"A Study of the Active Esters of the Stereoisomeric Mucic Acids in Relation to the Law of Optical Superposition"

with additional paper.

"Synthetic Approaches to the Colchicine Molecule."

T H E S I S

presented by

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May, 1940.

To my Parents.

Preface.

A brief account of the first part of the work described herein has been submitted by the author jointly with Professor T.S. Patterson and Mr. J. Robertson for publication in the Journal of the Chemical Society.

The author wishes to express his deep appreciation of the invaluable advice and assistance given by his supervisors, Professor Patterson, Professor Cook and Mr. Robertson. He also wishes to thank Mr. J.M.L. Cameron for carrying out the micro-analysis necessary in connection with this work.

The author further acknowledges his indebtedness to the University of Glasgow for the tenure of the Mackay-Smith and James Fleming Scholarships and to the Carnegie Trustees for a Research Scholarship during the period in which this work was performed.

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A Study of the Active Esters of the Stereoisomeric Mucic Acids in Relation to the Law of Optical Superposition.

HISTORICAL INTRODUCTION.

The so-called Law of Optical Superposition advanced by van't Hoff[1] from consideration of the spatial arrangements of the carbon atoms in a molecule states that the rotation of a substance containing several asymmetric C atoms should be an additive result of the rotation of the individual C atoms; or, as stated by Patterson[2]; "If a molecule contains several asymmetric C atoms and the part of the total rotation due to any one of them be $+a^{o}$, then on replacing that atom by its mirror image the latter should be responsible for $-a^{o}$ of the rotation of the new compound."

The accuracy of this rule is of some theoretical importance and various workers have carried out investigations in an attempt to establish its validity. The early work of Walden and Guye has been shown to be fallacious[3] but Hudson[4] by his work on the sugars obtained results which were held to justify the principle.

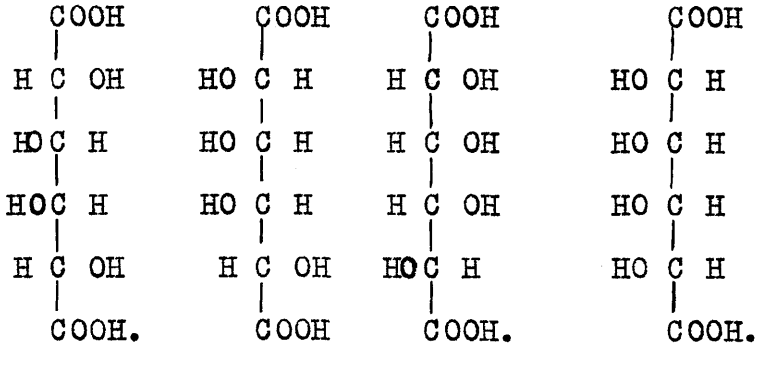
His work was adversely criticised by Patterson[5] who, with his collaborators, had compared the rotations

of the various l-menthyl di-acetyl tartrates[3,6,7], the l-menthylamine tartrates[2], the l-amyl di-methoxy succinates[2], the d-sec.-octyl tartrates[8], and the l-sec-octyl di-methoxy succinates[5]. These workers found that the mean value of the rotation of the d and l forms was not identical with the rotation of the inactive form, as would be the case if van 't Hoff's Rule held. The differences in some cases were considerable and seemed outwith the limits of experimental error, being in the case of the l menthyl tartrates[3,6,7], as much as 33°.

Following later work by Hudson[9] which was claimed by Patterson[10] to be open to the same criticism, Patterson and Fulton[11] attempted to extend their observations from the tartrates to the active esters of the tetra-hydroxy adipic acids. As is shown later the two acids mucic and allomucic are structurally especially suited to an investigation of this sort. These two authors were however unable to obtain the l-menthyl esters of the two acids by the action of l-menthol and HCl on the acids. They were therefore

forced to transfer their attention to the alkaloid salts. As they point out, these salts on account of their tendency to dissociate and decompose are not entirely suitable for accurate optical work, but in spite of these difficulties they obtained values for the l-menthylamine, brucine and strychnine salts of mucic and "allomucic" acids which were not in agreement with the law of optical superposition.

The history of the three stereo isomeric mucic acids; mucic acid I, d l-talomucic II, and allomucic III



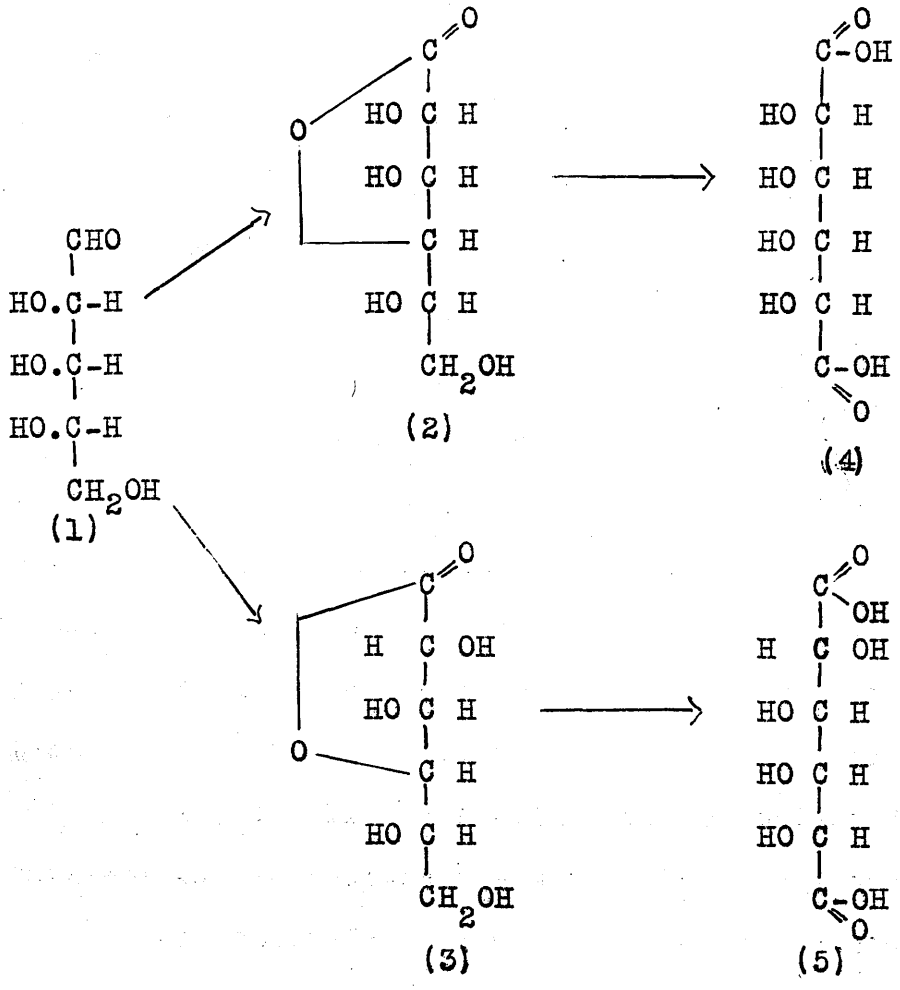
I II III

is in itself interesting. Mucic acid was first described by ~~Von~~ Scheele[12] in 1780, who prepared it from lactose. In 1891 Emil Fischer[13] heated mucic acid with aqueous pyridine and obtained by epimerisation a tetra-hydroxy adipic acid. This acid was

inactive. He gave it the name allomucic acid and assigned to it the configuration III. Fischer thought that both the carbon atoms α and α' in mucic acid had undergone epimerisation.

In 1935 Postemak[14] prepared the racemate from the d and l forms of talomucic acid II. He found that this racemate was identical with Fischer's "allomucic acid" which therefore was in reality dl-talomucic acid with the configuration II and which is inactive by external compensation and not by internal compensation as Fischer supposed. Fischer, incidentally, had prepared both d[15] and l[16] talomucic acid but not the racemate. Mucic acid was in fact the first dibasic sugar acid to which he had applied the principle of epimerisation and his previous experience with the monobasic hydroxy acids had shown that the α C atom undergoes inversion. From mucic acid he was able to isolate only one product which was inactive and which in turn on similar treatment with aqueous pyridine regenerated only the original mucic acid. These facts supported his view that the configuration of his product was III.

Posternak, however, synthesised the compound with structure III. Starting from l-ribose (1) by the method of Austin and Humoller[17] he obtained l allono (2) and l-altrono lactones (3). These on oxidation with nitric acid gave allomucic (4) and l-talomucic (5) acids, viz:



Allomucic acid was also synthesised independently a little later by Austin, McManus and Humoller.[18]

Objects of this investigation.

The objects of this investigation were two-fold. (a) Since both the d and l forms of talomucic acid are formed on epimerisation of mucic acid, it follows that both the α and α' carbon atoms in mucic acid must be free to undergo optical inversion and if both are rearranged then the real allomucic acid should be a product of the epimerisation of mucic acid.

Since epimerisation is a reversible reaction and an equilibrium is maintained between the isomers, the allomucic acid if produced might conceivably be in small yield and have been overlooked by earlier workers. Thus the initial aim was to investigate the products of this reaction carefully and from the known property of allomucic acid of staying in solution as lactone[18], in particular, the end mother liquors.

(b) If allomucic acid could be obtained by this method, to prepare the active l-menthyl and d-sec.-octyl esters from it and compare the optical rotations of these esters with those of the same active

esters of mucic acid. Now as Patterson and Fulton point out, mucic and allomucic acids are both optically inactive and their inactivities are due to compensation of the asymmetric carbon atoms in different ways. Thus a comparison of the rotations of the active esters of the two acids would provide a good demonstration of van 't Hoff's law. If the rotation of an active ester of one acid differs from that of the same active ester of the other acid, then the difference must be due to a different arrangement of groups attached to the asymmetric carbon atoms in the two acids and the rotation due to any asymmetric carbon atom would not be independent of the configuration of the groups with which it is combined.

Methods of this investigation.

A. The isolation of any allomucic acid from the mucic acid epimerisation products would naturally depend on the discovery of a method of separating these very similar isomers. The known properties of these acids showed a striking similarity. They are all insoluble in organic solvents and exist in solution as lactones. Mucic acid is practically insoluble in cold water and by several fractional crystallisations

it is possible to remove most of it from the others. dl-Talomucic and allomucic are both readily soluble in hot water as lactone. The rate of change of equilibrium of lactone to free acid is very slow, in fact in the case of allomucic acid it is such as almost to inhibit the deposition of free acid. The acid is only deposited after long standing.

One of the great difficulties of this work was in characterisation of the melting points of the acids. Melting point is the only readily available criterion of purity as analytical data is of course useless for characterisation. The melting point in all cases is masked by decomposition and considerable practice was necessary before a standard rate of heating was evolved. Again the acids do not depress each other's melting point to any great extent. Some preliminary experiments carried out on mixtures of mucic and dl-talomucic acids showed that a 20% impurity of either gave only a depression of some -5°C.

From these considerations therefore, and after one or two tentative experiments, it was decided not to attempt to separate the acids obtained from the end liquors by fractional crystallisation.

Now Posternak[14] had stated that the sodium salt of allomucic acid was, unlike that of mucic acid, soluble in excess of alkali. At first sight this seemed to give a possible method of separating mucic acid from the other two but it was found, since both dl-talomucic and allomucic are obtained by slow evaporation of their mother liquors, that it was difficult to free the end products from inorganic salts.

The problem of separation was now approached from a slightly different angle. It was decided to attempt a separation through a crystalline derivative of the acids. Mucic acid readily gives a crystalline tetra-acetyl derivative and it was hoped that allomucic acid might also acetylate. dl-Talomucic acid on the other hand, when treated with acetic anhydride and a trace of H_2SO_4, either gave no insoluble precipitate on pouring into water or precipitated a very small amount of crystalline material of m.p. about 230°. At first this was considered to be a little impure tetra-acetyl mucate (m.p. 242°) from mucic acid present in the dl talomucic as impurity. However, it was found that the melting point of this tetra-acetyl derivative could not, even after repeated

recrystallisation, be raised to that of a pure sample of tetra-acetyl mucate.

On close examination it was found that from aqueous alcohol crystalline plates were first deposited which were followed, on cooling slightly further, by needles. The significance of this was not at first appreciated, but ultimately by preferential filtration and subsequent recrystallisation a pure sample of plates and of needles was obtained. The needles were found to melt at 240°, which is the melting point of tetra-acetyl mucic acid to which the needles bore a close resemblance. Mixed melting point with tetra-acetyl mucic acid showed no depression and on hydrolysis of the needles an acid, m.p. 212°, which gave no depression with mucic acid, was obtained.

The plates on the other hand had m.p. 220° and on hydrolysis gave an acid, m.p. 199-200°, which was different from mucic acid, m.p. 212°, on the one hand and dl-talomucic acid, m.p. 172°, on the other, but in agreement with the value quoted by Posternak for allomucic acid, though higher than the value of McManus, Humoller & Austin. Analysis gave correct figures for a tetra-acetoxy adipic acid.

Some experiments were conducted on crystallisation with a pure specimen of tetra-acetyl mucic acid using various proportions of aqueous alcohol. It was found that from 50% aqueous alcohol tetra-acetyl mucic acid still crystallised in needles of unchanged melting point, viz, 242°C. and therefore the small amount of alcohol in the solvent used (15-20%) was not responsible for the difference in crystalline form. (Tetra-acetyl mucic acid, from alcohol, crystallises in plates which rapidly lose alcohol of crystallisation on exposure to air). Again by recrystallisation from homogeneous solvents it was not found possible to change the one form into the other. This evidence seemed to support the view that the plates and needles were two separate substances and not crystalline modifications of the same substance. Derivatives were prepared from this acid and compared with the corresponding derivatives of dl-talomucic and allomucic acids, viz:-

DERIVATIVE	A C I D		
	Mucic	dl talomucic	Allomucic
Free acid	m.p.212	m.p.172	m.p.199-200
Tetra-acetyl acid	" 242	-	" 220
Di-ethyl ester	" 169	" 137-138	" 155
Tetra-acetyl dichloride	" 189	-	" 165
Tetra-acetyl diethyl ester	" 189	" 108-109	" 136
Tetra-acetyl dl menthyl ester	" 153-154	-	" 136

As can be seen, the derivatives of allomucic acid all have appreciably different melting points from the corresponding derivatives of mucic and talomucic acids. It seemed fairly certain therefore that allomucic acid had been isolated but in this type of work involving isomers it was imperative to have independent confirmation. Accordingly specimens of allomucic acid and di-ethyl allomucate were sent to Professor Posternak at Geneva, who was good enough to compare the melting points of these specimens with those of his synthetic

allomucic acid and its di-ethyl ester. He found that the melting points were identical and that there was no depression on mixing.

B. The failure of dl-talomucic acid to give an acetyl derivative was in keeping with the behaviour of other hydroxy adipic acids but still somewhat surprising in view of the readiness with which mucic and allomucic acids gave insoluble acetyl derivatives. This question however has been investigated by Robertson[20], who tried various methods of acetylation but obtained no acetyl derivative.

The acetic acid mother liquors from these experiments were worked up and dl-talomucic acid recovered. This acid was treated with a fresh amount of acetic anhydride and rather surprisingly gave a further amount of tetra-acetyl derivative which it was found possible to separate into tetra-acetyl allomucic acid and tetra-acetyl mucic acid.

Once more the unchanged dl-talomucic acid was recovered and treated with fresh acetic anhydride. Again further quantities of tetra-acetyl mucate and tetra-acetyl allomucate were obtained.

The presence of tetra-acetyl mucic acid in the products from these experiments was highly significant. As has been previously stated, mucic acid very readily acetylates and it seemed inconceivable that it should persist in the dl-talomucic acid throughout these three treatments with acetic anhydride, particularly as the subsequent recovery of unchanged talomucic acid was made in one instance through the Ba salt and traces of insoluble mucic acid would tend to be taken out with the $BaSO_4$. The presence therefore of both the isomers, tetra-acetyl mucate and tetra-acetyl allomucate, in the products suggested that possibly dl-talomucic acid undergoes some kind of rearrangement in acetic anhydride akin to epimerisation.

To test this supposition the preparation of pure dl-talomucic acid was undertaken in the following manner:- The talomucic acid crystallised from water three times was esterified and the di-ethyl ester carefully purified by crystallisation. From this the tetra-acetyl di-ethyl ester was prepared and again rigorously purified. This was then hydrolised with dilute HCl back to the free acid (2 g.). On treatment of this acid with acetic

anhydride a small amount of tetra-acetyl derivative was obtained which was purified and gave needles, m.p. 240°. It was not possible to separate any plates from this product. However, to obtain this amount of tetra-acetyl derivative 3% mucic acid would require to have persisted in the purified dl-talomucic.

This experiment was repeated on a larger scale. On this occasion 120 g. dl-talomucic acid were crystallised from water, then treated with acetic anhydride and after separation of the acetylated derivative the unchanged dl-talomucate recovered through the Ba salt. This recovered acid was then purified as before by formation of the di-ethyl ester and tetra-acetyl di-ethyl ester. The acid obtained on hydrolysis gave on treatment with acetic anhydride 4g. of acetylated material. It was found possible to separate this product into the two pure isomers, tetra-acetyl mucic acid (1 g.) and tetra-acetyl allomucate (2 g.). The presence of allomucate was confirmed by the hydrolysis of a sample to the free acid.

C. The action of acetic anhydride on mucic acid was now investigated. If, as seemed the case, dl-talomucic acid was rearranged in acetic anhydride, it was possible that mucic acid might also undergo rearrangement in this medium. As in this case an insoluble acetyl derivative is readily formed and any rearrangement might conceivably be a secondary reaction, the conditions were modified and the heating prolonged from 1 hour to 48 hours. The acetic anhydride in the initial experiment contained the usual trace of concentrated H_2SO_4 and under these conditions a certain amount of charring and decomposition took place. From the products, however, a small amount, 5%, of pure tetra-acetyl allomucate was obtained.

The experiment was repeated with only a suspicion of concentrated H_2SO_4 present. On this occasion there was very little decomposition and a clear liquid was obtained. The experiment was controlled by taking equal samples at various times (5 hours, 13 hours, 17 hours, 22 hours, 28 hours, 40 hours and 48 hours). In every case the product was tetra-acetyl mucic acid. The yield of acetylated product was very small in the later stages, being only 15%. It was possible therefore that the reaction had not gone to completion initially. To determine if

initial vigorous reaction influenced the later course of the reaction, the conditions were arranged so that there was a definite initial reaction. After 30 hours no tetra-acetyl allomucate was identified among the products. Heating for a further 20 hours gave similar results.

D. In the course of this work an investigation was carried out of the various crystalline derivatives of the acids with a view to finding the most suitable and readily available sharp melting derivative for characterisation. These experiments were conducted on the easily obtained mucic and talomucic acids. Crystalline salts of some of the alkaloids had been prepared[11] but they all decompose on heating and have no very sharp melting point. Derivatives of these acids should be formed using either their acidic or alcoholic properties. However, except in the case of the tetra acetyl mucates and allomucates the latter type proved inaccessible, e.g., no solid derivative using p-toluene sulphonyl chloride was obtained. Various higher esters were prepared but were no improvement on the ethyl esters. These esters themselves show sharp melting points but have a tendency to decompose on heating with solvent. The most satisfactory derivatives are almost certainly the tetra-acetyl

di ethyl esters.

Veibel and Lillieland[21] have described a method for obtaining sharp melting derivatives of acids by use of benzyl iso-thio urea. An attempt to apply this method to these hydroxy acids gave negative results and it would seem that the method as described is not suitable for this type of compound.

E. In connection with the optical work, as no large supply of tetra-acetyl allomucate was available, it was important to get the maximum yield from the preparation of the active esters. The procedure adopted was to try out various methods on tetra-acetyl mucic acid with a view to applying the best of them to the tetra-acetyl allomucate. In this way formation of the acid chloride and its subsequent esterification with l-menthol was carefully investigated.

It soon became apparent that the properties and solubility of the allomucate differed from those of the mucate to such an extent, that methods suitable for the formation of the latter were not applicable to the preparation of the former. This was all the more disappointing as tetra-acetyl mucyl dichloride is an excellent reagent for identification of alcohols[20, 22]. The method employed is simply to heat the tetra-acetyl mucyl

dichloride with the alcohol in a non-hydroxylic solvent, usually benzene. All attempts to combine l-menthol with tetra-acetyl allomucyl dichloride in presence of a solvent failed and ultimately the wasteful method of heating menthol and the chloride directly had to be used. It was found also, that the slight excess of menthol necessary to prevent mono esterification interfered considerably in the purification and it was with the greatest difficulty that a pure sample of l-menthyl tetra-acetyl allomucate was obtained.

The preparation of the d-sec-octyl esters was also undertaken but here again, although the d-sec-octyl tetra-acetyl mucate was finally obtained in a pure condition:by analogous methods, it was not found possible to prepare a pure sample of d-sec-octyl tetra-acetyl allomucate. Although obtained as a solid, this compound has resisted all attempts to crystallise it from the usual solvents. The difficulties experienced with these two compounds is due mostly to their extreme solubility in alcohol and to their decomposition when heated above their melting point even in vacuo.

F. The rotation dispersion of di-l-menthyl tetra-acetyl allomucate and di-l-menthyl tetra-acetyl mucate

was determined in benzene for six colours of light. The solutions, owing to the amount of allomucate available, were necessarily dilute ($p \doteqdot 5$), but values were obtained for three separate specimens of allomucate and two different specimens of mucate. The readings for the mucate and allomucate were in each case taken concurrently so that the value for the rotation of each of the two isomers in a set was obtained as nearly as possible under identical conditions. From the results obtained the following specific rotations were calculated:-

A = Specific Rotation at 20°C. of di-l-menthyl tetra-acetyl allomucate,

B = Specific Rotation at 20°C. of di-l-menthyl tetra-acetyl mucate.

(1).

	A	B	Δ
r_1	-47.3	-32.1	15.2
r_2	-53.4	-37.5	15.9
y	-65.3	-44.5	20.8
g	-74.2	-49.9	24.3
b	-95.7	-64.9	30.8
v	-122.7	-83.1	39.6

(2).

	A	B	Δ
r_1	-47.4	-34.3	13.1
r_2	-53.7	-39.1	14.6
y	-64.2	-44.6	19.6
g	-72.8	-50.8	22.0
b	-92.9	-65.9	27.0
v	-124.8	-92.3*	31.5

(3).

	A	B	Δ	Mean A	Mean B	Mean Δ
r_1	-45.6	-31.2	14.4	-46.7	-32.6	14.1
r_2	-52.5	-36.6	15.9	-53.2	-37.8	15.4
y	-61.9	-42.6	19.3	-63.8	-43.9	19.9
g	-71.1	-49.9	21.2	-72.7	-50.2	22.5
b	-90.5	-63.8	26.7	-93.1	-63.9	29.2
v	-128.1*	-83.1	45.0	-123.7	-83.1	40.6

*These two values are erroneous (confirmed from graph): the mean value for violet light has therefore been calculated from only two readings.

EXPERIMENTAL - A.

Mucic Acid.

In course of this work large quantities of mucic acid were prepared by oxidation of lactose with excess 25% nitric acid. From each 100 g. of lactose about 35 g. of mucic acid were obtained.

Epimerisation of mucic acid.

150 g. of mucic acid were heated on an oil bath at 145-150°C. with 1½ litres of water and 150 g. of pyridine. The operation was carried out in a 3 ℓ. R.B. flask with an internal condenser made from a boiling tube of external diameter slightly less than the inside of neck of flask. The mixture under these conditions refluxed smoothly. At the end of 48 hours the hot solution was shaken with charcoal and filtered. The clear solution was vacuum distilled at 45° and 30 mm. for 10 hours and 50 g. mucic acid recovered unchanged. The remaining acids were precipitated with 150 g. crystalline $Ba(OH)_2$. After distilling off in vacuo most of the pyridine, the Ba salts were filtered (170 g.). Dried, suspended in 1 ℓ. of water, and 30 c.c. concentrated H_2SO_4 added. The mixture stirred for 2 hours on the water bath. The

filtrate concentrated to 250 c.c. in vacuo and then evaporated slowly at room temperature gave 37 g. of mixed acid, m.p. 163°. Further evaporation gave an additional 8 g. of m.p. 169-172°. Both crops were recrystallised from hot water and the initial precipitate, m.p. 210° mucic acid, filtered. The filtrate was allowed to evaporate in air and deposited 32 g. of acid, m.p. 165° (crude dl-talomucic). Further recrystallisation gave m.p. 168-170°. dl-talomucic acid.

Epimerisation in ammonia. (Posternak, Helv.Chim.Act., 1929, 12, 1181).

This method was adapted to the procedure of heating on an oil bath for 2 days at 135-140°C. 100 g. of acid, 60 c.c. concentrated ammonia. 1 ℓ. of water gave on so treating a light brown solution from which 1 ℓ. of alcohol precipitated 80 g. of ammonium salt. The alcohol was distilled off and the acids precipitated as their lead salts. The lead salts suspended in water were decomposed by passing in H_2S at 80°. The PbS was filtered and concentration of the mother liquors as before gave 12 g. of dl-talomucic acid, m.p. 169-172°C.

Epimerisation with aqueous pyridine in autoclave.

(E. Fischer, Ber., 1891, 24, 2136).

100 g. of acid, 1 ℓ. of water, and 100 g. pyridine heated for 3 hours at 4-5 atmospheres and 135°C.

Very heavy charring took place. The mixed acids were isolated through the Ba salts, and about 10 - 12 g. of dl-talomucic acid were obtained from each run.

Isolation of talomucic acid directly. (Cf. Haworth & Long, J.C.S., 1929, 345).

The pyridonium solution from 200 g. mucic acid was concentrated to 500 c.c. There separated 41 g. of unchanged mucic acid, m.p. 212°. On further concentration to 250 c.c., 20 g. mucic acid, m.p. 205-210°, were obtained. By continuous small addition of water and wash liquors the mother liquor as the pyridonium salt diminished, yielded various amounts of free acid, viz.,

	20 g.	m.p. 192-195°
	11 g.	m.p. 182°
	9 g.	m.p. 170°
	20 g.	m.p. 160°
(11+5+7+7)	30 g.	m.p. 165°
	5 g.	m.p. 167°.

156 g. of free acid in all had now been taken out and, as indicated by melting points, the amount of free mucic acid had steadily decreased.

The mother liquor, a thin syrup, now seemed to be inert. Alcohol in large quantities was added to a

small sample but practically no precipitate was obtained. The addition of 15 c.c. concentrated HCl gave 12 g. of acid, m.p. 170°. Further addition of HCl gave no further precipitate and the syrup would no longer evaporate. Thus some 30 g. of acid remained unaccounted for and total yield of dl-talomucic acid, m.p. 170-172°, was 42 g. on recrystallisation.

Treatment of dl-talomucic acid with acetic anhydride.

25 g. of dl-talomucic acid, prepared as on pages 22-23 once recrystallised from water, were heated gently with 65 c.c. acetic anhydride containing a trace of H_2SO_4. After the initial vigorous reaction the solution was refluxed for 45 minutes, cooled and poured into ice water. The crystalline solid was filtered and crystallised from 20% alcohol. A mixture of plates and needles (I) separated, m.p. 215° (5.2 g.). On further standing needles, m.p. 238° (.45 g.), came down.

(I) heated with 60-70 c.c. 20% alcohol almost to boiling. Filtered. The residue on recrystallisation gave plates (a) m.p. 215° (1.15 g.). The filtrate gave a mixture of needles and plates (II), m.p. 228° (2.45 g.).

(II) treated as before gave plates (b) m.p.215° (.13 g.) and mixture (III), m.p. 223° (1.5 g.).

(III) treated as before gave plates (c) m.p.218°

(.15 g.) and mixture mostly needles, m.p. 233° (1.5 g.).

(a), (b) and (c) on recrystallisation gave plates, m.p. 218-220° (1.1 g.). tetra-acetyl allomucate.

From a later experiment 120 g. dl-talomucic acid crystallised from water gave 5 g. tetra-acetyl allomucic acid, m.p. 220° plates, and 13.5 g. tetra-acetyl mucic acid, m.p. 239° needles.

The plates on analysis gave:

C, 40.73; H, 5.41; water, 8.68%.

$C_{14}H_{18}O_{12}.2H_2O$ requires:

C, 40.58; H, 5.37; water, 8.7%.

Talomucic acid and acetic anhydride.

50 g. of acid which had been previously treated with acetic anhydride and in that experiment had yielded tetra-acetyl allomucic acid, were recovered through the Ba salt and heated with a further 130 c.c. acetic anhydride. After heating for 1 hour the cold solution was poured into ice water and gave a crystalline precipitate which on purification and separation as previously described gave plates, m.p. 220° (tetra-acetyl allomucic acid) and needles, m.p. 240° (tetra-acetyl mucic acid). A little of the high melting fraction on hydrolysis gave an acid, m.p. 213°: mixed m.p. with mucic

acid (214°) gave 213°.

The acetic acid mother liquor when subjected to vacuum distillation and subsequent slow evaporation in air gave 22 g. of dl-talomucic acid, m.p. 168°. On treating this acid with fresh 60 c.c. acetic anhydride again plates, m.p. 220° and needles, m.p. 239°, which were identified respectively as tetra-acetyl allomucic and tetra-acetyl mucic acids, were obtained.

Treatment of purified dl talomucic acid with acetic anhydride.

dl-talomucic acid was vigorously purified in the following manner:- 12 g. of dl-talomucic were esterified by the method of Butler and Cretcher (J.A.C.S., 51, 2168) and after five recrystallisations 5 g. of pure ester were obtained, m.p. 136°.

These 5 g. of di-ethyl dl-talomucate were heated with 21 g. of acetic anhydride and a trace of sulphuric for 1½ hours. After several recrystallisations brilliant plates, m.p. 108°, were obtained. Yield, 6 g.

5 g. di-ethyl tetra-acetyl dl-talomucate were heated with 100 c.c. 10% concentrated HCl for 5 hours. On evaporation in air a white crystalline material was slowly deposited. This was an acid, m.p. 168-170°.

.2 g. of acid converted back to di-ethyl ester gave m.p. 135°.

2 g. thus purified dl-talomucic acid were treated with 7 c.c. acetic anhydride and heated for 1 hour. There seemed to be some reaction and a clear yellow solution resulted. This was poured into ice water and 100 mg. of tetra-acetyl mucic acid needles, m.p. 240° with decomposition were obtained. It was not possible to isolate any plates of tetra-acetyl allomucate from this product.

(2) The above experiment was repeated, viz:- 40 g. dl-talomucic, which had been purified with acetic anhydride, were transformed into the ester. 30 g. of di-ethyl ester, m.p. 135-136°, were obtained after two crystallisations from ethyl alcohol.

30 g. of di-ethyl ester were acetylated to give 35 g. tetra-acetyl di-ethyl ester: m.p. after three crystallisations 107-108°. This, on hydrolysis with dilute HCl, gave 15 g. acid, m.p. 166-168°. This acid with 65 c.c. acetic anhydride gave a very vigorous reaction. Heated for ¾ hour. Poured into ice water and stood over-night gave 4 g. of acetylated compound, m.p. 222-225°. Crystallised from 30% alcohol to give mixed needles and plates, m.p. 228°. These were separated as

previously described and on recrystallisation plates, m.p. 220-222° (.20 g.) and needles, m.p. 240° (1 g.) were obtained. A little of the plates were hydrolised with aqueous HCl to give free allomucic acid, m.p. 199°C.

Action of acetic anhydride on mucic acid.

(1) 10 g. mucic acid with 35 c.c. acetic anhydride and a trace of sulphuric acid were heated for 48 hours. Much charring took place and a solid was present for part of the time. The precipitate obtained on pouring into ice water was dissolved in 30% alcohol and cleaned with charcoal. 1 g. of tetra acetyl acid obtained. On further recrystallisation from 30% alcohol plates, m.p. 225°. Finally separated into plates, m.p. 220° tetra-acetyl allomucate and a little needles, m.p. 240°. tetra-acetyl mucate

(2) 50 g. of mucic acid, 130 c.c. acetic anhydride and .0014 g. concentrated H_2SO_4 heated for 48 hours. After three hours the solution was clear. At 17 hours, 22 hours, 28 hours, 40 hours and 48 hours 26 c.c. of solution (equivalent to 10 g. of mucic acid) were taken out and poured into water. Yield of acetylated product was (i) 2.3 g. (ii) 1.85 g. (iii) 1.8 g. (iv) 1.2 g. (v) 1.2 g. respectively. Crystallisation from 20% alcohol in water gave in each case needles tetra acetyl mucate

m.p. 242°C. There was no initial violent reaction.

(3) 20 g. mucic acid, 52 c.c. acetic anhydride, .0007 g. H_2SO_4 were heated for 5 hours. Then half the solution decomposed with water gave 2 g. of acetylated product. At 13 hours rest of solution gave 5.5 g. of acetylated product. There was present throughout the heating a certain amount of solid. There was no initial violent reaction.

(4) 20 g. of mucic acid, 52 c.c. acetic anhydride, .0028 g. H_2SO_4 were heated for 30 hours. On pouring sample (26 c.c.) into water, 7.5 g. of acetylated product were obtained which, on recrystallisation, gave needles, m.p. 240°. The heating of the other half of solution was continued for a further 20 hours. 8g. of acetylated acid were obtained. On purification once more needles (tetra-acetyl mucate) of m.p. 242° were obtained. The initial reaction was vigorous.

B. DERIVATIVES.

Allomucic Acid.

.2 g. of tetra acetyl allomucic acid was heated for 3 hours with 10 c.c. 10% concentrated HCl. The solution on standing in air for 3 days gave 100 mg. acid, m.p. 197-200°. Mixed m.p. with mucic acid (212°) 203 - 204°.

Analysis: C, 34.3; H, 4.87%. $C_6H_{10}O_4$ requires C, 34.28; H, 4.76%.

Di-ethyl allomucate.

By heating the free acid (100 mg.) in alcohol (2% HCl) white brilliant glistening plates, m.p. 155°. Mixed m.p. with di-ethyl mucate (169°) 145-146°.

Analysis: C, 45.3; H, 6.62%. $C_{10}H_{18}O_4$ requires C, 45.11; H, 6.77%.

As a further check the di-ethyl ester was acetylated and gave an identical tetra-acetyl di-ethyl ester as was formed by esterifying the tetra-acetyl di-chloride.

Tetra-acetyl allomucyl dichloride.

The tetra-acetyl acid was heated with PCl_5 in benzene for 1 hour and the crystalline compound obtained on recrystallisation from 120 petroleum ether had m.p.165°. Mixed m.p. with tetra-acetyl mucyl dichloride (189°)

gave m.p. 155°. It was found that $SOCl_2$ gave the best results and eventually benzene was replaced by toluene. 4 g. tetra-acetyl allomucic and 60 c.c. $SOCl_2$ in 40 c.c. toluene heated together for 6 hours. A clear solution was finally obtained and vacuum distilled to 20 c.c. Dichloride crystallised as fine needles, m.p. 155-160°. 2.7 g. obtained. Analysis: C, 40.36; H, 3.85%. $C_{10}H_{16}O_{10}Cl_2$ requires C, 40.48; H, 3.85%.

Tetra-acetyl di-ethyl allomucate.

The tetra-acetyl di-ethyl ester was obtained by heating the dichloride (50 mg.) with ethyl alcohol in benzene for 1 hour. On driving off solvent and crystallisation from alcohol, plates, m.p. 136°. Yield, 30 mg. Mixed m.p. with tetra-acetyl di-ethyl mucate (189°C.) gave 148°C. Analysis: C, 49.03; H, 5.84%. $C_{14}H_{26}O_{12}$ requires C, 49.76; H, 5.99%.

Tetra-acetyl di-ethyl dl-talomucate.

5 g. of di-ethyl dl-talomucate reacted readily with 21 g. acetic anhydride. Heated under reflux for 1½ hours. On pouring into water a white solid was obtained, m.p. 106°C. On repeated crystallisation from 40% aqueous alcohol 6.5 g. of ester, white needles, m.p. 108-109°. Analysis: C, 49.46; H, 5.68%.

$C_{14}H_{26}O_{12}$ requires C, 49.76; H, 5.99%.

Di-ethyl dl-talomucate.

12 g. talomucic and 12 g. absolute alcohol were heated with 1 c.c. concentrated H_2SO_4 for 5 hours. 10 g. of crystalline material, m.p. 105°C. were obtained. This was extremely soluble in alcohol and proved to be a mixture of the mono and di esters.

Tetra-acetyl mucyl dichloride.

The method of Diels & Löplund (Ber., 1914, 47, 2351) gave very poor results. The reaction did not go in the cold and at 40° with excess acetyl chloride and PCl_5, a Poor yield was obtained. The preparation was carried out in benzene with PCl_5 and gave good yield. Later, $SOCl_2$ was substituted for PCl_5. (Muller, Ber., 1914, 47, 2655). It is not necessary or desirable to use toluene as suggested by Karijome & Marotami (J.A.C.S., Abs. (1929), 4193).

Tetra-acetyl di-l-menthyl mucate.

This compound was prepared in various ways:

(a) Tetra-acetyl mucyl dichloride (500 mg.) and *l* menthol (500 mg.) were heated together on glycerine bath at 125° until evolution of HCl ceased. A poor yield, m.p. 153°, was obtained.

(b) Tetra-acetyl mucyl dichloride (500 mg.) and ℓ menthol (500 mg.) were heated in 10 c.c. 120/b.p. petroleum ether. HCl was given off and the solution went clear and then turbid. The turbidity was due to deposition of a small amount of free tetra acetyl acid. .4 g. ℓ menthyl ester, m.p. 151°, was obtained.

(c) Menthol, .7 g., was dissolved in 4 c.c. pyridine. The solution was/cooled in ice and tetra-acetyl mucyl dichloride slowly added. A precipitate appeared and was allowed to stand for 4 hours at 0°C. This on pouring into water gave a crystalline compound which, on recrystallisation from methyl alcohol, had m.p. 153°C. Yield, .3 g.

(d) Menthol, .2 g., and tetra-acetyl mucyl dichloride, .2 g., were heated with anisole, 5 c.c., for ½ hour. Moderate amount of HCl given off. On cooling free tetra acetyl mucic acid was deposited, m.p. 234° (purified 240°). The mother liquor on evaporation gave a gum from which free tetra-acetyl acid and a trace of ester, m.p. 152°, were isolated.

(e) According to method of Karijome & Marotami (loc. cit.). The reaction carried out in toluene gave considerable amount of free tetra-acetyl mucic acid and little ester.

Di-l-menthyl tetra-acetyl allomucate.

Tetra-acetyl allomucyl dichloride, 2.7 g. was added slowly to ℓ-menthol 3 g., kept at 125-130° on a glycerine bath. The heating was continued till no further evolution of HCl. On cooling, a solid mass was obtained which was dissolved in a minimum quantity of methyl alcohol. Repeated crystallisation from methyl alcohol and water gave .2 g. of ester, m.p. 135-136°. Analysis: C, 62.31; H, 8.29%. $C_{34}H_{54}O_{12}$ requires C, 62.4; H, 8.26%.

Of the previous experiments with di ℓ-menthyl tetra-acetyl mucate the cleanest and best method was that using pyridine. An attempt to apply it to the allomucate gave very poor yield of substance, m.p. 130° and a main acid portion.

Di-dl-sec-octyl tetra-acetyl mucate.

Tetra-acetyl mucyl dichloride, 1 g., was heated in benzene, 10 c.c., with sec-octyl alcohol, .6 c.c., for 8 hours. On taking off the benzene a semi crystalline mass smelling strongly of octyl alcohol was obtained. Attempts to crystallise from non hydroxylic solvents gave compound, m.p. 92-94°. The melting point could not be raised. Analysis: C, 56.87; H, 7.73% showed

low carbon. The rather wasteful method of crystallising from methyl alcohol finally gave plates, m.p. 102-103°. Analysis: C, 59.4; H, 8.4%. Theor. requires C, 59.8; H, 8.3%.

Purification d-sec-octyl alcohol. (Carried out after the method of Org. Syn., VI, 69).

The d-sec-octyl hydrogen phthalate after crystallisation from 98% acetic acid had $[\alpha]_g^{20}$ +57.95. The alcohol had boiling point 83°/20 mm. and rotation $[\alpha]_g^{20}$ +11.7.

di-d-sec-octyl tetra-acetyl mucate.

This compound was prepared similarly to the inactive ester. The solid obtained on evaporation proved exceptionally soluble in all common solvents. From methyl alcohol crystals, m.p. 114-115°C. C, 55.59, were obtained. This low carbon was at first put down to umesterung but six recrystallisations from methyl alcohol gave plates, m.p. 114-115°. Analysis: C, 59.8; H, 8.54%. Theor. C, 59.8; H, 8.3%.

di-d-sec-octyl tetra-acetyl allomucate.

2.5 g. of tetra acetyl allomucyl dichloride and 1.2 c.c. d-sec-octyl alcohol were heated together in 20 c.c. benzene for 12 hours. HCl was given off

continuously. On driving off the benzene a sticky mass was obtained smelling strongly of octyl alcohol. This mass when subjected to vacuum distillation at 120°/.04 mm. decomposed. In alcoholic solvents it was extremely soluble and could not be crystallised. From ether petroleum ether a non crystalline solid was obtained, m.p. 90-110°. It has proved impossible to purify this substance.

Benzyl iso-thio urea. (Veibel & Lillieland, Bull.Soc. Chim., 1938, 1154).

Thio urea 76 g., benzyl chloride 127 g. and alcohol 135 g. heated for 1 hour. The product crystallised from 2N HCl. On scratching 110 g. benzyl iso thio urea hydrochloride modification, m.p. 151°, were obtained.

Benzyl iso-thio urea dl talomucic acid.

dl-talomucic .2 g. in 2 c.c. water titrated with N NaOH to Me red then made very slightly acid. Benzyl iso thio urea .4 g. in 2 c.c. water added and on dilution with alcohol a neutral compound, m.p. 142°, with decomposition was obtained. On attempted purification the substance decomposed.

Benzyl iso-thio urea tetra-acetyl mucate.

Tetra-acetyl mucic acid .25 g. was treated as above and on standing gave a crystalline compound, m.p.

198°. On recrystallisation a neutral compound, m.p. 205°C. was obtained. Analysis: N found 7.54. $C_8H_{11}N_2S_2Cl$ requires N, 13.76. $C_{22}H_{28}O_{12}SN_2$ requires N, 5.14. $C_{30}H_{38}O_{12}S_2N_4$ requires N, 9.0. This substance must definitely be a mixture but no change in melting point, which was of a very indefinite character, could be obtained.

Benzyl iso-thio urea saccharate.

From .21 g. of crystalline (very soluble) saccharic acid no solid product could be obtained.

Brucine dl-talomucate.

dl-talomucic acid 1 g. with l-brucine 4.4 g. heated at boiling with 100 c.c. water for 15 minutes. On cooling needles formed in rosettes, m.p. 170°C. with decomposition.

d-strychnine dl-talomucate.

dl talomucate 5 g. and strychnine 7.95 g. treated in the same way gave needles, m.p. 182-185°C. with decomposition.

Tetra-acetyl di-p-nitro benzyl mucate.

1 g. of tetra-acetyl mucic acid was dissolved in 50% aqueous alcohol and titrated with 20% NaOH. The solution was turned just acid with a trace of HCl and the p-nitro benzyl bromide added. All constituents were

put into solution by addition of aqueous alcohol and the mixture refluxed for ½ hour. On cooling a compound, m.p. 195°, was obtained. Recrystallised to give m.p. 235°.

C. Rotation Dispersion di-l-menthyl tetra-acetyl mucate in benzene.

(1) Vol. of pyknometer at 20.05°C = 1.7061 c.c.
Density of solution = .88872
p = 5.5991g./100g. solution
Length of tube = .75 dm.

	λ	α	$[\alpha] = \frac{100\alpha}{\ell p d}$
r_1	6716.3	-1.20	-32.15
r_2	6234.3	-1.40	-37.50
y	5790.0	-1.66	-45.50
g	5460.0	-1.86	-49.91
b	4916.4	-2.42	-64.92
v	4358.6	-3.10	-83.10.

(2) Vol. of pyknometer at 20.05°C. = 2.3764 c.c.
Density of solution = .88978
p = 4.0283g./100g. solution
Length of tube = 1 dm.

	λ	α	$[\alpha] = \frac{100\alpha}{\ell p d}$
r_1	6716.3	-1.23	-34.33
r_2	6234.3	-1.40	-39.07
y	5790.0	-1.60	-44.65
g	5460.0	-1.82	-50.79
b	4916.4	-2.36	-65.87
v	4358.6	-3.35	-92.23

Analysis: C, 62.29; H, 8.29%. Required, C, 62.39; H, 8.26%.

(3) Vol. of pyknometer at 20.05°C. = 2.3764 c.c.
Density of solution = .88898.
p = 3.980g./100g. solution.
Length of tube = 1 dm.

	λ	α	$[\alpha] = \frac{100\alpha}{\ell pd}$
r_1	6716.3	-1.10	-31.2
r_2	6234.3	-1.30	-36.59
y	5790.0	-1.50	-42.57
g	5460.0	-1.76	-49.95
b	4916.4	-2.25	-63.86
v	4358.6	-2.93	-83.15

Rotation Dispersion di-l-menthyl tetra-acetyl allo-mucate in benzene.

(1) Vol. of pyknometer at 20.05°C. = 2.3764 c.c.
Density of solution = .88906.
p = 4.9114g./100g. solution.
Length of tube = .75 dm.

	λ	α	$[\alpha] = \frac{100\alpha}{\ell pd}$
r_1	6716.3	-1.55	-47.33
r_2	6234.3	-1.75	-53.44
y	5790.0	-2.14	-65.34
g	5460.0	-2.43	-74.20
b	4916.4	-3.13	-95.57
v	4358.6	-4.02	-122.76

(2) Vol. of pyknometer at 20.05°C = 2.3764 c.c.
Density of solution = .88612.
p = 2.4781g./100 g. solution.
Length of tube = 1 dm.

	λ	α	$[\alpha] = \frac{100\alpha}{\ell pd}$
r_1	6716.3	-1.04	-47.3
r_2	6234.3	-1.18	-53.7
y	5790.0	-1.41	-64.2
g	5461·0	-1.60	-72.8
b	4916.4	-2.04	-92.9
v	4358.6	-2.74	-124.8

Analysis: C, 62.07; H, 8.19%. Required, C, 62.39; H, 8.26%.

(3) Vol. of pyknometer at 20.05°C = 2.3764 c.c.
Density of solution = .89696.
p = 4.9017g./100g. solution.
Length of tube - 1 dm.

	λ	α	$[\alpha] = \frac{100\alpha}{\ell pd}$
r_1	6716.3	-1.23	-45.61
r_2	6234.3	-1.40	-52.49
y	5790 .0	-1.60	-61.88
g	5461 .0	-1.82	-71.05
b	4916.4	-2.36	-90.54
v	4358.6	-3.35	-128.12

Rotation of l-menthyl dehydro mucate in chloroform.

Length of tube = 160 mm. p = 3.459g./100 g. solution.

Vol. of pyknometer at 20.05°C. = 2.3764 c.c.

Wave length of light used Hg_y 5790; Hg_g 5461;

Hg_v 4358.6.

T°C.	d	α	$[\alpha] = \frac{100\,\alpha}{l\,p\,d}$
0°	1.535	y -5.43	-65.05
		g -6.20	-74.27
		b-10.24	-122.7
11.8	1.4692	y -5.34	-64.87
		g -6.09	-74.05
		b-10.05	-122.24
21	1.4660	y -5.18	-65.75
		g -5.99	-73.61
		b -9.95	-122.3
30	1.4510	y -5.19	-64.44
		g -5.90	-73.26
		b -9.73	-120.81
40	1.4341	y -5.08	-63.82
		g -5.80	-72.86
		b -9.53	-119.23
51	1.4139	y -5.06	-64.46
		g -5.75	-73.27
		b -9.43	-120.12

DISCUSSION.

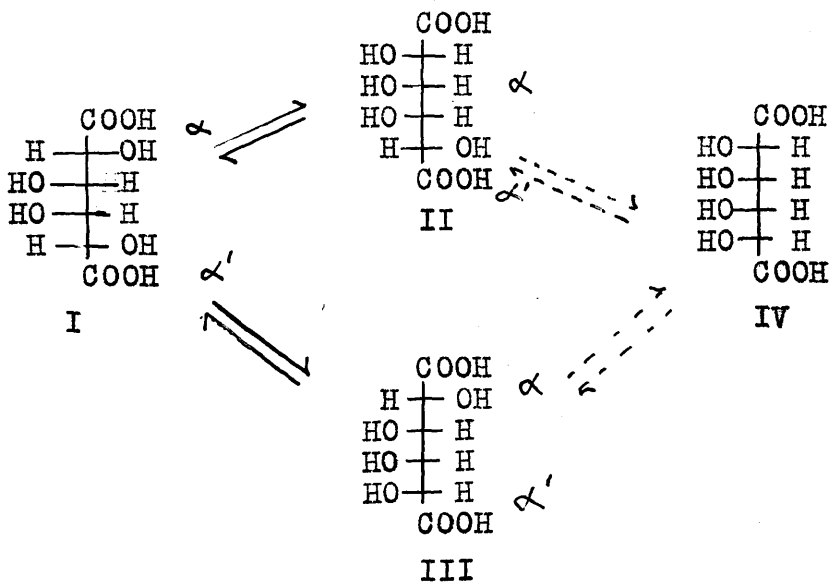
A. Epimerisation products of mucic acid.

Though allomucic acid was successfully isolated as previously described, the question of its formation by treatment of mucic acid with aqueous pyridine is still in some doubt. The main product of this treatment is dl-talomucic acid and this would necessarily be an intermediate in the formation of any allomucic acid. Now it has been shown in the present work that treatment of dl-talomucic with acetic anhydride, however rigorously the acid has been purified, always gives tetra-acetyl mucic acid and tetra-acetyl allomucic acid. The isomerism of these acids makes purification extremely difficult and it would still be possible that the acetylated products obtained were derived merely from the other two acids present as impurity. However, the fact that dl-talomucic twice recovered from such treatment and further treated with fresh acetic anhydride still yields tetra acetyl derivatives of both mucic and allomucic acids shows that dl-talomucic acid itself undergoes rearrangement in acetic anhydride.

This rearrangement, discussed later, complicated the investigation of the products of the epimerisation of

mucic acid. The allomucic acid isolated, was obtained by treatment of the product of this epimerisation with acetic anhydride. Consequently, the allomucate obtained could be derived either directly from mucic acid during epimerisation or formed by the action of the acetic anhydride on dl-talomucic acid.

Fischer[13] isolated only one product from this epimerisation, i.e., dl-talomucic acid, and Posternak[14] has stated, though he does not describe the methods he used, that he was unable to identify any product from the epimerisation of mucic acid other than dl-talomucic acid. The theoretical consideration that postulates the formation of allomucic acid (IV) in this epimerisation is that since both the d (II) and the l (III) forms of talomucic acid are obtained, then both the α and the α' carbon atoms in mucic acid I must be free to epimerise.

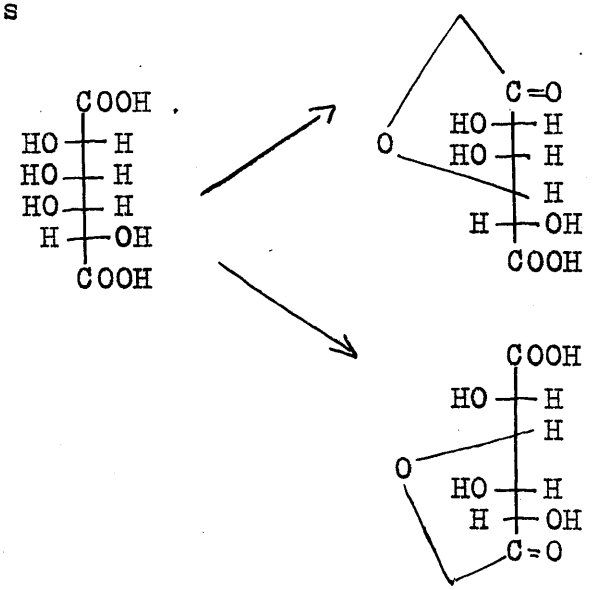


Consequently both the α and α' carbon atoms in mucic acid behave identically with aqueous pyridine. Since the product is inactive and a racemate, neither the α nor α' carbon is inverted at the expense of the other, i.e., both ends of the symmetrical mucic acid molecule have an equal chance of being inverted. Now if allomucic acid IV is not formed in the epimerisation, it must be concluded that in talomucic acid the α and α' carbon atoms do not behave identically in aqueous pyridine. In other words, that in talomucic acid the only terminal carbon atom which is free to invert is the one which has initially undergone inversion.

The evidence in support of this view is meagre. Firstly, we have the results of Fischer and Posternak. Secondly, when dl-talomucic acid is treated with acetic anhydride there is always produced tetra-acetyl allomucate. It is significant, that treatment of crude talomucic acid from epimerisation of mucic with aqueous pyridine (which should contain any allomucic acid produced in that reaction) does not give a higher yield of tetra-acetyl allomucate than dl-talomucic acid from which all acetylateable impurities have been previously removed.

On the other hand, it is difficult to see why, or how one of the terminal carbons should be blocked. A

study of carbon models shows that there is no apparent spatial consideration involved. Fischer has stated that one of the conditions for epimerisation is absence of lactone formation, and thus epimerisation is always carried out in presence of a base. The faint possibility of mono lactone formation at one end of the carbon chain being the inhibiting factor has been rendered even less likely by the work of Steiger and Reichstein[51]. They prepared from d-talomucic acid the two possible γ lactones



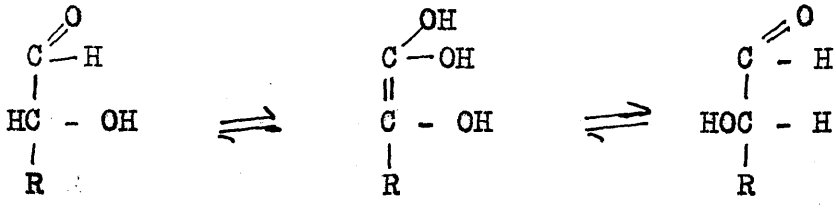
therefore both the α and α' terminal carbon atoms would be equally liable to be blocked by lactone formation. It must be concluded then, that there is insufficient evidence to show whether or not allomucic acid is a product of the epimerisation of mucic acid.

B. Rearrangement in acetic anhydride.

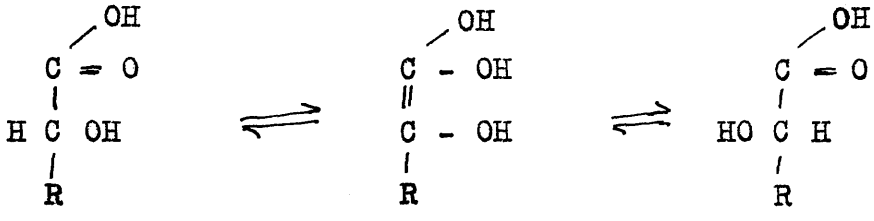
It has been shown herein, that dl-talomucic acid undergoes rearrangement in acetic anhydride to give the acetyl derivatives of mucic and allomucic acids. As far as can be ascertained by a careful search of the literature, the only acetylated derivatives of tetra-hydroxy adipic acids previously described are tetra-acetyl mucic acid[52] and the di-acetyl di-lactones of saccharic[53] and l-manno saccharic acids[54]. Thus it appears that with the new allomucic acid there are only two of the six dibasic sugar acids, saccharic, ido-saccharic, manno saccharic, mucic, talomucic and allomucic acids, which are capable of forming tetra-acetyl derivatives. Considering the extreme solubility of these hydroxy acids and the suitability of acetyl derivatives for characterisation, it is difficult to believe that no attempt has been made to prepare acetyl derivatives, but none has been reported.

The failure, therefore, of dl-talomucic acid to form an acetyl derivative is not in itself surprising. The fact, however, that it should undergo rearrangement akin to epimerisation in acetic anhydride is noteworthy. Epimerisation has been carried out in various mediums

(e.g., pyridine[13], quinoline[55], ammonium hydroxide[56], $Ca(OH)_2$[57], etc.) but so far as is known these rearrangements all take place in alkaline conditions. The present rearrangement is exceptional in the nature of the medium and for the fact that it takes place remarkably quickly for a reaction of this type. The heating in most cases was continued for only one hour and extension of this time made no difference to the result. The reaction, true to type, seems to involve an equilibrium as the amount of mucic and allomucic acids produced is always in the ratio of about 3:1. dl-Talomucic acid is a particularly suitable subject for rearrangement in acetic anhydride. The acid itself does not acetylate, therefore the possibility of secondary reaction is enhanced. Again the products of the rearrangement both form insoluble acetyl derivatives and are thus readily isolated. Even assuming that an acetyl derivative of dl-talomucic acid is first formed, this does not preclude the possibility of subsequent rearrangement. The work of Lewis and collaborators[57] on sugars strongly supports the view that rearrangement takes place through an intermediate "ene diol"



A similar mechanism is conceivable with acids



Lewis in the case of the methylated sugars and Haworth and Long[58] with methylated sugar lactones have shown that blocking the hydroxyl group on the α carbon atom with a methyl group does not prevent epimerisation, and therefore by analogy it would seem improbable that an acetyl group on this carbon atom would have any inhibiting effect.

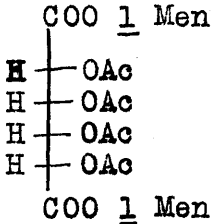
Recently it was decided to investigate the action of acetic anhydride on mucic acid. Mucic acid readily acetylates and to promote a possible secondary reaction the heating was prolonged. Under these conditions, in a preliminary experiment, much charring took place, but from the charred product tetra-acetyl allomucate was definitely isolated. Under modified conditions rearrangement did not take place. Time has not

permitted a full investigation, but it seems possible that mucic acid with acetic anhydride behaves similarly to dl-talomucic acid.

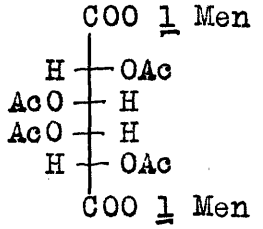
It will be readily appreciated that by means of this rearrangement in acetic anhydride, allomucic acid can be easily obtained, possibly from mucic acid and definitely from dl-talomucic acid. A new and time-saving route to synthetic sugars of the ribose structure can thus be envisaged.

C. Van 't Hoff's Law of Optical Superposition.

The successful preparation of l-menthyl tetra-acetyl allomucate (I) afforded a unique opportunity of testing the validity of the law of optical superposition by a comparison of the rotation value of this compound with that of l-menthyl tetra-acetyl mucate (II).



I



II

Now, if van 't Hoff's Law holds, the rotation due to the acid radicles would be zero and so the rotation of each ester would be that due to the two l-menthyl

radicles, i.e., identical. The actual values obtained for green light for three separate samples of allomucate A and two samples of mucate B were

	$[A]^{g}_{20}$	$[B]^{g}_{20}$	Δ
1.	-74.2	-49.9	24.3
2.	-72.8	-50.8	22.0
3.	-71.1	-49.9	21.2

It will be seen that there is a considerable difference between the rotation of l-menthyl tetra-acetyl allomucate and l-menthyl tetra-acetyl mucate. This difference in the three cases is far outwith the limits of experimental error and it must be concluded therefore that van 't Hoff's Law does not hold.

This conclusion is in agreement with that reached by Patterson and his co-workers. In previous work (2, et seq.) the mean value for the specific rotation of the two active esters of the d and l forms of an acid has been compared with the rotation of the corresponding active ester of the inactive form. The present case offers a much more direct and rigid comparison. Again in this case the difference is much larger than in some of the previous work and is such as to preclude the possibility of experimental error. It is interesting to

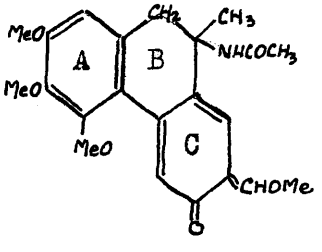
note that the rotation of the allomucate is greater than that of the mucate. This is further corroborative evidence as to the authenticity and purity of the allomucate. For instance, it might be suggested because of its lower melting point, that it was merely the mucate with some impurity present. It is almost certain that the impurity would also have lowered the rotation and that [A] would have been less than [B].

In conclusion, to quote Patterson and Fulton, "The difference can hardly be ascribed to anything else than the different arrangement of the groups attached to the asymmetric carbon atoms in the mucic and allomucic acids; and such a difference, we consider, would be a sound disproof of van 't Hoff's conception."

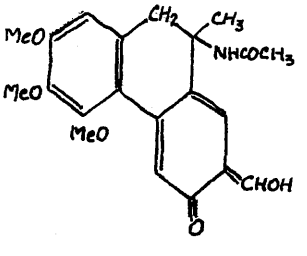
Synthetic Approaches to the Colchicine Molecule.

INTRODUCTION.

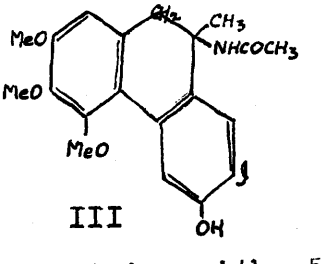
The alkaloid colchicine was first isolated in 1820 by Pelletier and Caventou[19] from the seeds and corms of the autumn crocus. Zeisel[23] first obtained it in a pure condition and carried out preliminary research into the structure of the degradation products. He gave it the molecular formula $C_{22}H_{25}O_6N$. In 1923 Windaus[24], after a careful investigation, gave the structure (I) to colchicine and assigned structures to the transformation products.



I



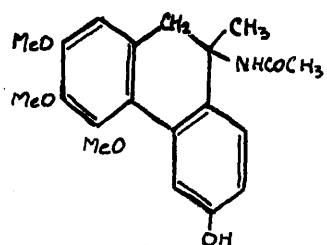
II



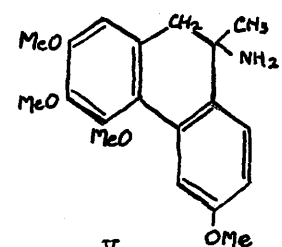
III

By hydrolysis of colchicine with .5% hydrochloric acid

he obtained readily the hydroxy methylene ketone colchiceine (II). Treatment of colchiceine with iodine and alkali gave N-acetyl iodo colchinol (III) and reduction of this compound N-acetyl colchinol (IV.) Further degradation to colchinol methyl ether (V) was carried out by methylation and subsequent hydrolysis of the acetyl group.

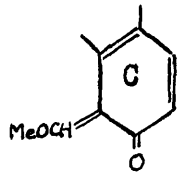


IV

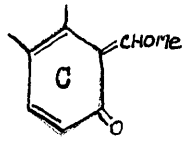


V

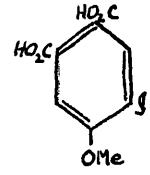
The Windaus constitution for colchicine is probably essentially correct, but recently the growing biological importance of the alkaloid has led to further investigation. The hydrogenation of colchicine was studied by Windaus who obtained what he thought was an octa-hydro derivative. Recently Bursian[25] investigated the hydrogenation of colchicine and colchiceine and found that actually a hexa-hydro derivative is formed. Bursian also found that the ultra violet absorption spectra agreed with the Windaus structure. In ring C however he suggested, from erroneous evidence supplied by Grewe, that the position of the substituents was as in (VI) or (VII.)



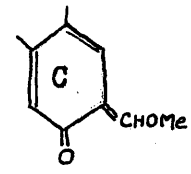
VI



VII

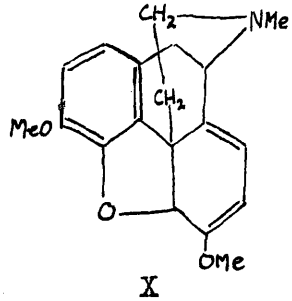


VIII

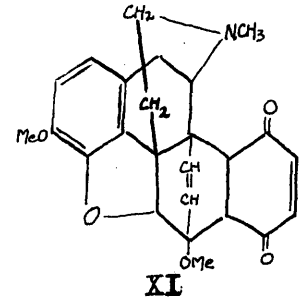


IX

Grewe[26] however states in a later paper that the product of the permanganate oxidation of N-acetyl colchinol methyl ether is identical with 5 iodo 4 methoxy phthalic acid (VIII) and therefore ring C in colchicine has the structure (IX.) It is still possible that the position of the substituents requires to be interchanged. It is interesting to note that Sandeman[27] has observed that thebaine (X,) an alkaloid with certain points of resemblance to colchicine, adds p quinone to form the compound (XI.)



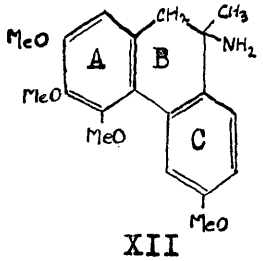
X



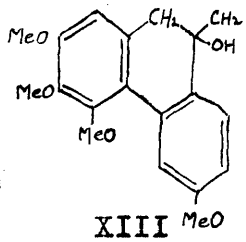
XI

He has however failed to obtain any similar condensation between colchicine and maleic anhydride. This might suggest an absence of diene structure in ring C.

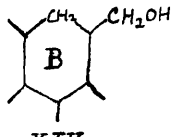
Cohen, Cook and Roe[28] have pointed out various inconsistencies in the Windaus structure. Ring B, as postulated, fails to account for certain behaviour of colchinol methyl ether (XII)



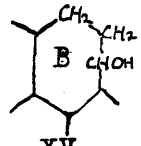
XII



XIII



XIV



XV

This structure is a 9.amino 9:10-dihydrophenanthrene and as such should readily lose ammonia to give the parent phenanthrene. Windaus himself with Eikel[29], in a synthesis of a simple analogous compound, has recorded such behaviour. Colchinol methyl ether does not show this instability.

Again Cohen and Cook[28] have prepared by the action of nitrous acid on colchinol methyl ether a carbinol which, according to the colchicine formulation of Windaus, should have structure (XIII.) They state, however, "The stability of this carbinol is quite incompatible with the structure of a tertiary carbinol related to 9:10 dihydrophenanthrene." These authors suggest that the amino

group in colchinol methyl ether might be in the side chain and the carbinol therefore have the structure (XIV.) N-acetyl colchinol methyl ether is, however, resistant to dehydrogenation with Pt black at 280° and this stability is not consistent with that of a dihydrophenanthrene with unsubstituted hydrogen atoms at positions 9 and 10 given by their formula. Again the behaviour of dihydrophenanthrenes with numerous substituents in rings A and C (e.g., highly methoxylated dihydrophenanthrenes) has not been investigated. It is still possible therefore, that a dihydrophenanthrene structure is present in (XII), (XIII), etc., and that the instability of the normal dihydro form is removed by such substitution. Attempts have been made to differentiate between primary, secondary and tertiary structures for this carbinol but oxidation failed to yield any identifiable aldehyde or acid and tests with phthalic anhydride were inconclusive, though a secondary carbinol seemed to be indicated, and the formation of a hydrogen phthalate seemed to preclude a tertiary carbinol.

The evidence for the phenanthrene structure in colchicine rests on the degradation of colchinol methyl ether by exhaustive methylation, subsequent demethylation and distillation with Zn, to 9-methyl phenanthrene. Cohen,

Cook and Roe point out that it is possible that ring B undergoes molecular rearrangement in the process of distillation with Zn dust and suggest that a seven membered ring at B.(XIII) would accommodate all the above evidence. Again, Wallach[30] has shown that in the case of cyclo pentyl methylamine and cyclo hexyl methylamine the action of nitrous acid causes ring enlargement to give an alcohol in a six and seven membered ring respectively. It is possible then, that in this case a seven membered ring with a secondary carbinol could arise in a similar fashion.

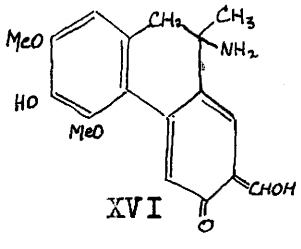
Colchicine is of considerable biological importance. It has the property of inhibiting mitosis or cell division and has been used for this purpose in various biological fields. In plants it causes enlargement of cells and abnormal nuclei. It also leads to the formation of tissue containing cells with double the number of chromosomes.

Since colchicine arrests dividing cells in metaphase, the growth response to various substances can be accurately plotted by the use of the alkaloid as an indicator of divisional capacity in cells.

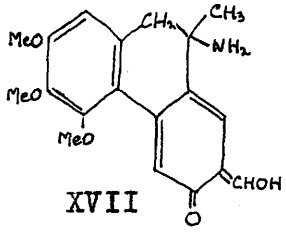
In 1935 Amoroso[31] carried out experiments with colchicine and found inhibition of tumour growth in mice

and a dog, but uniform results have not been obtained by subsequent workers.

Brues and Cohen[32] have investigated the various degradation products of colchicine on the regenerating liver of the rat and have found that, with the exception of di-methyl (XVI) and tri-methyl colchinic acids (XVII), they all showed the characteristic mitotic effect of colchicine.



XVI

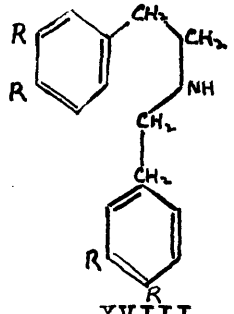


XVII

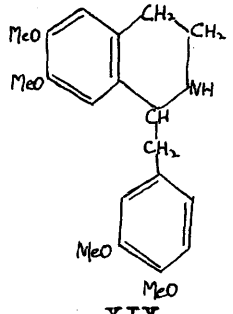
The toxicity of colchicine and its transformation products is such as to limit severely the dose and this was a serious handicap. From their investigation, Brues and Cohen came to the conclusion that it cannot be said that any single group is essential for the mitotic inhibiting action, though from the fact that the lethal effect only occurs after the mitotic effect has worn off, they suggest that the two effects may be dissociated and therefore due to different groups in the molecule.

It has been shown in the case of some alkaloids that complete ring systems are not essential to their biological properties and Buth, Kulz and Rosenmund[33] have

recently prepared a series of dicyclic compounds (XVIII) (R = MeO, methylene dioxy, etc.) analogous to tetra hydro papaverine (XIX) in which the characteristic spas molytic action of papaverine is retained.

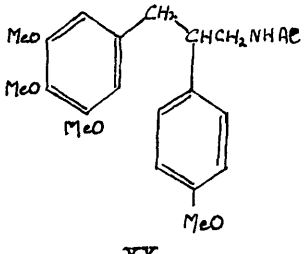


XVIII

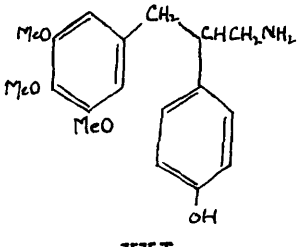


XIX

Cook and Engel[34], in an attempt to prepare less toxic compounds which would retain the action of colchicine on cell division, obtained the substituted diphenyl propylamine (XX) which is possibly an open chain analogue of colchinol methyl ether.



XX

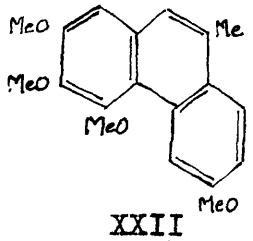


XXI

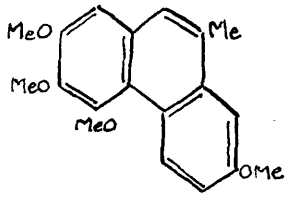
This compound has some activity and a certain effect on mitosis in the liver of a rat. Further extensive tests have shown that it is practically devoid of further general pharmacological activity, due probably to the low solubility.

Objects of the present work.

If colchinol methyl ether is a dihydrophenanthrene, the tetra methoxy compound formed on exhaustive methylation should be 2.3.4.6(XXII) or 2.3.4.7(XXIII) tetra methoxy 9 methylphenanthrene



XXII



XXIII

The initial aim of the present work was therefore to synthesise both these compounds and so determine whether or not colchicine has the phenanthrene structure.

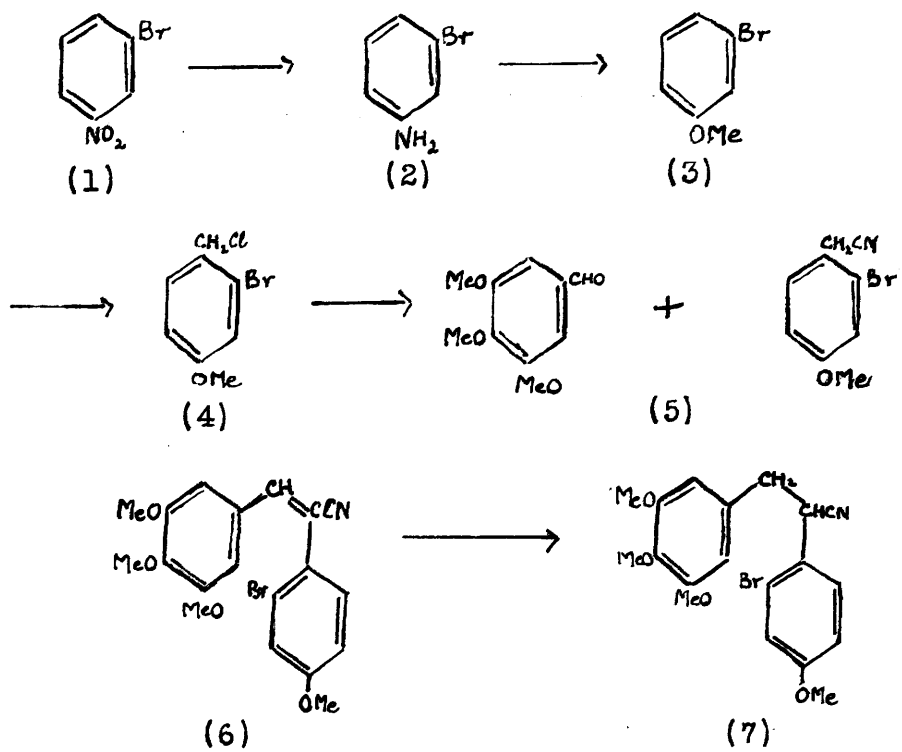
Simultaneously, it was hoped to synthesise analogous compounds to colchicine of possible biological importance; in particular to prepare the analogue (XXI) of Cook and Engels' compound, in the hope of increasing the solubility.

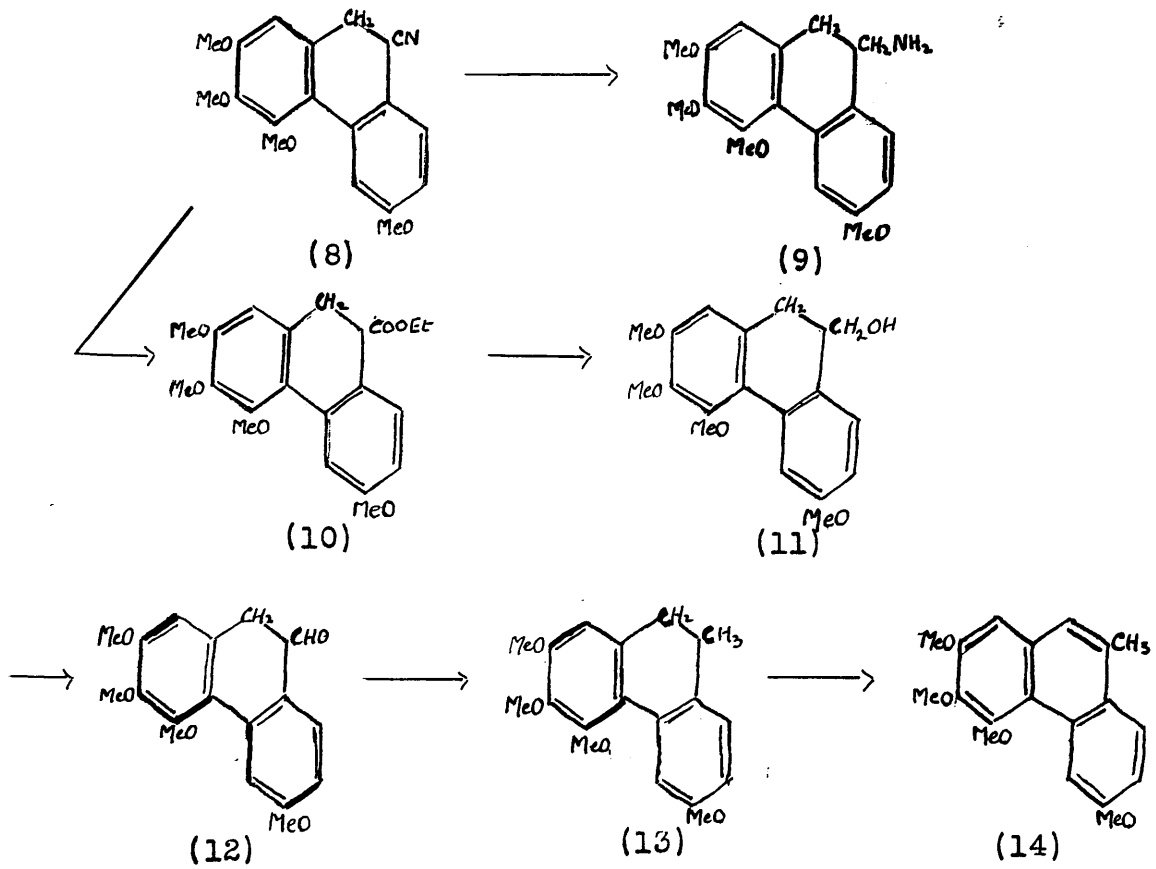
Synthetic approaches to the above structures.

The synthesis of this methoxylated phenanthrene skeleton is complicated by the very poor yield of 2-nitro-3.4.5-tri methoxy benzaldehyde obtained by nitration of 3.4.5-tri methoxy benzaldehyde. The nitration of this

latter compound has been investigated by Sharp[35], who obtained a very poor yield. Again Cook and Engel attempted to nitrate the anil but with no better success. Since failure to obtain this nitro aldehyde precludes the application of the Pschorr synthesis to these phenanthrenes, a further attempt was made to prepare this compound using the diacetate of the aldehyde which was readily prepared. Various conditions and methods of nitration were tried but no product was obtained other than a gum from nitration in acetic anhydride. This did not yield to purification.

A. In the absence of the nitro aldehyde then, the following scheme was worked out for the synthesis of 2.3.4.6-tetra methoxy-9 Me-phenanthrene:-



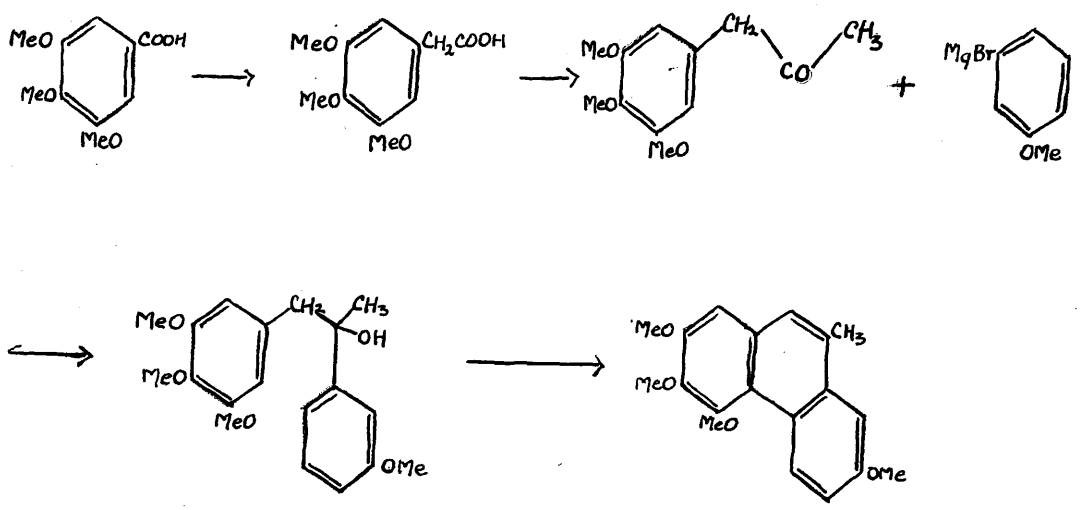


From the above scheme it will be seen that from the intermediate compound (8) there are two possibilities. Thus simple catalytic reduction should give (9) which is a possible structure for colchinol methyl ether. Again, hydrolysis of the nitrile (8) to the acid, esterification (10), reduction to the alcohol (11) by the Bouveault method, oxidation to the aldehyde (12) and reduction by the Wolff-Kishner method should give the dihydro methyl phenanthrene (13) which on subsequent dehydrogenation should give the desired 2.3.4.6-tetra methoxy 9 Me phenanthrene.

The preparation of m-bromo aniline was carried out smoothly after some initial difficulty in reduction of the nitro compound. The method of Holleman[36] using Fe and H_2SO_4 was unsatisfactory, probably due to quality of Fe powder available. The preparation of m-bromo anisole by the method of Hewitt[37] was very successful.

Disappointing results were obtained on chloromethylation of this anisole. Similar methods to those used by Quelet and Allard[38] in the chloromethylation of anisole gave unchanged starting material, while an adaptation of the method of Darzen and Levy[39] gave a product contaminated by several by-products. From the most hopeful fraction the nitrile was prepared but failed to give a homogeneous acid on hydrolysis. A small amount of neutral product of the hydrolysis was obtained crystalline, but the acid could not be purified. The non homogenity of the acid might be due to the production of both the 2 & 4 chloro methyl-3-bromo anisoles.

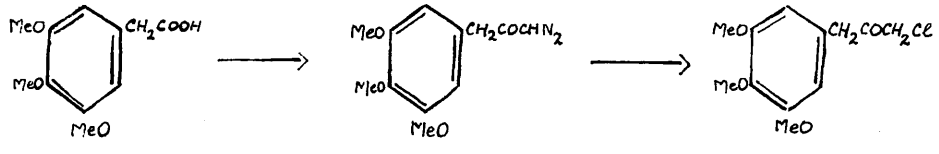
B. Since the preparation of chloro methyl anisole did not yield the desired compound, it was decided to utilise the bromo anisole to prepare 2.3.4.7-tetra methoxy-9-Me. phenanthrene as outlined below:



The preparation of the higher homologue of tri methyl gallic acid was carried out through the diazo ketone as described by Baker, Morgan and Robinson[40]. Using the method of Arndt and Eistert[41], the acid amide was prepared from this ketone. All attempts to condense this amide with methyl magnesium iodide were unsuccessful. Application and modification of the methods of Beis[42] and Jenkins[43] gave no identifiable ketone. It was not found possible to dehydrate this amide to the corresponding nitrile in good yield.

Hydrolysis of the amide with alkali gave 3.4.5-tri methoxy phenyl acetic acid identical with that described by Mauthner[44]. Application of a method of Warren and

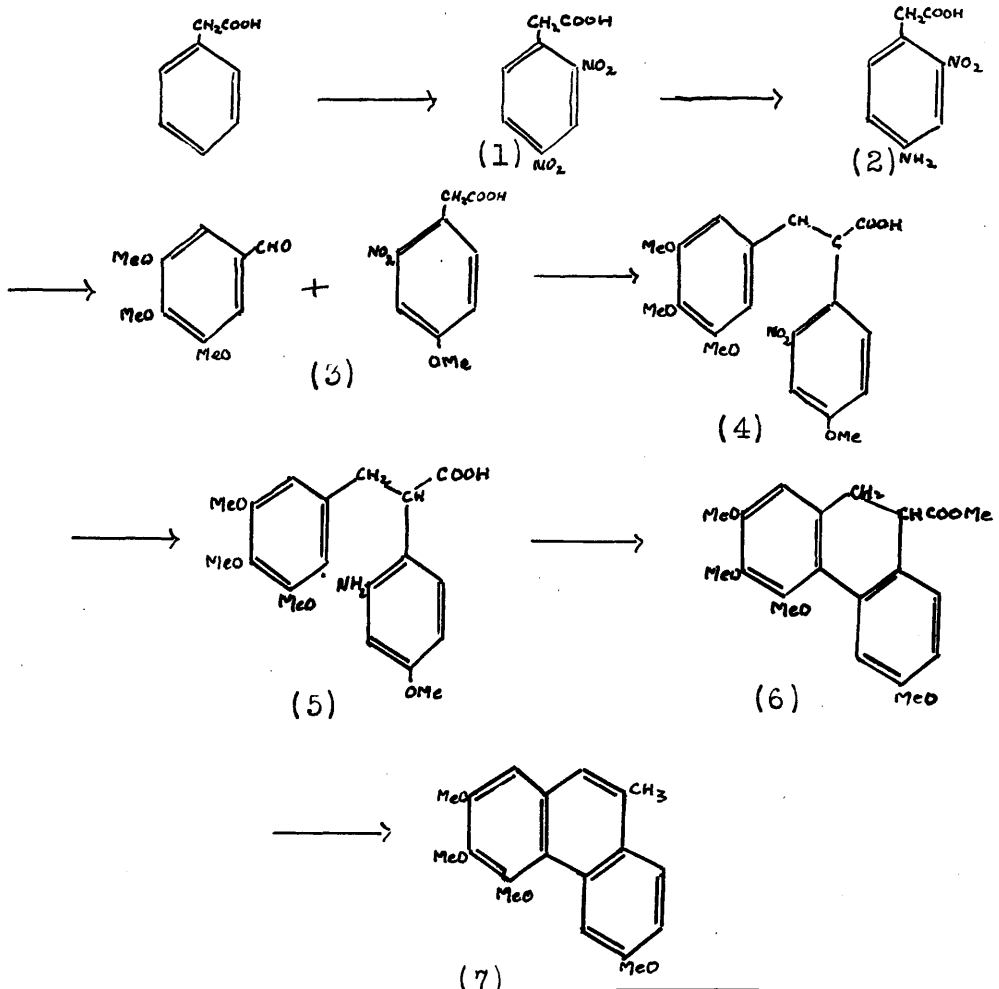
Williams[45] to obtain the acid direct from the diazo ketone gave an indifferent yield. Considerable difficulty was experienced in the formation of the 3.4.5-tri methoxy phenyl acetyl chloride. The highly methoxylated phenyl acetic acid showed a tendency to instability towards chlorinating agents. By employing mild conditions the chloride was formed by the action of thionyl chloride, but not isolated. A solution in ether was used for further reaction with diazo methane. The diazo ketone formed was treated with ethereal HCl and γ-chloro α-(3.4.5-tri methoxy phenyl) acetone formed (the analogous γ-chloro-α-(3.4-di methoxy phenyl) acetone has been prepared by Haworth and Atkinson[46]) viz:-



This compound promises to be a very useful reagent in the preparation of this type of phenanthrene compound, as the chlorine should be replaceable by NH_2, OH, etc. Some difficulty was experienced in obtaining the chloro acetone pure, due entirely to difficulty in forming the acid chloride without any decomposition. Surprisingly it resisted reduction with hydrogen and palladium. (Haworth and Atkinson state that they were unable to obtain

condensation products with their chloro compound and Na aceto acetic ester.) The chlorine does not seem to be exceptionally labile. Lack of material and time prevented a further investigation of this line, but a preliminary condensation of the chloro ketone with m-anisyl magnesium bromide was carried out.

C. Since the proposed route to 2.3.4.6 tetra methoxy 9 methyl phenanthrene had not given the desired result, an alternative scheme for the preparation of this compound was drawn up as outlined below:



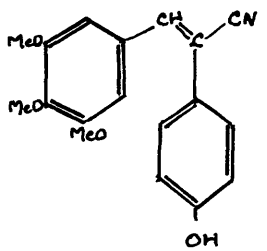
The ring closure at (5) to (6) could in this scheme be carried out by the Pschorr method. The intermediates between stages (6) and (7) were identical with the previous scheme.

2.4-dinitro-phenyl acetic acid was prepared by the method of Borsche[47]. As can be seen, the synthesis depends on partial reduction of this dinitro compound to 2-nitro-4-amino-phenyl acetic acid. Borsche claims to have carried out this partial reduction, but does not state definite conditions. Reduction with sodium trisulphide gave a mixture of 2-nitro-4-amino -toluene and 2.4-dinitro toluene. Attempts to apply the method of Curtius[48] using hydrazine hydrate were also unsuccessful, giving decarboxylation to dinitrotoluene. In an attempt to overcome this difficulty, the methyl ester was prepared and treated with hydrogen in presence of Pd. charcoal catalyst. The solubility of the ester in alcohol or acetic acid is not very high and it was found that the product decomposed on concentration of these solutions even in vacuum. Unsatisfactory results were also obtained using dioxan as solvent.

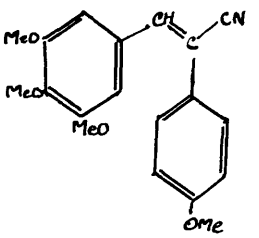
Further evidence was obtained on the stability

of N-acetyl colchinol methyl ether to dehydrogenation. Using a method of dehydrogenation described by Ritter and Sharp[49], the N-acetyl colchinol methyl ether was heated with iso amyl disulphide at 240-250° for 14 hours. It was recovered unchanged.

Unpublished work by Lawrence[50] was repeated and extended. Lawrence had prepared α-cyano α-(p hydroxy phenyl)- β (3.4.5 tri methoxy phenyl) ethylene (1) by condensation of 3.4.5 tri-methoxy benzaldehyde and p-hydroxy benzyl cyanide



(1)



(2)

The condensation was carried out in presence of Na-ethoxide. This condensation was repeated and the product definitely identified by methylation of the hydroxyl group. It then proved identical with α cyano α. p-anisyl β -(3.4.5 tri methoxy phenyl) ethylene (2) prepared by Cook and Engel[34] by condensation of 3.4.5 tri methoxy benzaldehyde and sodium p-anisylacetate.

Preliminary experiments were carried out on the catalytic hydrogenation of this compound. It proved resistance to hydrogenation with Pd catalysts. It also resisted hydrogenation in presence of platinum. This last experiment was inconclusive and is being reinvestigated with more active catalyst.

EXPERIMENTAL.

Colchiceine.

5 g. of colchicine and 3 c.c. concentrated HCl were heated to boiling in 300c.c. water. After 1 hour spontaneous crystallisation took place. Filtered, washed well with water and dried. Yield, 3.2 g.

N-acetyl-iodo colchinol.

2.5 g. of colchiceine were stirred into 50 c.c. N NaOH. Cooled in ice and 250 c.c. of a solution of 5 g. iodine and 25 g. potassium iodide run in slowly. No green colour developed when a sample was treated with acid and $FeCl_3$. Acidified with dilute H_2SO_4 and SO_2 bubbled in for 15 minutes. Filtered, washed and dried. Titurated with methyl alcohol, crystallised from absolute alcohol in yellow transparent plates, m.p. 225°C.

N-acetyl colchinol.

2 g. N-acetyl iodo colchinol boiled with excess zinc and 60 c.c. N NaOH for two hours. Acidification gave white precipitate recrystallised from 20% Me alcohol in white needles, m.p. 149° with decomposition. Yield, .85 g.

N-acetyl colchinol methyl ether.

.8 g. N-acetyl colchinol were dissolved in 40 c.c.

10% NaOH and 4 c.c. Me_2SO_4 added. Shaken for 3 hours and filtered. This was repeated until no more solid was obtained. Recrystallised from aqueous methyl alcohol in plates, m.p. 198-199°. Yield, .4 g.

3:4:5-trimethoxy benzoyl chloride.

135 g. trimethoxy benzoic acid were refluxed with 390 c.c. thionyl chloride for 2 hours. Excess thionyl chloride taken off and solid crystallised from benzene petroleum ether. Finally obtained as light red needles, m.p. 79-80°. Yield, 110 g.

Repeated with 67 g. trimethoxy benzoic acid. The product vacuum distilled, b.p. 165-167°/10 mm.: white crystalline solid, m.p. 80°. Yield, 55 g.

3:4:5-trimethoxy benzaldehyde.

Reduction of acid chloride carried out according to Nierenstein (J.pr.Chem., 1931, 132, 200) gave unchanged chloride, m.p. 79° and white crystalline non-aldehydic, non-acidic compound, m.p. 157-158°. (Analysis: C, 58.98; H, 5.81). Yield, 4 g. Repetition of this experiment gave similar results, no aldehyde being obtained. This was probably due to incorrect catalyst.

3:4:5-trimethoxy benzaldehyde diacetate.

2 g. 3:4:5-trimethoxy benzaldehyde dissolved in

12 c.c. acetic anhydride in the cold. A trace of concentrated H_2SO_4 added. Solution very dark. Allowed to stand for one and a half hours. Poured into ice water. Yellow precipitate recrystallised from ethyl alcohol to give white needles, m.p. 112-113° mixed m.p. with aldehyde (75°) 68°C. Yield, 2.13 g. (C, 56.62; H, 6.09. $C_{14}H_{18}O_7$ required C, 56.5; H, 6.08).

Nitration of acetate.

Addition of acetate to fuming nitric at 5° gave brilliant red solution but no solid obtained on working up after standing 45 minutes.

Nitration in acetic acid with fuming nitric at room temperature gave no solid product. Time allowed varied from 1 hour to 48 hours. Temperature raised to 50°C. but no success.

Nitration with fuming nitric in acetic anhydride and standing overnight gave, on neutralisation with sodium carbonate, a viscous gum which could not be solidified.

p-acetoxybenzyl cyanide.

Acetylation of p-oxybenzylcyanide carried out on water bath with acetic anhydride in pyridine $2\frac{1}{2}$ hours.

Pouring into water gave white solid, crystallised from methyl alcohol to give plates, m.p. 47-48°. 4 g. of p-oxy compound gave 4 g. acetylated product.

Condensation p-acetoxybenzylcyanide with 3:4:5-trimethoxybenzaldehyde.

.45 g. Na wire in dry ether 1:1 c.c. absolute alcohol added, stood and then refluxed. 3.4 g. nitrile added, heated for 1 hour, cooled and 3.8 g. aldehyde added. Heated for 3 hours. Filtered residue treated with dilute H_2SO_4 and recrystallised from ethyl alcohol and water, gave white needles, m.p. 171°C. identical with authentic p-oxy condensation product. Yield, .25 g.

The ether filtrate treated with dilute H_2SO_4 and crystallised from methyl alcohol gave low melting (65-68°) crystalline plates.

Condensation p-oxybenzylcyanide and 3:4:5-trimethoxybenzaldehyde. Cook and Lawrence (unpublished).

.2 g. sodium in alcohol (10 c.c.), 5 g. p-oxybenzylcyanide, 8.6 g. 3:4:5-trimethoxybenzaldehyde. Faintly yellow crystalline needles, m.p. 170-171°. Yield, 8 g.

m-bromonitrobenzene. (Org. Syn., VIII, 46.)

Carried out in 135 g. lots of nitrobenzene each

135 g. nitrobenzene giving from 135-145 g. m-bromonitrobenzene, m.p. 56°C. In all about 1 kilo prepared. m-bromoaniline. (Hölleman, Rec. Trav. Chim., 1906, 25, 186.)

This gave largely unchanged starting material. The temperature of the reaction was raised almost to boiling with no improvement in yield of amine. Failure probably due to type of Fe powder available.

Reduction with Hg/Al couple.

10 g. m-bromonitrobenzene in 100 c.c. absolute alcohol. 10 g. Hg/Al couple added (prepared by cleaning aluminium foil with 2N NaOH, washed, covered with 5% mercuric chloride for 1½ minutes, washed with water then alcohol). 10 c.c. boiling water added. Vigorous reaction kept under control by cooling. Then heated on water bath for 1½ hours adding further 10 c.c. boiling water thrice in first hour. Distil off alcohol in vacuum. Dissolve up in dilute HCl. Extract with carbon tetrachloride. Neutralise aqueous solution with NaOH. Extract with carbon tetrachloride, dry, distil off solvent. Vacuum distil. Yield, theor., b.p. 135°/14 mm. This reduction was not successful on a large scale. With quantities of m-bromonitrobenzene of 50 g. and upwards the yields were about 20% of

amine and an unidentified basic by-product was also formed as golden needles, m.p. 112°.

m-bromoaniline.

To 100 g. m-bromonitrobenzene and 110 g. tin, 210 c.c. concentrated HCl slowly added. Heated for 1 hour on water bath made strongly alkaline and steam distilled. Purified through hydrochloride and finally distilled, b.p. 130-135°/12 mm. Yield, 65 g. 75%. In all, 320 g. amine obtained.

m-bromophenol. Hewitt (J.C.S., 1936, 50).

250 g. amine with 1250 c.c. methyl alcohol, 166 c.c. concentrated H_2SO_4, 210 c.c. amylnitrite gave on working up heavy, slightly pink liquid, b.p. 120°/10 mm. Yield, 140 g. 56%.

Methyl-p-toluene sulphonate. Org. Syn., IX, 29.

500 g. p-toluene sulphonyl chloride gave 405 g. methyl toluene sulphonate, b.p. 161-168°/10 mm. It is important in this preparation to stir for at least 1 hour after last addition of alkali and then test with litmus.

m-bromoanisole. Hewitt (loc. cit.).

100 g. phenol, 135 g. Me p-toluene sulphonate 373 c.c. 25% KOH heated with stirring and reflux condenser on water bath for 4 hours. 200 c.c. 10% KOH added

and mixture steam distilled, extracted with ether and vacuum distilled, b.p. 89°/10 mm. Yield, 85 g. In all, 200 g. m-bromoanisole prepared.

Chloromethylation of m-bromoanisole at 0°C. (Cf. Bull. Soc. Chim., 1936, 3, 1794).

Dry HCl passed into mixture 5 g. m-bromoanisole and 10 c.c. 40% formaldehyde at 0° for 1 hour. Decomposed with ice water. Washed with water 2N NaOH, then water again. Extracted with benzene. Vacuum distilled to give main fraction 92-110°/10 mm. A little 120-140°/10 mm.

At 15°C. with $ZnCl_2$.

Dry HCl passed into 3.9 c.c. m-bromoanisole 1.5 g. para formaldehyde 1.5 g. $ZnCl_2$ in 25 c.c. petroleum ether (80-100°) did not heat up after 40 minutes. Worked up as before. Distilled to give fraction I, 90-105°/10 mm.: II, 132-142°/10 mm.: III, 142-152°/10 mm.

At 35°C. with $ZnCl_2$.

Above experiment repeated but at 35°C. Gave mostly unchanged anisole and a high boiling solid fraction.

In acetic acid at 66°C. (Cf. Darzen & Levy, Compt. Rendu, 1936, 202, 74).

3.7 g. m-bromoanisole; 1.07 trioxymethylene in 13 c.c. glacial acetic acid. Heated at 66° for 2 days.

On working up as before, unchanged anisole obtained.

The above experiment was repeated but this time the reaction mixture was vigorously mechanically stirred. Using double quantities .8 g., b.p. 100-130°/10 mm. 1.3 g., b.p. 110-135°/1 mm. 7.1 g., 135-150°/10 mm. This last product seemed to be the desired compound.

Nitrile from chloromethylation product.

7.1 g. from above with 50 c.c. alcohol 2 g. KCN in 4 c.c. water. Refluxed for 2 hours. Cooled KCl filtered. Alcohol taken off and residue taken up in ether. Ether taken off and residue vacuum distilled. Fraction, b.p. 152-180°/12 mm. taken. Yield, 4.7 g.

Hydrolysis of nitrile with alkali.

1.7 g. nitrile heated on water bath. Shaken with 25 c.c. 20% methyl alcoholic KOH. Deep red colour. Oil extracted on pouring into water to give neutral fraction. From this crystalline plates, m.p. 174°, were obtained and a little oil, b.p. 110-130°/10 mm.

The aqueous portion acidified and extracted to give an oil which could not be crystallised from usual solvents.

Hydrolysis of nitrile with acid.

2 g. nitrile heated 20 c.c. 50% by volume concentrated H_2SO_4 for 8 hours. Extracted with ether and ethereal solution, shaken with Na_2CO_3. The

alkaline extract acidified. Solid filtered. Would not crystallise. Taken up in NaOH, and again precipitated solid m.p. 119-130°, obviously a mixture.

ω-diazo-3:4:5-trimethoxyacetophenone. (Baker, Morgan & Robinson, J.C.S., 1933, 374).

5.4 g. 3:4:5-trimethoxy benzoyl chloride added to diazo methane solution from 10 c.c. nitroso methyl urethane, 200 c.c. dry ether, 15 c.c. 25% methyl alcoholic KOH. Moderate effervescence. Allowed to stand at room temperature for 4 hours. Taken down in vacuo to ¼ volume, equal volume ligroine added. Yellow crystalline needles separated, m.p. 102°C. Mixed m.p. dichloride (79°) 72°C. Yield, 4.4 g. C, 56.10; H, 5.12; N, 11.95. $C_{11}H_{12}O_4N_2$ required C, 55.95; H, 5.08; N, 11.86).

3:4:5-trimethoxy-phenyl acetamide. (Cf. Arndt & Eistert, Ber., 1935, 68, 200).

2 g. ω-diazo-3:4:5-trimethoxyacetophenone added to well stirred mixture of 24 c.c. 20% NH_4OH 2.4 c.c. 10% $AgNO_3$ and mixture heated to 60° then slowly raised to 80°C. When the evolution of gas ceased the solution was heated for 1 hour on reflux. Treated with charcoal and to the clear solution about 30 g. Na_2SO_4 added.

On standing overnight crystalline plates, m.p. 123-124° were obtained. From 7 g. diazo ketone 5 g. amide were obtained.

Grignard with Me.Mg.I on amide. (Cf. Beis, C.r., 137, 575).

Grignard compound (3 mol.) prepared smoothly from .29 g. Mg 1.71 g. Me.I .9 g. (1 mol.) dry amide added and the suspension heated for 6 hours. The solution and suspension decomposed with 25% of concentrated HCl. The ethereal solution dried Na_2SO_4. The crystalline material obtained on taking off ether was unchanged starting product, m.p. 120°. The ethereal residue gave no test for ketone with 2:4-dinitrophenylhydrazine.

In benzene.

Above experiment carried out using 6 mol. Grignard reagent 1 mol. of amide. The whole refluxed with 50 c.c. benzene for 5 hours. Unchanged starting material obtained. No 2:4-dinitrophenylhydrazone. From aqueous portion further amount unchanged amide salted out.

Using large excess. (Cf. Jenkins, J.A.C.S., 1933, 703).

A .9 molar solution of Grignard was prepared as before and .9 g. 1 mol. amide added. Heated on reflux

for 15 hours. Decomposed with sludge of ice and concentrated HCl, extracted with ether. The ether distilled off and .4 g. semicarbazide and .4 g. Na acetate added to residual oil in alcohol. On standing overnight no precipitate. Heated for 2 hours. A crystalline deposit separated, m.p. 256-265°C. On further standing good crystals though insignificant in quantity, m.p. 190-192°, were obtained.

Preparation of nitrile from amide. (Dumas, Ann., 64, 332).

.5 g. of amide heated at 200° on metal bath 10 minutes with 1 g. P_2O_5. Decomposed with water, .15 g. of solid which was distilled to give 50 mg. crystalline material, m.p. 72-74°, and considerable residue.

By method of Michaelis and Siebbert, Ann., 274, 312.

.5 g. amide heated with 5 c.c. benzene 1.5 g. $SOCl_2$ for 2 hours. Vigorous reaction to give dark solution. It was impossible to vacuum distil the residue after removing solvent.

The above was repeated but heated only for 20 minutes. The benzene distilled off and the residue vacuum distilled at 10 mm. A dark oil which solidified was obtained. This crystallised from benzene and petroleum ether to give crystals, m.p. 70-72°. Poor yield.

3:4:5-trimethoxy phenyl acetic acid.

2.2 g. of 3:4:5-trimethoxy phenyl acetamide heated for 5 hours with 20 c.c. 10N NaOH. Diluted with water. Extracted with ether to remove unchanged amide. Then acidified with dilute HCl. Standing overnight gave long white needles, m.p. 119-120°C. Mixed m.p. with amide (123°) gave 105°C. Yield, 1.1 g. The aqueous mother liquor yielded on extraction with ether a further small amount of acid (.25 g.).

3.9 g. ω-diazo-3:4:5-trimethoxy aceto phenone in 25 c.c. dioxan were added to 1.4 g. AgO_2 in 3.4 g. $Na_2S_2O_3$ in 100 c.c. water and well stirred. During 3 hours a further amount of AgO_2 1.4 g. was added in small quantities. The solution was heated to 60° and then stirred for 1 hour. Filtered and neutralised with 2N HNO_3, extracted with ether. Well washed, then taken out as Na salt. On acidification and subsequent recrystallisation needles, m.p. 116°. Yield, 1.3 g. (Cf. Warren & Williams, J.C.S., 1939, 1839).

3:4:5-trimethoxy phenyl acetyl chloride.

1 g. of 3:4:5-trimethoxy phenyl acetic acid was heated on water bath for 2 hours with excess of thionyl chloride. The dark residual mass on taking off excess

thionyl chloride and vacuum distilling charred and generally decomposed. A small amount of crystalline material obtained proved to be free acid, m.p. 114°.

.5 g. of acid in 10 c.c. benzene treated with .5 g. PCl_5. Allowed to stand in cold for 1 hour, then heated for 20 minutes on water bath. The benzene and phosphorus oxychloride distilled off in vacuo. On attempting to vacuum distil the residue, decomposition set in. The above experiment was repeated, but residue on taking up in benzene and precipitation with petroleum ether gave unchanged acid.

1 g. of acid heated with 2.5 g. pure thionyl chloride for 30 minutes at 40° then to boiling for 5 minutes. A little dry benzene added and excess thionyl chloride taken off in vacuo. This was repeated twice. The residue was then taken up in dry ether and the dark red solution used in next experiment.

γ-chloro α-(3:4:5-trimethoxy phenyl) acetone. (Cf. Haworth & Atkinson, J.C.S., 1938, 805).

The ethereal acid chloride solution from 3 g. of acid was added to a solution of diazo methane in ether from 7.2 c.c. methyl nitroso urethane and allowed to stand for 4 hours. An ethereal solution of HCl was then added till there was no further effervescence. The

solution allowed to stand for 1 hour, washed with water, dilute Na_2CO_3, dried over Na_2SO_4 and the ether distilled off. Very dark solid obtained. Proved exceptionally difficult to purify. Finally, after running a benzene solution through an alumina adsorption tube, the product was crystallised from ether in white needles, m.p. 75°C. Gave a positive test for chlorine and 2.4 di nitro phenyl hydrazone, m.p. 118°.

α-(3.4.5-tri methoxy phenyl) acetone.

A little of the crude chloro compound from the previous experiment was mixed with excess Zn dust and 10 c.c. absolute alcohol and slowly raised to boiling. Refluxed for 15 minutes and the alcoholic solution concentrated to give a gum which still gave test for chlorine.

1 g. of γ chloro α-3.4.5 tri methoxy phenyl acetone was recovered unchanged after shaking with hydrogen for 3 hours with 100 mg. Pd black (prepared by method of Heilbron, Sexton & Spring, J.C.S., 1929, 929) catalyst. There was no absorption of hydrogen.

Grignard from m brom anisole.

To .114 g. Mg in a little ether a 20% ethereal solution of .96 g. m brom anisole was added. In spite of tickling up with MeMgI, etc., the reaction did

not go. Using five times these quantities a Grignard was formed sluggishly. Heated for two hours. The two layers obtained were merged by addition of a little anisole.

γ-chloro-β-hydroxy-β-m-anisyl-α(3.4.5 trimethoxy phenyl) propane.

A fifth part of the solution from the above Grignard (2 mols.) was cooled in ice and .4 g. γ-chloro α-3.4.5 tri methoxy phenyl acetone added. Kept in ice for 4 hours then at room temperature for 2 hours. Ether added and the mixture well shaken with NH_4Cl solution. The ether was distilled off, a little water added, and the residue steam distilled. The residue was then extracted with ether, dried, and the ether distilled off. A little brown gum was obtained which could not be crystallised from hydrocarbon solvents.

α-cyano α-p anisyl β-(3.4.5 tri methoxy phenyl) ethylene.

1 g. of nitrile of α-p hydroxy phenyl β(3.4.5 tri methoxy phenyl) acrylic acid was heated on the water bath with 15 c.c. 12% KOH and 1 g. Me p toluene sulphonate with stirring for 1 hour. On cooling the solid which separated was filtered and crystallised in leaflets

from rectified spirits, m.p. 111-112°C. Recrystallised m.p. 114°C. Mixed m.p. with authentic methoxy compound (m.p. 114-115°) 114°C.

Reduction α-cyano α(p hydroxy phenyl) β-(3.4.5 tri methoxy phenyl) ethylene.

2 g. of nitrile in 20 c.c. alcohol were shaken with hydrogen in presence of 200 mg. Pd black for three hours. There was no absorption. Shaken with hydrogen in alcohol in presence of Pt. 2 g. of nitrile were again recovered unchanged. Using acetic acid as solvent there was an absorption of half a double bond. Possibly the substance itself is a catalyst poison.

Dehydrogenation N acetyl colchinol methyl ether. (Cf. Ritter & Sharp, J.A.C.S., 1937, 59, 2351).

,4 g. N-acetyl colchinol methyl ether was heated with 3 c.c. iso amyl disulphide on a metal bath at 240-250° for 14 hours. Excess disulphide was taken off at 10 mm., and the residue distilled at 5 mm. A reddish liquid which shed a few crystals was obtained. The remaining tar sublimed in needles at 175/.1 mm. Crystallised from benzene petroleum ether had m.p. 195°C. Mixed m.p. with N-acetyl colchinol methyl ether gave no depression.

2.4 di-nitro phenyl acetic acid. (Borsche, Ber., 1909, 42, 1313).

7 g. phenyl acetic acid were stirred into 30 c.c. concentrated H_2SO_4. A nitrating mixture of 7.5 c.c. bench concentrated nitric and 15 c.c. concentrated H_2SO_4 were run in so that the temperature did not exceed 60°. Allowed to stand over-night and poured into ice water. Crystallised twice from hot water in needles, m.p. 175°. Yield 5 g.

The method using alcohol as catalyst (J.C.S.I., 1936, 190T) gave a product of very low melting point which was only raised after repeated crystallisation.

2-Nitro 4-amino phenyl acetic acid.

8 g. of 2.4 di-nitro phenyl acetic acid were heated in 100 c.c. alcohol. A solution of 16 g. crystallised sodium sulphide and 3.4 g. sulphur in 50 c.c. water was added slowly to the hot alcoholic solution so that the mixture just kept boiling. Heating continued for 2 hours. Alcohol distilled off and residue diluted with water. Light golden crystals obtained from water, needles, m.p. 75°. Non acidic (m.p. 2-nitro 4-amino toluene 77°C.).

Reduction with hydrazine hydrate (Cf. Curtius, J.pr. Chem., 1898, 58, 211).

2 g. 2.4-di-nitro phenyl acetic acid heated on

water bath 1 hour with 6 c.c. alcohol and 4 c.c. 50/50 hydrazine hydrate. Alcohol distilled off and crystalline solid separated, m.p. 70°C. Addition of HCl gave evolution of gas and further quantity of solid. This on crystallisation gave faintly yellow needles, m.p. 70°C. Non acidic non basic and did not acetylate. Mixed m.p. with 2.4 di-nitro toluene (70°) gave no depression. Alteration of temperature and time of heating gave identical products.

Me-ester 2.4-di-nitro phenyl acetic acid. (Borsche, loc. cit.).

4 g. 2.4 di-nitro phenyl acetic acid heated with 30 c.c. methyl alcoholic HCl for 3 hours. On concentration of solution an oil was obtained. Taken up in benzene. Washed with carbonate. Dried over $CaCl_2$. Concentrated. The solid obtained crystallised from methyl alcohol in rectangular needles, m.p. 83-84°C.

2 nitro 4 amino phenyl acetic acid Me ester.

2 g. of ester in alcohol shaken with hydrogen in presence of 1 g. 10% $PdCl_2$ charcoal. After theoretical absorption charcoal filtered. On concentration of solution in vacuo it decomposed.

The experiment repeated with acetic acid as solvent with same result.

With 4 g. of ester in dioxan the reduction was still unsatisfactory. No identifiable nitro amine was obtained.

SUMMARY.

(1) Allomucic acid has been prepared from mucic acid and characterised. It has been found by Professor Posternak to be identical with his synthetic allomucic acid.

(2) dl-Talomucic has been shown to rearrange in acetic anhydride to mucic acid and allomucic acid. A simple route is possibly available for synthesis of the ribose type of sugar structure.

(3) The specific rotations of the l-menthyl esters of tetra-acetyl mucic and tetra-acetyl allomucic acids have been compared. The specific rotations are not in agreement with van 't Hoff's Law of Optical Superposition.

Additional Paper.

(1) A synthetic route to 2.3.4.7-tetra methoxy 9 methyl phenanthrene has been extensively explored.

(2) The stability of N-acetyl colchinol methyl ether to dehydrogenation has been further investigated and found to be in agreement with previous work.

(3) Preliminary work on the synthesis of 2.3.4.6-tetra methoxy 9 methyl phenanthrene has been carried out.

(4) Preliminary work has also been done on the synthesis of a possible simple analogue of colchinol methyl ether.

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