° throughout the pyrolysis. After a few moments the compound began to fuse slowly and evolve gas. After the reaction had subsided (3-5 minutes), the vessel was cooled and the residue weighed: 786 mg. The condenser of the sublimation apparatus had collected 28 mg. of white material, m.p. 158-163°. The residue was extracted with 7 ml. of warm water in 4 portions to leave 109 mg. of material. This was washed several times with acetone to afford 81 mg. of a light yellow powder which was soluble in base, wherein it formed a reddish-orange solution, and could be recovered upon acidification. It failed to melt below 360°, and was presumed to be Graebe's "dilactone" (XXVII).

The sublimate, aqueous and acetone washing were combined, preadsorbed and chromatographed on 30 g. of silicic acid. The column was eluted with 100 ml. fractions of eluate. Two Sk.B, two 20% ether-Sk.B and two 40% ether-Sk.B fractions afforded only oils. Elution with twenty-five 50% ether-Sk.B fractions afforded solids. The column was eluted finally with two fractions of ether and two of acetone.

Crystallization of fractions 1-5 of 50% ether afforded 108 mg. of 4-

carboxyphthalide (IXXIII) while 6-11 contained materials melting at ca. 220°. Fractions 12-13 gave 56 mg. of aldehyde (CXVIII or CXIX) upon crystallization, 14 contained oils, 15-20 afforded 107 mg. of hemimellitic acid (IV) after crystallization and 21-25 contained unidentified oily solids. The mother liquors and all unresolved solids and oils were combined and rechromatographed as above to yield 12 mg. of 4-carboxyphthalide, 34 mg. of Graebe's aldehyde and 59 mg. of hemimellitic acid after crystallization. The materials melting in the 220° range would not separate upon recrystallization. They amounted to ca. 30 mg. and were not characterized further. Thus the pyrolysis afforded 81 mg. of dilactone, 120 mg. of 4-carboxyphthalide, 225 mg. hemimellitic acid, 90 mg. of Graebe's aldehyde and ca. 300 mg. of unseparated oils and solids.

Hemimellitic acid and 4-carboxyphthalide were identified by melting point, mixed melting point with authentic material and infrared spectra.

An infrared spectrum (see figure 14) of the aldehyde was obtained but the compound was not characterized any further.

2-Methylisophthalic Acid

The procedure of Elderfield (27) was modified slightly. 6-Carboxyphthalonic acid (XXIII), 111 mg., was heated at 250° until bubbling had ceased, the entire residue dissolved in 3 ml. of 10% sodium hydroxide solution at 90°, 302 mg. Raney nickel alloy added in small portions over an 80 minute period, and the suspension allowed to stir at 90° for an additional hour. The solution was decanted from the nickel residue and the latter washed twice with water. The combined basic solutions were concentrated to ca. 2 ml. and added rapidly to 3 ml. of concentrated HCl. Upon vigorous stirring a thick paste was obtained which was washed several times with small portions of ice-cold water. The residue, ca. 13 mg., was sublimed to yield 7 mg. of a substance which, upon recrystallization three times from water afforded material with m.p. 237-240° (lit. 236-238°) (27). The infrared spectrum of the compound (see figure 14) was consistent with the assigned structure (see Discussion) but different from that of 4-carboxyphthalonic acid (LXXIII). Admixture of the two compounds brought about a depression in melting point.

4-Carbomethoxyphthalic Anhydride (CXXI)

A solution of 290 mg. of hemimellitic anhydride (XVII) in tetrahydrofuran, freshly distilled from $LiAlH_4$, was treated with an excess of diazomethane in dry ether-tetrahydrofuran 1:1. The excess diazomethane and solvents were removed under reduced pressure and the residue was crystallized from acetone to give 156 mg. of crude 4-carbomethoxyphthalic anhydride (CXXI) m.p. 138-143°. Upon repeated crystallization from acetone, an analytical sample was obtained, m.p. 143-145°, which exhibited an infrared spectrum (see figure 11) consistent with the assigned structure.

Anal.

Calculated for $C_{10}H_6O_5$: C, 58.26; H, 2.93. Found: C, 58.26; H, 3.00.

3-Carbomethoxyphthalic Acid (CXXII)

Crystallization of 4-carbomethoxyphthalic anhydride (CXXI) from aqueous acetone afforded crude 3-carbomethoxyphthalic acid (CXXII), m.p. 194-199°. The melting point was quite dependent on the rate of heating. Its wide range was due probably to a combination of slow crystal transformations and decomposition near the melting point. Sublimation led to 4-carbomethoxyphthalic anhydride (CXXI) identified by melting point, infrared spectrum and failure of the melting point to be depressed upon admixture with authentic anhydride. Purification was accomplished easily by first subliming the crude acid and crystallizing the sublimate from aqueous acetone. Repeated crystallization from acetone afforded an analytical sample, m.p. 193-204° d., with an infrared spectrum (see figure 11) consistent with the assigned structure.

Anal.

Calculated for $C_{10}H_8O_6$: C, 53.58; H, 3.60. Found: C, 53.46; H, 3.53.

Dimethyl 3-Carboxyphthalate (CXXIII)

Crystallization of 4-carbomethoxyphthalic anhydride (IXXI) from methanol afforded a new product, m.p. 157-163°. Concentration of the mother liquors gave additional material, but successive crops were progressively more rich in a second component. The latter, isolable in ca. 10% yield, was shown to be Graebe's dimethyl ester XX (7) by comparison of melting point, infrared spectrum, and failure of the melting point to be depressed upon admixture with authentic material. The major component, upon repeated crystallization from ether afforded an analytical sample, m.p. 160-163° which was depressed upon admixture with authentic dimethyl ester prepared by Graebe's procedure,/and which exhibited an infrared spectrum (see figure 12) consistent with the assigned structure but different from the Graebe diester spectrum (see figure 12). Upon sublimation, 4-carbomethoxyphthalic anhydride (CXXI) was obtained and identified on the basis of melting point, mixed melting point and infrared spectrum.

Anal.

Calculated for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23. Found: C, 55.30; H, 4.37.

2-Carbomethoxyisophthalic Acid (XIX)

Crystallization of hemimellitic anhydride (XVII) from methanol afforded a compound m.p. 200-210° which upon repeated crystallization from methanol gave an analytic sample m.p. 204-210° (lit. 203-205°) (7). The melting point was depressed upon admixture with 3-carbomethoxyphthalic acid (CXXII). Upon sublimation, hemimellitic anhydride (XVII) was obtained and identified on the basis of melting point, mixed melting point, and infrared spectrum. The infrared spectrum of the ester (see figure 11) is consistent with the assigned structure and different from that of 3-carbomethoxyphthalic acid (CXXII) (see figure 11).

Anal.

Calculated for $C_{10}H_8O_6$: C, 53.58; H, 3.60. Found: C, 53.38; H, 3.63.

Dimethyl 2-Carboxyisophthalate (XX)

A solution of 200 mg. of hemimellitic acid (IV), previously dried at 100 for 8 hours, in absolute methanol was saturated with gaseous HCl and allowed to stand in a stoppered flask at room temperature for 14 hours. Upon concentration, the reaction mixture afforded 3 crops of material, 115 mg. with m.p. 144-155°. Repeated crystallization from ether gave an analytical sample, m.p. 148-153° (lit. 148-150°) (7). The melting point was depressed upon admixture with dimethyl 3-carboxyphthalate (CXXIII). Upon sublimation, 4-carbomethoxyphthalic anhydride (CXXI) was obtained. The diester exhibited an infrared spectrum (see figure 12) consistent with the assigned structure, but different from that of dimethyl 3-carboxyphthalate (CXXIII).

Anal.

Calculated for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23. Found: C, 55.74; H, 4.14.

Sodium Borohydride Reduction of the Diester Acid Chlorides

A mixture of 132 mg. of dimethyl 3-carboxyphthalate (CXXIII) and 10 ml. of freshly distilled thionyl chloride was stirred with heating at 80-90° for 4 hours. The solution was taken to dryness under reduced pressure and dissolved in 5 ml. of dry diglyme. The ester acid chloride solution was stirred and heated at 75° while a centrifuged solution of 37 mg. of sodium borohydride in dry diglyme was added. Stirring and heating were maintained for 1.5 hours, and water was then added to the reaction mixture. The solution was taken to dryness under reduced pressure and the residue partitioned between $CHCl_3$ and water. The aqueous layer was extracted several times with $CHCl_3$ and the combined $CHCl_3$ solutions treated with $MgSO_4$ and taken to dryness under reduced pressure, yielding 80 mg. of oil. The oil was dissolved in methanol and concentrated, giving upon cooling 10 mg. of crystals, m.p. 145-173°. Further concentration afforded ca. 24 mg. of crystalline material, m.p. 95-101°. The oils did not afford any additional material. Crystallization of the two fractions separately showed them to be primarily the two carbomethoxyphthalides obtained previously. Thus ca. 12% of the material isolated was reduced on the central carbon while ca. 30% was reduced on the outside carbon.

By a similar procedure dimethyl 3-carboxyphthalate (CXXIII) was converted to the acid chloride and reduced with sodium borohydride. Three crops of crystals were obtained from 102 mg. of oil isolated from the reaction by the procedure described above: 42 mg., m.p. 96-105°, 5 mg., m.p. 92-104°, with part not melting until 150°, and 3 mg., m.p. 92-102°. Upon purification the fractions were found to be predominantly 7-carbomethoxyphthalide. The higher melting component could not be purified directly and its identity as 4-carbomethoxyphthalide was not proven. However, yields of crystalline material showed that ca. 45% of the reduction had occured on the outer carbon and less than 5% on the central carbon.

SUMMARY

The Diels-Alder adduct of maleic acid and furfurylamine acetate, upon treatment with sodium hypoiodite undergoes cyclization to form an iodolactone. Through a series of reactions, a benzenesulfonamidomethylacetylbenzoic acid can be obtained, the structure of which depends upon which carboxyl group in the Diels-Alder adduct undergoes lactonization. The synthesis of the aromatic acid, and hence, proof of structure of the adduct, is presented.

Attempts to synthesize 2-(β-hydroxyethyl-)-1,3-dihydroxymethylbenzene, the key intermediate in a proposed synthesis of erythrocentaurin, are presented.

During the course of these investigations, the chemistry of hemimellitic acid and 6-carboxyphthalonic has been studied. The resulting compounds, useful as possible synthetic intermediates, are discussed.

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