A SYNTHETIC ATTACK ON THE OESTRONE PROBLEM

by

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Submitted in Partial Fulfillment of
the Requirements for the Degree
of
DOCTOR OF PHILOSOPHY
from the
Massachusetts Institute of Technology
1937

Signature of Author.......................................

Department of Chemistry, May 13, 1937

Signature of Chairman of Department
Committee on Graduate Students.......................

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ACKNOWLEDGEMENT.

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During the course of this work, the constant association with the members of the organic chemical division has been most pleasurable. Without their help and counsel, always generously and unstintingly given, the completion of this work would have been immeasurably more difficult.

The author wishes to take this opportunity to express his sincere appreciation for the award of the Austin Research Fellowship, and for the liberal grants of supplies and facilities placed at his disposal.

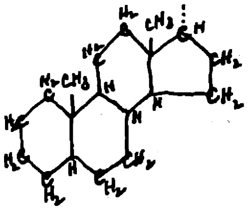
To Professors James F. Norris and Avery A. Morton, who have taken a particular interest in the work, and to Professor L. F. Hamilton, whose kind offices have again and again been of great value, a special debt of gratitude is due.

INTRODUCTION

The determination by analytical methods of the probable structures of the sterols, hormones and other naturally occurring phenanthrene derivatives has been the triumph of organic chemistry in the past decade. The problem must be considered unfinished, however, until the present views have been confirmed by the total synthesis of one or more of these important substances. It is not surprising then that a number of laboratories have iniiated the attack on the problem.

Many of the outstanding contributions to organic chemistry in the past have been in the sphere of total sythesis. Kommpa's synthesis of camphor is a noteworthy example, since it resulted in the confirmation of the camphor formula of Bredt, which had been correctly inferred from degradative experiments.

The synthetic problem in the hydrophenanthrene group, though similar in nature, is considerably more complex. This complication is not due primarily to the larger number of carbon atoms, but rather to the involved stereochemistry of the multiplanar cholane nucleus (I).



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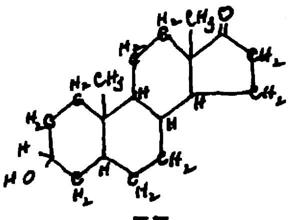
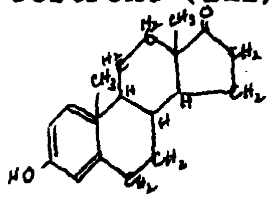


II

Thus, androsterone (II) is capable of existence in no less than 128 optically active modifications, while the simplere oestrone (III)



III

might have any one of sixteen configurations.

It is true that the spacial arrangement about certain carbon atoms of the naturally occurring cholane derivatives may be inferred from degradative experiments. The number of such cases is few, however, and the necessarily vigorous character of the reagents used in the resolution of these large molecules into simpler ones may well result in configurational changes.

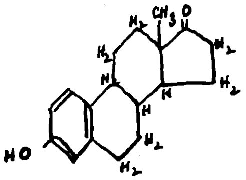
This investigation was concerned with an attack on the problem of the total synthesis of oestrone. Although the final goal was by no means reached, a good deal of information has been accumulated, and a path has been beaten for some distance into the untracked forest which surrounds the objective.

I. PUBLICATION

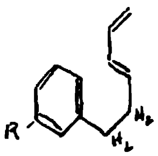
Synthesis in the Hormone and Sterol Group I. The 2- (β - phenylethyl) furanes as Components in the diene Synthesis.

R. B. Woodward.

The synthetic approach to substances of the hormone or sterol group has attracted much attention in recent years (1). The investigation undertaken by this laboratory had as its ultimate object the synthesis of oestrone (I) or a stereo-isomer.



I.



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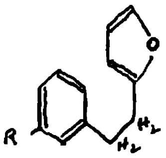


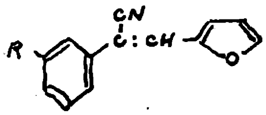
III.

In view of its wide applicability in the synthesis of cyclic substances ,(2) the diene synthesis of Diels and Alder was investigated as a favorable vehicle for such a project. Other investigators have explored the possibilities of this method. Cohen (3) was able to add maleic anhydride to 1- (β -phenylethyl)- $\Delta^{1,3}$-butadiene (II: R = H). The yield, however, was small and the extension of the reaction to the pertinent case of 1 - (β -(m-methoxyphenyl) ethyl)- $\Delta^{1,3}$ butadiene was unsuccessful. The use of 1-vinyl naphthalenes was attended by more success (4).

Cohen attributed his difficulties to isomerism to derivatives of 1-vinyltetralin, and their subsequent polymerization. Our success in view of his failure is easily explained on this basis. The choice of 2- (β -phenylethyl) - furanes (III) as diene components afford compounds whose individual double bonds are not active enough to be subject to prototropic isomerization, but whose diene character is still so marked (5) as to permit their participation in the Diels - Alder reaction.

The parent compound, 2 - (β -phenylethyl-) - furane had been prepared by Freundand Immerwahr (6). Phenylacetonitrile was condensed with furfural to give α- phenyl-β - (2-furyl-)- acrylic nitrile (IV : R = H). The reduction of the latter substance by molten sodium and absolute alcohol gave the desired substance in addition to β - phenyl- γ (2 - furyl) propylamine.

IV.



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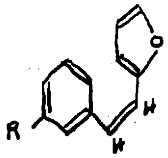
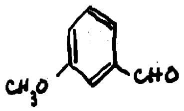


Since this method involved two concurrent reactions, one of which gave a product unsuitable for further synthetic work, it was hoped that a more direct process could be used. Two alternatives were investigated. The reaction of benzylmagnesium chloride with furfural proceeded smoothly but it was impossible to obtain a homogeneous sample of benzyl (2- furyl)- carbinol, water being split to some extent even on distillation in a high vacuum. Dehydration of the crude carbinol gave the new stilbene isolog, α -phenyl-β -(2 - furyl)- ethylene (V) characterized by the ease with which it forms a beautifully crystalline dibromide, and by its its catalytic hydrogenation to the desired 2- (β -phenyl-ethyl-)- furane. The overall yield of the latter substance by this method, however, was no better than that obtained by the older process.

Again, the reaction of benzylmagnesium bromide with 2 - furfuryl bromide was the subject of considerable investigation. Certain 2- substituted furanes had been prepared in this manner by Paul (7). The latter investigator found that unless a large excess of the Grignard reagent was used, small quantity of unchanged 2- furfuryl bromide invariably induced conjunct polymerization during the working up of the reaction-mixture, with the result that no product was obtained.

Such a procedure was not feasible when a relatively rare substance such as m-methoxybenzyl magnesium bromide was being used. Accordingly, the device was adopted of using equi-molecular proportions of the (un) substituted benzyl halide, and of 2- furfuryl bromide, and adding a large excess of butyl-magnesium bromide after the reaction was complete to destroy the sensitive 2- furfuryl bromide. It was found also that greater success was obtained with this type of reaction if certain variation were made in the original preparation (8) of 2-furfuryl bromide. While Zanetti and Paul freed the crude bromide of water, unreactioning 2- furfuryl alcohol, and other impurities by means of potassium hydroxide, a better product is obtained by treatin the crude ethereal solution with a small molar proportion of freshly prepared methyl magnesium iodide or butyl magnesium bromide. The separation of small amounts of 2-ethyl or 2-(n- amyl)-furanes formed by this process from the 2- (β- phenylethyl-)-furanes is easily effected by distillation. If these conditions are carefully observed, it is possible by this method to obtain better yields of the 2 - (β- phenylethyl-) - furanes than by the older procedure. On the other hand, since the reactions of the latter method may be carried out more easily and quickly, it is the better method for preparative purposes.

M - methoxyphenylacetonitrile (IX) obtained in 75% overall yield by the following four step process. M- hydroxybenzaldehyde (9) was methylated according to Reimer (10) with methyl sulphate in alkaline solution. Large runs gave better yiedls than small ones. The methylation of the aldehyde by means of diazomethane was unsatisfactory (11).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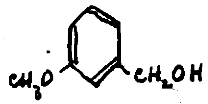
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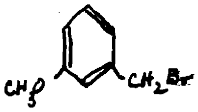
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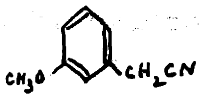

IX.

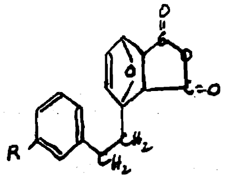
The m-methoxybenzaldehyde VI was reduced quantitatively by hydrogen using the Adams catalyst to m- methoxy benzyl alcohol (VII). The conversion of the alcohol into m- methoxybenzyl bromide (VIII) by the action of hydrogen bromide in benzene proceeded essentially as described by Lapworth (12). A remarkable observation was made in the course of experiments conducted in connection with the conversion of the bromide into m- methoxy phenyl-acetonitrile. The m-methoxy- benzyl bromide obtained as mentioned above was unstable,_and turned green or greenish -violet on standing for some time, even after several distillations in vacuo. After refluxing in acetone solution over potassium cyanide for some time, however, the substance was recovered, substantially unchanged, with the exception that it was now perfectly stable, and gave an excellent yield (88%) of the corresponding nitrite on treatment in the usual manner with aequeous - alcoholic potassium cyanide. It is possible that a highly reactive impurity, capable of catalyzing ether- formation and hydrolysis in the preparation of the nitrile, was removed by the acetone-potassium cyanide treatment.

The condensation of m- methoxy- phenyl acetonitrile with furfural to α- (m- methoxyphenyl-)- β - (2-furyl-)-acrylic nitrile (IV : R = OCH_3) proceeded smoothly: the product, an oil, may if desired be isolated by distillation in vacuo, but it was more convenient for synthetic work, reduce the crude condensation product directly by molten sodium and absolute alcohol to 2- (β - (m-methoxy-phenyl-)-ethyl-) furane (III : R = OCH_3).

2 - (β -phenylethyl-) - furane reacted on long standing with pure maleic anhydride in anhydrous ether to give a beautifully crystalline addition product, 3 - (β - phenylethyl-)- 3,6- endoxo- Δ^4-cyclohexene- 1,2-dicarboxylic anhydride (IX : R =H). On the other hand, if the reaction-mixture was irradiated with ultra-violet light, reaction took place much more rapidly, with the formation of a different, higher melting addition product. The latter β - addition product was also formed when an ethereal solution of the α- addition product was irradiated. Both of the substances on heating above the melting point alone or in solvents dissociated into their components. On dissolving in ligroin, particularly, a clear solution was obtained which deposited crystals of maleic anhydride on standing in the ice-box. Again, the colorless solution in dimethylaniline on heating developed the characteristic orange color of maleic anhydride in this reagent. In the case of the α -addition product, a bromohydroxy derivative was prepared and characterized.

Similar phenomena are observed in the reaction of 2- (β - (m-methoxy phenyl-)-ethyl-)- furane with maleic anhydride. Two addition products,3- (β-m- (methoxy phenyl-)-

ethyl-)- 3,6-endoxo- Δ^4 cyclohexene-1,2-dicarboxylic anhydrides (IX : R = OCH$_3$), are obtained.



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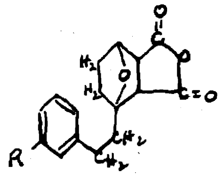

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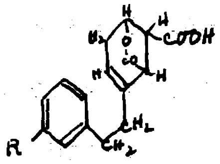


XII.

In this case the α-product was an oil, whose formation required considerable time, while the β-product crystallized beautifully in a few hours.

Tentatively we may assume that one series of addition products possesses the endo-configuration of the five-membered anhydride ring, while the other series has the exo-configuration (13).

The original synthetic plan involved the catalytic hydrogenation of the addition products to dihydro-derivatives. (XI: R = H,OCH$_3$), theoretically susceptible to isomerization to substances (XII: R = H,OCH$_3$), a reaction analogous to the change cantharidine ⟶ cantharic acid (14).

In actual practice, the addition products were formed to be remarkably resistant to hydrogenation. 3-(β-phenylethyl)- 3,6- endoxo - Δ^4 - cyclohexene - 1,2- dicarboxylic anhydride (α) was unaffected on shaking with hydrogen for an hour in methayl alcohol, or ethyl acetate solution in the presence of palladium or platinum black.

Hydrogenation in glacial acetic acid with a platinum catalyst over a period of twelve hours gave succinic acid as sole product, dissociation evidently having taken place. Similar difficulties were experienced in reducing the methoxylated addition product (β). On the other hand, using a platinum catalyst of maximum activity, 3- (β -m-(methoxy phenyl-)- ethyl)- 3,6- endoxo - Δ^4- cyclohexene- 1,2- dicarboxylic anhydride (β) could be partially reduced on shaking in ethyl acetate solution with hydrogen under a pressure of three atmospheres.

It is probable that this remarkable resistance to hydrogenation is the result of a mutual saturation of affinities involving the extra cyclic double bond and the aromatic nucleus. Cook (15) has offered a similar explanation for the inactivity of the double bond in 1- (α -naphthyl-) - Δ^1 - cyclohexene. The unexpected resistance to cyclization of Cohen's (3). 3- (β -phenylethyl-)- Δ^4- cyclohexene-1, 2-dicarboxylic anhydride is also interesting in this connection.

Unlike its precursors, 3- (β -m-methoxy-phenyl-)- ethyl-)- 3,6- endoxo-cyclo-hexane-1,2-dicarboxylic anhydride, was a stable substance, which could readily be crystallized from various solvents, and showed no tendency towards dissociation.

EXPERIMENTAL

EXPERIMENTAL

α-phenyl-β-(2-furyl-)-acrylic nitrile (IV : R =H) was obtained by Frost'(16) method from phenyl-acetonitrile and furfural in the presence of alcoholic sodium ethylate. The substance crystallized from aequeous alcohol as slightly yellow needles, m.p. 42-43°.

2-(β-phenylethyl-)-furane. (III: R = H).

(a). The material was first prepared according to Freund and Immerwahr (6). The substance was purified more easily by steam distillation than by the procedure recommended by these authors. From 63 g. of the nitrile, an average of 30 g. of the furane, $\text{b.p.}_{760\ \text{mm.}}$ 241-243°, was obtained as a colorless oil of pleasant aromatic odor, reminiscent of stilbene.

(b). 9.6 g. of freshly turned magnesium was dissolved in 50 g. of benzyl chloride and 200 cc. of anhydrous ether in a three necked flask equipped with dropping funnell, reflux condenser, and mercury seal with mechanical stirrer. To the large excess of benzyl magnesium chloride obtained in this manner, 2-furfuryl bromide, prepared as described below from 40 g. of 2-furfuryl alcohol, was added slowly with good stirring. A white or slightly yellow precipitate began to form immediately and precipitation continued throughout the course of the reaction. When the addition was complete, the reaction mixture decomposed in the usual manner with ammonium chloride solution, the yellow ethereal extract was washed with water and dried over anhydrous sodium sulfate. After removal of the ether, the residual oil was fractionated. 20g. of 2- (β -phenyl- ethyl-) - furane was obtained identical with that prepared by the method outlined in (a).

The preparation could also be carried out using equimolecular proportions of the reactants if the precautions observed in the theoretical part are observed. (cf. 2-(- β -(m- methoxy-phenyl)- ethyl-)-furane, (b), below).

<u>α -phenyl- β -(2- furyl-)- ethylene (V)</u> To the Grignard solution from 12.2 g. of magnesium, 63 g. of benzyl chloride and 300 cc. of anydrous ether, 48 g. of furfuraldehyde was added slowly, with mechanical stirring. When the addition had been completed the reaction mixture was heated on the water bath for a short time. There was now suspended in the ether a yellow crystalline precipitate. The whole was poured into ice and stirred well to effect decomposition. The ethereal solution was separated, the residual sludge of magnesium oxychloride was dissolved on dilute acetic acid and the resulting solution is extracted with ether. The combined ethereal extracts are dried over anhydrous

sodium sulphate, and the ether was carefully removed. The deep yellow residual oil (35 g.) was distilled in vacuo over 20 g. of pure potassium hydrogen sulphate, or 7 g. of anhydrous aluminum sulphate. The fraction b.p.$_{8\text{mm.}}$ 150-165° solidifies on cooling and may be purified further by crystallization from alcohol, 10 g. of α - phenyl- β -(2-furyl-)- ethylene was obtained in long yellowish needles, of pleasant aromatic odor, reminiscent of stilbene. (mp. 49-50)

2- (β -phenylethyl-)- furane (III : R = H) is readily obtained from the above substance by shaking with hydrogen in the presence of Adam's catalyst. The reduction is complete in less than 1/2 hour, and the product is in every respect identical with that obtained above.

Dibromide 0.5 g. of the ethylenic compound was dissolved in 15 cc. of pure chloroform. 0.5 g of bromine was added, and the reaction mixture allowed to stand for three days. At the end of this time magnificent crystals of the dibromide had separated in long transparent prism. m.p. 232.0-232.3°, reminiscent in appearance of hydroxylamine hydrochloride.

m-methoxybenzaldehyde (VI) was obtained in 83% yield by the methylation of m-hydroxy benzaldehyde in weakly alkaline solution by means of dimethyl sulphate. The yield of pure product obtained when the crude aldehyde is distilled invacuo in a current of nitrogen is appreciably higher than that obtained when no precaution is taken to protect the substance from oxidation (b. p. $_{30mm}$129-130°)

m-methoxybenzyl alcohol was prepared in quantitative yield by the catalytic hydrogenation of the aldehyde. In a typical experiment, 40 g. of m- methoxy-benzaldehyde 200 cc. of reagent ethyl alcohol, 0.2 g. freshly prepared Adams platinum oxide, and 2.0 cc. 0.1 m. ferrous sulphate solution were placed in the pressure bottle of the Adams hydrogenation apparatus. Shaking was started at 3 atmospheres. Within ten minutes the theoretical absorption (0.294 moles = 23 lbs) had taken place. It was possible to use the same catalyst for a second or a third reduction, but the time required for complete hydrogenation in this case was considerable longer. The alcohol was removed by distillation under reduced pressure, and the residual oil distilled in vacuo in a current of nitrogen. m-methoxybenzyl alcohol is a clear colorless liquid of peculiar odor, b.p. $_{25mm.}$ 150°.

m-Methoxy benzyl bromide (VIII) 167 g. of m-methoxy benzyl alcohol was dissolved in 300 cc. of dry thiophen free benzene and saturated with dry hydrogen bromide in the cold. Water collected under the clear benzene solution of the bromide which was decanted and allowed to dry over-night over calcium chloride. The benzene was removed by vaccum distillation in a current of dry nitrogen. The resulting oil was distilled in vacuo in a current of nitrogen. 238 g. of m-methoxy benzyl bromide b.p.$_{\text{e mm.}}$ 116° were obtained. The substance is a clear highly refractive liquide which rapidly turns green or greenish purple on standing. Care must be taken not to inhale the substance nor to allow it to come in contact with the skin, since it is an extremely irritating lachrymator and vesicant.

If the bromide, dissolved in anhydrous acetone, was refluxed in a current of hydrogen for four to five hours over an equi-molecular proportion of potassium cyanide, the product recovered from the acetone after distillation, did not change in color and gave in the reactions below a better yield than the bromide not treated in this manner.

m-Methoxy phenyl acetonitrile (IX) 100 g. of m- methoxy benzyl bromide was refluxed 2 1/2 hours with 32g. of sodium cyanide 30 cc. of water and 55 cc. of reagent ethyl alcohol. At the end of this time the alcohol was distilled in vacuo from the orange-brown mixture, the residul sludge was shaken with water, and the oil which separated dried over a small amount of anhydrous sodium sulphate. On distillation

64 g. (87.5%) of m-methoxy phenylacetonitrile, b.p.$_{20}$ 164-165°, was obtained as a highly refractive liquid, of faint characteristic nitrile odor.

Anal. Calc. C, 73.5% H, 6.10% N, 9.50%
Found. C, 73.6%, 73.7% H, 6.3%, 6.3% N, 9.6%

α-(m-methoxyphenyl-)-β-(2-furyl-)-acrylic nitrite (IV: R = OCH_3). To a mixture of 64 g. of m-methoxy phenyl acetonitrile and 42 g. of furfural, 20 cc. of 20% alcoholic sodium ethylate was added, in small portions, with shaking. A good deal of heat was liberated, and the color of the reaction mixture deepened considerably. From time to time the flask was cooled under the tap. Considerable water separated on the side of the vessel. When the reaction was complete, the dark brown oil was washed several times with water dried over a small amount of anhydrous sodium sulphate and distilled in a gigh vacuum (b.p.$_{1mm.}$ 180°). 90 g. of α-(m-methoxyphenyl)-β-(2-furyl-)-acrylic nitrile was obtained as a clear yellow oil. For conversion into 2-(β-m-methoxy-phenyl-)-ethyl-)-furane, the purification was superfluous. The crude brown oil gave satisfactory results.

Anal. Calc. C, 74.8% H, 4.98% N, 6.23%
Found. C, 74.6% H, 5.2% N, 6.4%

2 - (β -me-methoxyphenyl-)-ethyl-)-furane. (III: R = OCH_3)

A.

90 g. of α-(m-methoxyphenyl)- β - (2-furyl) acrylic nitrile was dissolved in 1200 cc. of absolute ethyl alcohol and poured onto 138 g. of metallic sodium cut into chips (this was an escess of 2 1/2 time the theoretical amount for complete reduction of β -(m-methoxyphenyl(- γ -(2-furyl-)- n-propylamine). A three necked flask equipped with two reflux condensers and one stopper was used for the reduction. If the reaction becomes too violent, the clogging of the condensers was easily remedied by removing the stopper for a moment. The flask was set in a pail so that cold water could be dashed on the sides of the flask in case the reaction got out of control. When the reduction was complete, the greenish reaction mixture was made acid with hydrocholric acid. Since a good deal of unreacted sodium remained in the flask, it was advisable to conduct this operation with considerable care. It was advantageous to place a quantity of dry iceon the surface of the reaction mixture before each addition of acid. The contents of the flask were then subjected to a vigorous steam distillation, when the desired product passed over as a yellowish oil. Since this process was very slow, it was found that it was quite as sat-

isfactory to extract the contents of the flask with ether, wash with dilute hydrochloric acid, then with water, and evaporate the ether. In either case the oil was distilled in vacuo after drying over anhydrous sodium sulphate. 39 g. of 2- (β -(m-methoxy-phenyl-)-ethyl-)-furane was obtained as a colorless oil, b.p.$_{10\ \text{mm.}}$ 153°, of aromatic odor, which turned yellow on standing. The same change was noticed with 2- (β -phenyl-ethyl-)-furane and 2- (γ -phenyl-n-propyl)-furane.

B. BY THE GRIGNARD REACTION

3 g. of magnesium were placed in a dry 500 cc. three necked flask equipped with dropping funnel, reflux condenser, and mercury seal bearing a mechanical stirrer. A few drops of m-methoxy benzyl bromide were allowed to fall onto the magnesium. When the reaction had started, the remainder of the bromide, in all 25 g. dissolved in 60 cc. of anhydrous ether was added slowly. The reaction was not vigorous. Stirring and refluxing were continued for three hours after the bromide had been added. To the solution of m-methoxy-benzyl magnesium bromide obtained in this manner, an ethereal solution of 2-furfuryl bromide, prepared from 40 g of 2-furfuryl alcohol as described below, was added, slowly,

with good stirring. A shiny purple precipitate of magnesium bromide covered the walls of the flask as the addition proceeded. When the addition of the 2- furfuryl bromide was complete a large excess of freshly prepared butyl magnesium bromide was added rapidly, and the reaction mixture was allowed to stand for 1/2 hour. Ammonium chloride solution was then added to decompose unreacted Grignard reagents, the yellow ethereal solution was separated, washed, with water, and dried over anhydrous sodium sulphate. On fractionation in vacuo, 13 g. of 2-(β-(m-methoxy-phenyl-)-ethyl-)-furane was obtained identical in every respect with that prepared by method (a).

Anal. Calc: C, 77.3% H, 7.1%
Found: C, 77.1% H, 7.1%

3- (β -phenylethyl-)-3,6-endoxo- Δ^4-cyclohexene-1,2-dicarboxylic anhydride (α). (X : R = H).

3 g. of pure maleic anhydride and 5.4 g. of 2-(-phenylethyl-)-furane dissolved in anhydrous ether (30 cc.) were allowed to stand in a well stoppered flask for several months. At the end of this time, the contents of the flask had become a solid mass of beautiful needles. On filtering and washing with anhydrous ether, the addition product was obtained in almost quantitative yield as white needles, m.p. 71-73°. Due to its tendency to dissociate, the substance was difficult to recrystallize. Satisfactory

results were obtained, however, by dissolving in cold chloroform, adding petroleum ether, and allowing to stand in the ice box, when long fine needles gradually separate.

Anal. Calc: C, 71.2% H, 5.18%

Found: C, 71.2% H, 5.3%

3-(β -phenylethyl-)-3,6-endoxo Δ^4-cyclohexene-1,2-dicarboxylic anhydride- (β). (X : R = H).

A.

A saturated solution in anhydrous ether of the addition product was exposed in a quartz tube to ultra violet light for a period of twenty-four hours. The fine white solid which separated was dissolved in chloroform, petroleum ether was added, and the solution allowed to stand in the ice-box. Beautiful needles of the β, addition product separated, m.p. 159-161°.

B.

3 g. of maleic anhydride and 5.4 g. of 2-(β - phenylethyl-)- furane were dissolved in 30 cc. of anydrous ether and exposed to ultraviolet light overnight. The mass of crystals which separated, after being filtered, washed with anhydrous ether and dried proved to be identical with those obtained in A.

Anal. Calc: C, 71.2% H, 5.18%

Found: C, 71.2%, 71.3% H, 5.4%, 5.3%

If either of these substances was dissolved in ligroin (b.p. 70-90°) and the resulting solution allowed to stand in the ice-box, needles separated, which proved to be maleic anhydride, m.p. 57-59°, mixed m.p. 57-59°. Orange color with diethylaniline.

Bromo-hydroxy-derivative. The addition product (1.0 g.) was dissolved in excess sodium carbonate and the basic solution was exactly neutralized. This solution of free dicarboxylic acid was shaken vigorously with a slight excess of bromine. Reaction took place immediately with the quantitative precipitation of the bromo-hydroxy acid. After recrystallization from boiling water (Norite) the acid melted at 142-143°, with decomposition.

Anal. Calc: C, 52.3% H, 4.18%

Found: C, 52.1% H, 4.4%

3-(β -(m-methoxy phenyl-)-ethyl)-3,6-endoxo- Δ^4 - cyclohexene - 1,2 dicarboxylic anhydride (α) (X : R = OCH_3) was obtained as an oil when an ethereal solution of its components was allowed to stand for several months. The corresponding β - addition product crystallized quantitatively in beautiful transparent rosettes when 31.6 g. of 2-(β -(m-methoxyphenyl-)-ethyl-) furane and 15.3 g. of pure maleic anhydride were dissolved in 200 cc. of anhydrous ether and irradiated for twelve hours. After washing with anhydrous ehter, drying, and crystallizing by the chloroform petroleum ether procedure, long transparent needles were obtained, m. p. 78-80°.

Like the unsubstituted addition products, this methoxy-derivative gave maleic anhydride on heating with ligroin, gave no color in the cold with diethylaniline, and was unstable to cold dilute alkaline permanganate.

Anal. Calc: C, 68.0% H, 5.33%

Found: C, 68.0% H, 5.4%

3-(β -m-methoxyphenyl-)-ethyl-3,6-endoxo-cyclohexane-1,2-dicarboxylic anhydride. (XI : R = OCH_3).

20 g. of 3-(β -(m-methoxy-phenyl-)-ethyl-)-3,6-endoxo- Δ^4- cyclohexene-1,2-dicarboxylic anhydride (β) were dissolved in 1.75 cc of anhydrous ethyl acetate, 0.8 g. of freshly prepared active Adams platinum oxide were added, and the whole shaken with hydrogen under 3 atmospheres pressure for six hours. At the end of this time, the solvent was removed by distillation in vacuo. The oil which remained crystallized after shaking for some time with petroleum ether. After twelve recrystallizations from ligroin (b.p. 70-90°),

a crystalline product, m.p. 90-91°, which gave no color with diethylaniline was obtained. In each crystallization, the solute was dissolved in the boiling solvent, and the clear solution was allowed the stand in the ice-box for some time. The separation of the product from maleic anhydride was followed by melting point and by solution in diethylaniline, which gives a deep orange-red coloration with the simpler anhydride.

The dihydro-derivative crystallized in stable slender white needles.

Anal. Calc: C, 67.5% H, 5.96%
Found: C, 67.6% H, 6.0%

If 1 g. of 3-(β-phenylethyl-)-3,6-endoxo- Δ^4-cyclohexene-1,2-dicarboxylic anhydride (α) dissolved in 30 cc. of glacial acetic acid was shaken with 0.2 g. platinum (palladium) oxide under 3 atmospheres of hydrogen for fifteen hours, succinic acid was obtained after washing the residue from the acetic acid (removed in vacuo) with dry benzene. m.p. 186-187°, mixed m.p. 185-187°.

SUMMARY

The synthesis of 2-(β -phenylethyl-)-furane and 2-(β -(m-methoxyphenyl-)-ethyl)-furane has been accomplished.

The Diels Alder reaction has been applied with success to these substances.

An interesting new type of stereo-isomerism has been discovered.

It has been found that the Diels-Alder reaction is facilitated enormously, at least in certain cases, by irradiation with ultraviolet light.

Approximately one-half of the original plan for the total synthesis of oestrone has been successfully attacked.

II. ADDENDUM.

II. ADDENDUM

1.

The ready availability of the cresols led to the consideration of possible methods by which these substances could be converted into desirable intermediates.

The oxidation of m-cresol methyl ethers by alkaline permanganate was employed in the early work in the field as a source of suitable m- substituted derivatives. In this case, the oxidation proceeded completely to m-methoxy benzoic acid. It would be desirable to carry out the oxidation in such a way as to stop at the aldehyde stage. To this end a number of unsuccessful experiments were carried out using manganese dioxide and sulfuric acid, for which reagents excellent results have been claimed in the case of anisaldehyde, and benzaldehyde.

It is a known fact that the transformation by strong acids of an o, p - directing substituent such as NH_2, into a strong positive dipole (in this case- $\overset{+}{NH_3}$) $\overset{-}{HSO_4}$) is accompanied by the loss of their o,p - directive influence in favor of meto-orientation. It was this line of reasoning which led to an attempt at the direct side chain bromination of m-cresol methyl ether in concentrated sulphuric acid solution in the presence of a strong light source.

Since nothing of value resulted from these experiments, no details are appended here.

2.

The ready accesibility of m-nitrotoluene led to the institution of a series of experiments directed towards the synthesis from this substance of opposite meta-substituted derivatives of the 1- (β-phenyl-ethyl) furane template.

The bromination of m-nitrotoluene was found to proceed most readily in boiling nitrobenzene solution in the presence of a very powerful source of light. It was not possible to effect the conversion of the m-nitrobenzyl bromide obtained in this way into m-nitrophenyl-acetonitrile in satisfactory yield. The nitrile was, however, transformed into 1-(β-(m-nitrophenyl)ethyl) furane, and a few reduction experiments were made with the latter substance.

EXPERIMENTAL

Commercial m-nitrotoluene was fractionated in vacuo. The material obtained in this way (68.5 gr.) was dissolved in nitrobenzene (150 gr.) The solution was brought to reflux and illuminated by means of a 2000 watt lamp. Bromine (80.0 gr.) was now dropped slowly into the boiling solution. Hydrogen bromide was evolved continuously. The addition of the bromine was completed in about one hour and one half. At this point the solution was considerably darker than it had been at the beginning of the preparation.

After refluxing for one half hour more, the nitrobenzene was removed in the vacuum of the water pump. Fractionation in vacuo of the residual oil gave m-nitrobenzyl bromide (50.0 gr) as a light yellow oil (b.p.$_{10\,mm.}$ 156-157°) which solidified on cooling. A small sample crystallized from petroleum ether in yellow plates (m.p. 57°).

Sodium cyanide (15 gr.) was dissolved in boiling water (20 cc.). Ethyl alcohol (50 cc.) was then added, the mixture was brought to reflux, and m-nitrobenzyl bromide (54.0 gr.) was added in the course of 15 minutes. The reaction mixture was then allowed to boil for two hours.

Since the dark solution obtained in this manner could not be filtered, it was poured into water and extracted with ether. The ethereal extract was dried over sodium sulphate, the ether was removed, and the residue fractionated in vacuo. m-nitrophenyl acetonitrile (20.0 gr.) was obtained as a yellow highly birefringent oil (b.p.$_{10\,mm.}$ 193-194°) which solidified on standing.

Crystallization from aqueous alcohol gave slightly yellow needles. (m.p. 60-62°).

m-nitrophenylacetonitrile (6.0 gr.) and freshly vacuum distilled furfural (3.86 gr.) were mixed in a small beaker, and treated drop by drop with stirring with twenty percent alcoholic sodium ethylate solution (2.0 cc.)[1.]

[1.] from ethylalcohol (45.0cc.) and metallic sodium (2.0 gr.).

As the catalyst was added, condensation took place immediately with the evolution of heat; when the addition was complete, the reaction mixture was a solid yellow mass.

α-(m-nitrophenyl)-β-(2-furyl)-acrylic nitrile (6.1 gr.) crystallized readily from glacial acetic acid in beatiful shining yellow needles. mp. 136-7. On standing in air for a long period, the crystals develop a reddish tinge.

The reduction of the substance with stannous chloride in hydrochloric acid did not proceed smoothly, complete conversion being very difficult to obtain because of the rather great insolubility of the substance. Although alcoholic titanium trichloride solutions were readily oxidised in small scale experiments, this reagent was too costly for preparative use. Nascent hydrogen could not be used in view of the danger of reducing the inter-annular double bond. Catalytic hydrogenation with a catalyst of minumum activity gave products which did not behave as amines.

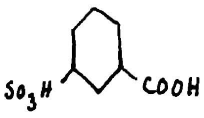
The problem was still in this unsettled state when this line of attack was abandoned in order to throw all available energy and facilities into the more propitious phases of the research. Since no definitive solution to the problem of reduction has yet been obtained, no experimental details are appended.

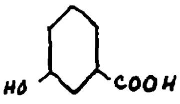
3.

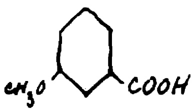
Since m-methoxy benzoic acid had been shown to be a convenient source for the preparation of m-methoxy benzyl alcohol on a small scale, the development of a satisfactory method for the production in quantity of this acid was a prerequisite to the change from small to large scale work.

Hitherto the substance had been obtaine d by the alkaline permanganate oxidation of m-cresol methyl ether. Unfortunately the relatively huge quantities of permanganate solution necessary for the oxidation on a large scale would have made this process inconvenient to say the least.

In consequence, a large amount of m-hydroxy benzoic acid was made by a process essentially like that described by Offermann (16). Benzoic acid was converted into sodium hydrogen m - sulfobenzoate, which on mixed caustic fusion gave the desired hydroxy acid.







The methylation of this acid best in boiling aqueous alkaline solution with methyl sulfate, gave fair yields of m-methoxy benzoic acid.

The average over-all yielded of m-methoxy benzoic acid from benzoic acid by this process is approximately 40%.

EXPERIMENTAL

The procedure was essentially that of Offermann.

Pure benzoic acid (500g.) in a three liter round bottom ring necked flask was treated with fuming sulfuric acid (2 lbs; 20-26% anhydride content). The temperature was quickly brought to 210°, and maintained there for four to five hours. The reaction mixture darkens considerably, but in no case did the solution become so dark as to be unpentrable to a strong light. Unless the flask was equipped with an air condenser, the evolution of oxides of sulfur was so considerable as to be quite unpleasant.

After cooling, the reaction mixture was poured into a four liter beaker half full of ice. If the reaction had been properly carried out, a clear amber solution was obtained at this point. It was not usually necessary to filter. The clear solution was then poured into boiling saturated salt solution (5 liters[1]), to which 150 grams of solid salt have been added, contained in a twelve liter flat bottomed flask.

The clear solution is allowed to cool over-night, when the sodium hydrogen m-sulfobenzoate separates as a beautifully crystalline mass, which is filtered, washed with

[1] Prepared from 1651 grmas Nall and 4164 grams H_2O.

T. : GMS. NaCl/100g. H_2O; Sp. gr. = 107°: 39.65g.: 1.1631 saturated salt solution, and sucked dry at the pump. The substance at this point presented the appearance of lustrous plate, which on drying a vacuo lost water and became opaque.

The yields obtained in several runs were comparable.

Run	Gms. Sodium Hydrogen m- Sulfobenzoate
I	690 gms .
II	720 gms.
III	700 gms.
IV	800gms,[a]

[a] The substance crystallized poorly falling to the bottom of the flask as a heavy cake rather than separating as a crystalline mask which filled the solution.

Alkaline fusion of sodium hydrogen m - sulfobenzoate.

In the first series of experiments the fusion was carried out in a copper autoclave of about one liter capacity. The fusion was carried out in the open autoclave. When the reaction was complete, the top was bolted on. The latter was equipped with two holes, one of which served as an inlet for air under pressure, while through the other passed a copper tube 3/4 inch in diameter, reaching nearly to the bottom of the autoclave on the inside, and bending over on

a. In this case an excess of salt over the amount specified was used, it is evident that the product here was contaminated with salt.

the outside to form a nozzle pointing downwards.

Sodium hydrogen m-sulfobenzoate (400 g.) was rapidly stirred to a paste with concentrated sodium hydroxide solution (from water (160 g.) and sodium hydroxide (160 g.)). Considerable heat was developed, and steam was evolved. The pasty semi-solid mass was added to a mixture of potassium hydroxide (200 g.) and sodium hydroxide (200 g.) *maintained at 210-220° in the autoclave* . The addition was completely as rapidly as was consistent with the maintenance of a temperature of 210°. The fusion was continued at this temperature for tw and one half hours, the reaction being stirred from time to time.

At the end of this time the cover of the autoclave was bolted on, air pressure was applied, and the molten reaction mixture was poured directly on to ice (2 liters) contained in a four liter beaker. The solution thus obtained *was made barely alkaline* by the addition of hydrochloric acid and filtered.

The clear solution was further acidified with concentrated hydrochloric acid until no more precipitation took place. Much sulfur dioxide was evolved, while m-hydroxybenzoic acid precipitated as a white foamy mass. The acid was filtered at the pump, washed with cold water, and dried. It was then a slightly yellow crystalline substance of sweet taste, which one recrystallization from water had a melting point 200-201°.

One larger run was made in a large iron kettle of capacity about three or four liters. In this case it was necessary to remove the molten reaction mixture with a large ladle- a very inconvenient process.

The yields of m- hydroxy- benzoic acid may be seen from the following table.

Run	Grams m- hydroxy-benzoic acid
I (500 gms.)	273 gms. (88.6%).
II (400 gms.)	185 gms. (77.0%)
III (400 gms.	195 gms. (81.2%)
IV (1000 gms.)	480 gms. (80.0%)

Methylation of m - hydroxy- benzoic acid.

M- methoxy-benzoic acid is obtained in best yield by the methylation of m-hydroxy-benzoic acid with methyl sulfate in methanolic sodium hydroxide (17). The method is not feasible on a preparative scale, however, so the process of Cohen and Dudley (18) was applied.

M- hydroxy - benzoic acid (273 g.) was dissolved in 10% sodium hydroxide (from water (1800 g.) and sodium hydroxide (200 g.)). To the clear boiling solution, methyl sulfate (240 cc.) was added as rapidly as was consistent with safety. The reaction mixture was then allowed to reflux for 2 and 1/2 hours. After standing over-night, the clear solution was acidified with concentrated hydrochloric acid. The pure snow-white beautifully crystalline m- methoxy benzoic acid separated as a paste, and was filtered at the pump, washed with cold water, and dried. (m.p. 103-104°).

Several runs gave an average yield of m-methoxybenzoic acid of 64.0% of the theoretical.

4.

The electrolytic reduction of m - methoxy benzoic acid.

Certain investigators (19) have claimed excellent yields of substituted benzyl alcohols by the reduction of the corresponding aromatic acids. The factors to which particular attention must be paid are (1) purity of electrodes and materials, (2) high solution current density, (3)Electrolyte. If these facters are carefully controlled, the yields of alcohols are said to be as much as 70-80% of the theory.

This method appeared to afford an attractive source of the m- methoxy benzyl alcohol needed for this investigation, and experiments were undertaken with this end in view. The small scale reduction of m- methoxy benzoic acid was easily accomplished. It was possible to reduce, say, twenty grams of the acid, partially dissolved in thirty percent alcoholic sulphuric acid in a small cell with plate lead electrodes (volume solution: cathode surface = 1 : 1) quite easily. It was m- methoxy benzyl alcohol prepared in this way which was used in the preliminary stages of this research.

The extension of the electrolytic process to relatively large scale operation, however, was accompanied by quite extraordinary experimental difficulties.

These fall roughly into groups. (1) There being no porous cup of appropriate size available, either in the stock of the laboratory, or from the various ceramic manufacturers, it was necessary to have one especially constructed. (2) External cooling being obviously insufficient to vitiate the large heat effect (the cell drew somewhat over 15,000 watts from the line) it was necessary to resort to the use of lead pipe, through which cold water ran continually. (3) None of the chemical research laboratories possessed current sources sufficient for the operation of the cell. Some 70-80 ampires at 220 volts were needed; it was necessary to carry out the work in the Department of Mining and Metallurgy[1] where such a source was available. (4) Once having obtained the source, the electrical circuit necessitated considerable attention, since it was necessary to insert resistances into the line. The large current and the continuous operation for long periods of time indicated the use of water-cooled resistors, but such could not be obtained. Two "stoves"obtained from the Electrical Engineering Department[2], did valiant service, but the great amount of

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[1] This was made possible by Professors Locke and Hutchinson of the Department of Mining and Metallurgy through whose kindness the facilities were made available.

[2] The author is indebted to Mr. C. E. Hentz of the Electrical Engineering Department, who was instrumental in supplying the "stove" and other necessary electrical apparatus.

heat generated necessitated more or less constant attention while the reduction was in progress, and careful insulation of the resistors from the surroundings.

These difficulties having been overcome one by one, a cell of one liter capacity was at last constructed which could be operated continueously for forty-eight hours with a seventy ampire current at 220 volts, without raising the temperature of the cathode solution above 30°C.

On a large scale, however, the reduction could not be accomplished with yields greater than 20-30%, even when the acid was scrupulously purified and the electrodes carefully treated by the process recommended by Tafel (20). In view of consistently poor yields and the frigidy of a considerable amount of useful extra-departmental apparatus and space occasioned by the continued life of the apparatus, this line of experiments was at last reluctantly but wisely abandonded.

EXPERIMENTAL

On electrolytic reduction of m-methoxy benzoic acid.

The cell was constructed as follows: Within an eight inch battery jar was placed the anode, which was cylindrical in shape. The latter was constructed of 1/8 of inch lead plate, in which three large circular holes (diameter ca. 3 inches) had been bored to permit circulation. The edges of the original flat pieces of lead were bolted together with brass bolts in order to form a cylinder, and the whole anode was then bolted to a piece of brass to which the anode lead was attached. The anode covered tightly the porcelain cell of medium porosity, eight inches in height and ca. 6.5 inches internal diameter. In this cell was placed thecathrode of 1/4 inch lead pipe 26 feet in length, coiled into a cyclinder of external diameter slightly less than the internal diameter of the porous cup. The two ends of the cathrode were brought out over the edge of the cell and attached, one to inlet cold water from the tap, and the other to a drain. A brass collar secured around one, the lead pipe served as the cathode lead attachment. The dimensions of the cup and cathode were such that when the latter was just covered, the cathode solution occupied 1000cc., while the cathode surface was 1000sq. cm, giving a ratio of unity (essential under condition (2) of experimental part). The cathode solution was agitated by a motor-driven stirrer, while a thermometer was inserted below the surface of the solution in order to check aggainst an undesirable elevation of temperature. A separatory funnel was set up in such a way that the rather appreciable loss by evaporation from the anode chamber was constantly replenished. The leads were of number 3 copper stranded copper wire (diamer = ca. 1/4 inch) obtained from the Simplex Wire and Cable Company (Cambridge).

The current was measured by the use of a Westinghouse millivoltmeter, using an external shunt, of such size that the millivolt reading gave the current in amperes directly (21). The cell, and the measuring system were in series with two standard forty ohm resistors(22).("stoves"), themselves in parallel. The power was drawn from a 220 volt- 60 ampere outlet situated in the ore-dressing laboratory of the Mining and Metallurgy laboratory of this Institute.

Before each experiment one liter of 30% alcoholic sulfuric acid (from alcohol (8,000 cc.) and concentrated sulfuric acid (370 cc.)) was placed in the cathode chamber, and the anode chamber was filled with 30% aequeous sulfuric acid (from water (700 cc.) and concentrated sulfuric acid (162 cc.)). The stirrer and the refrigerating stream were set in operation, The current was then started, <u>using the cathrode</u> as anode, and vice versa. The cell was operated at twenty amperes for a period of 1 - 1 1/2 hours. When the cathode had been <u>prepared</u> in this manner, the actual reduction was begun.

M-methoxy benzoic acid (100g. = 0.66 moles) was added to the cathode compartment. A current of seventy amperes was then passed through the cell, this time the cathode being used as such. The reduction was allowed to proceed without interruption for thirty hours. This involved the production of an excess of hydrogen corresponding to three times the theoretical quantity necessary for the complete reduction of the acid. The current steadily dropped because of the increase in circuit resistance as the "stoves" heated up (Joule effect). As the resistors approached red heat, the current stabilized at 65-66 amperes and remained approximately constant throughout the remainder of the reduction. (This great heat developed by the resistors necessitated their insulation from the table and surrounding apparatus by several layers of sixteenth inch asbestos paper). The temperature of the liquid in the cathode compartment was easily maintained below 30°C.

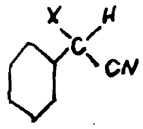
At the end of thirty hours the contents of the cathode compartment were siphoned into two liters of ice-water. A small amount of unchanged m-methoxy benzoic acid which separated in crystalline form at this point was removed by filtration.

The resultant clear solution, on the surface of which floated some oily material, was extracted several times with ether in a large separating funnel, the combined ethereal extracts were washed well with dilute sodium carbonate, then with water, and finally dried over anhydrous sodium sulfate. Removal of the ether and fractioation of the resultant oil in vacuo gave m- methoxy-benzyl alcohol (ca. 20 g) as a clear limpid liquid of characteristic odor (b.p.$_{25mm}$ 150).

The poor yield unfortunately was not bettered by increasing the time of the reduction, or by preparing the cathode according to Tafel (23).

5.

The hydrogen atoms of phenyl acetonitrile possess great reactivity. Their ability to condense with aldehydes has been put to use with great success in this investigation. It was hoped that the hydrogen atoms of substances of the type



where X = ·OH, ·O.CO.C_6H_5, etc. and R is an aryl residue would exhibit similar reactivity. If such were the case, the proper application would lead to (i) a synthesis of unsymmetrical benzoins, and more pertinent to this research,(ii) a short route to derivatives of the much desired α-(β -phenylethyl) furane template.

If aromatic aldehydes are shaken with benzoyl chloride and aequeous potassium cyanide, the beautifully crystalline α-benzoyloxyphenylacetonitriles are very easily obtained. It was these substances which were chosen as test materials in the scheme outlined above.

It was intended to condense these substances with aldehydes, particularly furfural, in the presence of sodium ethylate. Unfortunately, it was found that the compounds reacted almost instantly with sodium ethylate in this sense.

This reaction, though of considerable intrinsic interest, effectively blocked further progress in this direction.

EXPERIMENTAL

a-benzoyloxypehnylacetonitrile

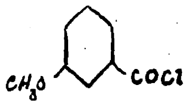
Benzoyl chloride (14.0 g.), benzaldehyde (10.6 g.) and potassium cyanide (6.7 g.) dissolved in water (60 cc.) were shaken in a strong tightly-stoppered tube. Considerable heat was developed as the reaction proceeded. Gradually the oil was replaced by a crystalline mass which was filtered and crystallized from alcohol. α-benzoyloxyphenylacetonitrile (13.0 g.) crystallized in short, shining needles (m.p. 63-64°).

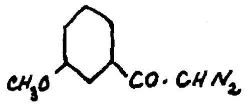
If this substance, either mixed with an equivalent quantity of furfural, anisaldehyde, or benzaldehyde, or alone, was treated with alcoholic sodium ethylate (10% ,20%, 30%), sodium cyanide was precipitated immediately, and could be filtered off and transformed into Prussian blue. The residual oil on shaking with a large excess of saturated sodium bisulfite solution left ethyl benzoate (b.p.$_{\text{atm.}}$ 212°; hydrolysis to BzOH), while the bisulfite solution on standing deposited beautiful plates of benzaldehyde-sodium bisulfite.

6.

The failure to work out a satisfactory method for the large scale electrolytic reduction of m-methoxy-benzoic acid occasioned a desire to utilize the surplus of this acid which had accumulated. The conversion to m-methoxy benzoyl chloride by the action of excess thionyl chloride proceeded easily, and gave a substance whose reactivity could possibly be used to advantage.

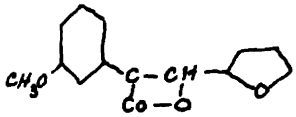
The first experiments involved the conversion of the chloride into m-methoxy benzoyldiazomethane by the method elaborated by Ardnt (24) and co-workers.

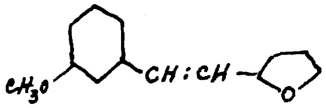




On heating with aniline, the diazo-ketone was converted only in small amounts into the desired m-methoxyphenylacetanilide, the larger portion of the material being consumed in the formation of polymers, and of an extremely evil-smelling oil, probably an iso-nitrile.

On the other hand, advantage was taken of the supposed ketone intermediary stage in the isomerization of diazoketones by heating the substance with furfural. The reaction was carried out in boiling pyridine, or quinoline, in the presence of copper-bronze, and it was expected that the β-lactone formed by the addition of the furfural to m-methoxy phenyl ketene would lose carbon dioxide in situ to form α-(m-methoxyphenyl)-β-(2-furyl)ethylene.





Surprisingly enough the product actually obtained in small yields was 2-(β-(m-methoxy phenyl-ethyl)-furane. It is evident that an oxidation-reduction process similar to that described by Paul (25) for the 2-furylcarbinols is involved in this unexpected change.

Since these methods were of no preparative value, the remainder of the m-methoxy benzoyl chloride was easily reduced catalytically by hydrogen, with a palladiumised barium sulphate catalyst, to m-methoxy benzaldehyde, which was added to that obtained from other sources.

EXPERIMENTAL

m-Methoxybenzoyl chloride

m-Methoxy benzoic acid (100 g.) was refluxed with three times its weight of thionyl chloride and a few drops of pyridine. Copious evolution of sulfur dioxide and hydrochloride acid took place. When the vigorous gas evolution had ceased, a few more cubic centimeters of pyridine were added, and the mixture refluxed for 1/2 - 1 hour longer. (bath temperature 125-130°). At the end of this time the excess thionyl chloride was distilled over. The residual yellow highly refractive oil was distilled in vacuo in a current of nitrogen. m-Methoxy benzoyl chloride (90 g.) was a colorless highly refractive liquid (b.p. $_{11\text{mm.}}$ 127-128°).

diazo-methane

Diazomethane is best prepared for preparative work by the simpler process given in Organic Synthesis (26). To anhydrous ether (100cc.) is added forty percent potassium hydroxide, and the mixture is cooled to 5° with continued cooling and shaking. Finely powdered methyl-nitroso-urea (10 g. of p. 48) is added in small portions. The deep yellow layer is decanted, and contains about 2.8 g. diazo-methane. It is advisable to filter this solution through a clean dry piece of filter paper to remove small pieces of potasium hydroxide if the diazomethane is to be used for the preparation of diazoketones. If it is desired to free from a small amount of moisture present in this ethereal solution, it is allowed to stand for three hours over pellets of pure potassium hydroxide (not necessary for the preparation following).

nitrosomethyl urea

Nitrosomethyl urea, the most convenient source of diazomethane is very easily prepared by the method of Organic Syntheses (27).

In warm water (600 cc.) contained in a 1.5 liter round bottomed flask, methylamine hydrochloride (100 g. = 1.48 moles) and C.P. granular potassium cyanate (150 gr.) are dissolved. The solution is boiled gently for ten minutes, then vigorously for five minutes. The hot clear solution is added to a solution of 95% sodium nitrite (100 g. = 1.38 moles) in water (200 cc.). The whole is cooled to -5° in an ice salt bath and poured in small portions with vigorous agitation (hand stirring is preferable) into a mixture of ice (600 g.) and concentrated sulfuric acid (100 g.) contained in a 4 liter beaker immersed in a pail and surrounded by ice and salt. The temperature is not allowed to rise above 0°, The addition takes about 45 minutes.

The product separates as a white crystalline precipitate which is filtered at once by suction, well pressed and washed with cold water (30 cc.). After sucking as dry as possible at the pump, the nitrosomethyl urea (125 g.) is dried in a vacuum desiccator in the ice-box, where it may be kept without appreciable decomposition for several months, portions being withdrawn as desired for the preparation of diazomethane.

<u>m-Methoxy benzoyl diazomethane</u>

A diazo-solution[1] was prepared from nitroso methyl

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[1] It is interesting that diazomethane has an odor very much like that of diazoacetic ester.

urea (35 g.), 40% potassium hydroxide (80.0 cc.) and anhydrous ether (500 cc.).

M-methoxy benzoyl chloride (13.6 g.) was added at 5°. Slow but regular evolution of nitrogen took place. After one hour at 5°, the solution was allowed to come to room temperature and stand for a few hours. The ether was removed from the solution by distillation in vacuo at not more than 30°. When most of the ehter was gone, petroleum ether was added, and the mixture shaken well.

The resulting yellow oil was separated. m-methoxy benzoyl diazomethane (13 g. = 10 cc.) is a yellow oil of sweet odor. It reacted vigorously with hydrochloric acid with the evolution of nitrogen, and gave other reactions typical of diazo-ketones.

m-methoxyphenylacetanilide.

m-Methoxy benzoyl diazomethane (13 g.) was added drop by drop to boiling aniline (30 g.) in a large test tube. Nitrogen was evolved rather violetntly, while the originally clear solution became very dark. When all the diazo-compound had been added, the aniline solution was poured into dilute hydrochloric acid and the mixture shaken well. The viscous tar which resulted could not in any way be induced to give a crystalline product,equally futile were attempts to obtain pure m-methoxy phenylacetic acid from it by saponification with aqueous or alcoholic potassium hydroxide (magnificent green colorations produced.).

Only the resort to distillation of the "saponified" tar gave a crystalline product. The first fraction (small) was mainly aniline, the second was an extremely evil-smelling oil which darkened rapidly in color, while the last fraction crystallized immediately. The m-methoxy phenylacetanilide (0.5 g.) obtained from it crystallized well from alcohol. (m.p. 120°)

(m-methoxy benzoyl)-diazomethane and furfural.

m-methoxy benzoyl diazomethane (13.0 g.) mixed with furfuraldehyde (7.1 g.), freshly distilled in vacuo, were dropped slowed into boiling pyridine or quinoline (25. cc.) containing copper-bronze powder (2.5 g.). A slow current of nitrogen passed through the solution served to prevent violent bumping, and to protect from reaction mixture from the air. As each drop of the reactants was added, the reaction mixture foamed up, indicating the evolution of gas as the reaction proceeded. The gases from the apparatus were led through a wash bottle containing dilute bary ta solution. The precipitate in this wash bottle indicated the evolution of carbon dioxide from the reaction mixture.

Previous experience with the decomposition of this diazo-ketone in organic bases having indicated the futility of acid treatment, the reaction mixture was allowed to reflux for one hour after the addition of the reactants had been completed, and then distilled directly in the vacuum of the water pump. The larger portion of the distillate consisted of unchanged furfural, the solvents, and decomposition products of the diazo ketone. Much tar was left in the flask and considerable carbonization took place during the distillation. Not until the last fraction (about 20 drops) was a small quantity of 2-(β-(m-methoxyphenyl)ethyl) furane obtained as a colorless oil which rapidly turned yellow in air.

With maleic anhydride this furane derivative gave an addition product identical with that from an authentic sample prep ared in this laboratory.

CONCLUSION

The synthesis of 2-(β-phenyl-ethylfurane and 2- (β -(m-methoxy-phenyl-)-ethyl-)furane has been accomplished. The Diels-Alder reaction has been applied with success to these substances. An interesting new type of stereo-isomerism has been discovered. It has been found that the Diels-Alder reaction is facilitated enormously, at least in certain cases, by irradiation with ultraviolet light. Approximately one-half of the original plan for the total synthesis of oestrone has been successfully attacked. A number of incidental observations has added considerable factu al material to the body of organic chemical knowledge.

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BIOGRAPHICAL NOTE

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