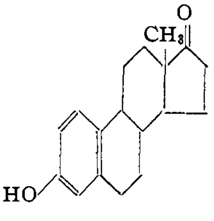
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 224]

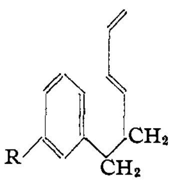
Experiments on the Synthesis of Oestrone. I. The 2-(β-Phenylethyl)-furans as Components in the Diene Synthesis

BY ROBERT BURNS WOODWARD[1,2]

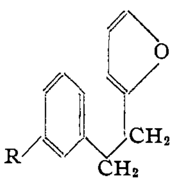
The synthetic approach to substances of the hormone or sterol group, culminating in the brilliant synthesis of equilenin by Bachmann, Cole and Wilds,[3a] and of a stereoisomer of oestrone by Dane,[3b] has attracted much attention in recent years. The investigation undertaken in this Laboratory had as its ultimate object the synthesis of oestrone (I) or a stereoisomer. In view of its wide applicability in the synthesis of cyclic systems, the diene synthesis of Diels and Alder was investigated as a favorable vehicle for such a project. Other investigators[4] have explored the possibilities of this method. Cohen[4a] 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 (II, R = OCH_3) was unsuccessful. The use of 1-vinylnaphthalenes[4b] and 1-vinyl-$\Delta^{1,2}$-dihydronaphthalenes[4c] has been attended with more success.



I



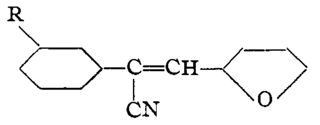
II



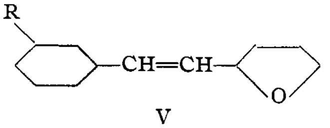
III

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

The parent compound, 2-(β-phenylethyl)-furan (III, R = H) had been prepared by Freund and Immerwahr.[5] 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 compound in addition to β-phenyl-γ-(2-furyl)-propylamine.



IV



V

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 method could be used. Two alternatives were investigated. The reaction of benzylmagnesium chloride with furfuraldehyde 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, R = H), characterized by the ease with which it forms a beautifully crystalline dibromide, and by its catalytic hydrogenation to the desired 2-(β-phenylethyl)-furan. The over-all yield of the latter substance obtained by this method, however, was slightly less than that obtained by the older process.

Again, the reaction of benzylmagnesium halide with 2-furfuryl bromide was the subject of considerable investigation. Certain 2-substituted furans had been prepared in this manner by Paul.[6] This investigator found that unless a large excess of the Grignard reagent was used, a small quantity of unchanged 2-furfuryl bromide invariably induced conjunct polymerization during the working up of the reaction mixture, with the result

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(1) Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Massachusetts Institute of Technology, June, 1937.

(2) At present member of the Society of Fellows, Harvard University.

(3) (a) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940); (b) Dane and Schmitt, *Ann.*, **537**, 246 (1939).

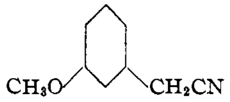
(4) (a) Cohen, *J. Chem. Soc.*, 429 (1935); (b) Cohen and Warren, *ibid.*, 1318 (1937); Bachmann and Kloetzel, THIS JOURNAL, **60**, 2204 (1938); (c) Dane and co-workers, *loc. cit.*

(5) Freund and Immerwahr, *Ber.*, **23**, 2847 (1890).

(6) Paul, *Compt. rend.*, **200**, 1481 (1935).

that no product was obtained. Such a procedure was not feasible when a relatively rare substance such as *m*-methoxybenzyl bromide was being used. Accordingly the device was adopted of using equimolecular proportions of the (un)substituted benzyl halide and of 2-furfuryl bromide, and adding a large excess of butylmagnesium 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 variations were made in the original preparation[7] of 2-furfuryl bromide. While Zanetti and Paul freed the crude bromide of water, unchanged 2-furfuryl alcohol, and other impurities, a better product is obtained by treating the crude ethereal solution with a small molar proportion of freshly prepared methylmagnesium iodide or butylmagnesium bromide. The separation of small amounts of 2-ethyl- or 2-(*n*-amyl)-furans formed by this process from the desired 2-(β-phenylethyl)-furans 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)-furans than by the older process. 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.

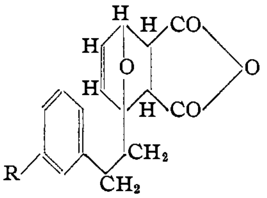
m-Methoxyphenylacetonitrile (VI) was obtained in 70% over-all yield by the following four-step process. *m*-Hydroxybenzaldehyde[8] was methylated according to Reimer[9] with methyl sulfate in dilute alkaline solution. The methylation of the aldehyde by means of diazomethane was unsatisfactory.[10] The methoxybenzaldehyde was reduced quantitatively by hydrogen using the Adams catalyst with ferrous ions to *m*-methoxybenzyl alcohol. The conversion of the alcohol into *m*-methoxybenzyl bromide by the action of hydrogen bromide in benzene proceeded essentially as described by Lapworth.[11] The bromide gave an excellent yield of *m*-methoxyphenylacetonitrile (88%) (VI) on treatment in the usual manner with aqueous alcoholic potassium cyanide.



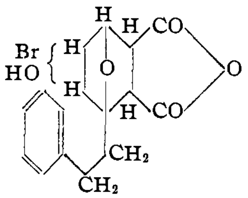
VI

The condensation of *m*-methoxyphenylacetonitrile 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 to reduce the crude condensation product directly by molten sodium and absolute alcohol to 2-[β-(*m*-methoxyphenyl)-ethyl]-furan (III, R = OCH_3).

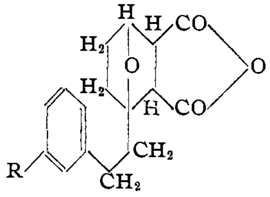
2-(β-Phenylethyl)-furan reacted on standing with pure maleic anhydride in anhydrous ether to give a beautifully crystalline addition product, 3-(β-phenylethyl)-3,6-endoxo-Δ^4-tetrahydro-*o*-phthalic anhydride (VII, R = H). This substance on heating above the melting point alone or in solvents dissociated into its components. On dissolving in ligroin, particularly, a clear solution was obtained which deposited crystals of maleic anhydride on standing in the ice-box for a short time. Again, the colorless solution in dimethylaniline on heating developed the characteristic orange color of maleic anhydride in this reagent. When the substance is warmed on the steam-bath in a current of nitrogen, maleic anhydride sublimes into the condenser. A bromo-hydroxy derivative (VIII) of the addition product was prepared by the action of bromine on a neutralized solution of the addition product in sodium carbonate. As would be expected, this latter substance exhibited no tendency to dissociate.



VII



VIII



IX

Similar phenomena are observed in the reaction of 2-[β-(*m*-methoxyphenyl)-ethyl]-furan with maleic anhydride. A beautifully crystalline addition product, 3-[β-(*m*-methoxyphenyl-)-ethyl]-3,6-endoxo-Δ^4-tetrahydro-*o*-phthalic anhydride

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[7] Zanetti, THIS JOURNAL, **49**, 1066 (1927).

[8] The *m*-hydroxybenzaldehyde used in this research was obtained through the kindness of the General Aniline Company of New York.

[9] Reimer, THIS JOURNAL, **55**, 4644 (1933).

[10] *Cf.* Asahina and Yasue, *Ber.*, **68**, 2026 (1935).

[11] Lapworth, *J. Chem. Soc.*, **121**, 1396 (1922).

(VII, R = OCH_3) is obtained in excellent yield. This substance, like the unsubstituted adduct, dissociates readily into its components.

The original synthetic plan involved the catalytic hydrogenation of the addition products to dihydro derivatives (IX, R = H, OCH_3), theoretically susceptible of isomerization to substances possessing a substituted hydrophenanthrene template similar to oestrone or its degradation products. In practice the addition products were found to be remarkably resistant to hydrogenation. 3-(β-Phenylethyl)-3,6-endoxo-Δ^4-tetrahydro-*o*-phthalic anhydride was unaffected on shaking with hydrogen for long periods in 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 crystalline product, dissociation evidently taking place. Similar difficulties were experienced in reducing the methoxylated addition product.[12]

Experimental

α-Phenyl-β-(2-furyl)-acrylic nitrile (IV, R = H) was obtained by Frost's method[13] from phenylacetonitrile and furfuraldehyde in the presence of alcoholic sodium ethylate. The substance crystallized from aqueous alcohol as slightly yellow needles, m. p. 42–43°.

2-(β-Phenylethyl)-furan (III, R = H).—(a) The material was first prepared according to Freund and Immerwahr.[5] 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 furan, b. p. (760 mm.) 241–243°, was obtained as a colorless oil of pleasant aromatic odor, reminiscent of stilbene.

(b) 9.6 grams 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 funnel, reflux condenser, and mercury seal with mechanical stirrer. To the large excess of benzylmagnesium 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 was 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. Twenty grams of 2-(β-phenylethyl)-furan was obtained, identical with that obtained by the method outlined in (a).

The preparation could also be carried out using equimolecular proportions of the reactants if the precautions mentioned in the theoretical part are observed (*cf.* 2-[β-(*m*-methoxyphenyl)-ethyl]-furan, (b), below).

α-Phenyl-β-(2-furyl)-ethylene (V).—To the Grignard solution from 12.2 g. of magnesium, 63 g. of benzyl chloride and 300 cc. of anhydrous ether, 48 g. of furfuraldehyde was added slowly, with mechanical stirring. When the addition had been completed, the reaction mixture was heated on the steam-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 by the addition of dilute acetic acid, and the resulting solution was extracted with ether. The ether extract was dried over anhydrous sodium sulfate, and the ether was removed. The deep yellow residual oil (35 g.) was distilled *in vacuo* over 20 g. of pure potassium hydrogen sulfate, or 7 g. of anhydrous aluminum sulfate. The fraction b. p. (3 mm.) 150–165° solidified on cooling and was purified further by crystallization from alcohol. Ten grams of α-phenyl-β-(2-furyl)-ethylene was obtained in long yellowish needles, of pleasant aromatic odor, reminiscent of stilbene (m. p. 49–50°).

Anal. Calcd. for $C_{12}H_{10}O$: C, 84.7; H, 5.88. Found: C, 84.6; H, 5.93.

2-(β-Phenylethyl)-furan (III, R = H) is obtained readily from the above substance by shaking with hydrogen in the presence of Adams catalyst. The reduction is complete in less than one-half hour, and the product is identical in every respect with that obtained above.

Dibromide.—One-half gram 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 as long transparent prisms, m. p. 232.0–232.3°, reminiscent in appearance of hydroxylamine hydrochloride.

Anal. Calcd. for $C_{12}H_{10}OBr$: Br, 48.48. Found: Br, 48.5.

***m*-Methoxybenzaldehyde** was obtained in 83% yield by the methylation of *m*-hydroxybenzaldehyde in weakly alkaline solution by means of dimethyl sulfate. The yield of pure product obtained when the crude aldehyde is distilled *in vacuo* in a current of nitrogen is appreciably higher than that obtained when no precaution is taken to protect the substance from oxidation (b. p. (30 mm.) 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*-methoxybenzaldehyde, 200 cc. of reagent ethyl alcohol, 0.2 g. of freshly prepared Adams platinum oxide, and 2.0 cc. of 0.1 *M* ferrous sulfate solution were placed in the pressure bottle of the Adams hydrogenation apparatus. Shaking was started at three atmospheres. Within ten minutes, the theoretical absorption (0.294 mole = 23 lb.) had taken place. It was possible to use the same catalyst for a second or third reduction, but the time required for complete hydrogenation in this case was considerably longer. The alcohol was removed by distillation under reduced pressure, and the residual oil distilled *in vacuo* in a current of nitrogen.

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[12] More recent work which will be described in a subsequent communication has led to the quantitative hydrogenation of 3-[β-(*m*-methoxyphenyl)-ethyl]-Δ^4-tetrahydro-*o*-phthalic anhydride by shaking a suspension in methyl alcohol with hydrogen in the presence of platinum black.

[13] Frost, *Ann.*, **250**, 159 (1888).

m-Methoxybenzyl alcohol is a clear colorless liquid of peculiar odor, b. p. (25 mm.) 150°.

***m*-Methoxybenzyl Bromide.**—167 grams of *m*-methoxybenzyl alcohol was dissolved in 300 cc. of dry thiophene-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 overnight over calcium chloride. The benzene was removed *in vacuo* in a current of dry nitrogen; 238 grams of *m*-methoxybenzyl bromide, b. p. (8 mm.) 116° was obtained. The substance is a clear, highly refractive liquid which rapidly turns green or greenish purple on standing. Care must be taken not to inhale the substance nor allow it to come in contact with the skin, since it is an extremely irritating lachrymator and vesicant.

***m*-Methoxyphenylacetonitrile** (VI).—100 grams of *m*-methoxybenzyl bromide was refluxed for two and a half hours with 32 g. 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 residual sludge was shaken with water, and the oil which separated dried over a small amount of anhydrous sodium sulfate. On distillation 64 g. (87.5%) of *m*-methoxyphenylacetonitrile, b. p. (20 mm.) 164–165°, was obtained as a highly refractive liquid, of faint characteristic nitrile odor.

Anal. Calcd. for C_9H_9ON: C, 73.5; H, 6.10; N, 9.50. Found: C, 73.6; H, 6.3; N, 9.6.

α-(*m*-Methoxyphenyl)-β-(2-furyl)-acrylic Nitrile (IV, R = OCH_3).—To a mixture of 64 g. of *m*-methoxyphenylacetonitrile 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 sides 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 sulfate and distilled in a high vacuum (b. p. (1 mm.) 180°). Ninety grams of α-(*m*-methoxyphenyl)-β-(2-furyl)-acrylic nitrile was obtained as a clear yellow oil. For conversion into 2-(β-(*m*-methoxyphenyl)-ethyl)-furan, the purification was superfluous. The crude brown oil gave satisfactory results.

Anal. Calcd. for $C_{14}H_{11}O_2N$: C, 74.8; H, 4.98; N, 6.23. Found: C, 74.6; H, 5.2; N, 6.4.

2-[β-(*m*-Methoxyphenyl)-ethyl]-furan (III, R = OCH_3).—(a) (The preparative method.) Ninety grams 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 excess of two and a half times the theoretical amount for complete reduction to 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 became too violent, the clogging of the condensers was easily remedied by removing the stopper for a moment. The flask was set in a pail, or in the sink, 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 hydrochloric acid. Since a good deal of free sodium remained in the flask, it was advisable to conduct this operation with considerable care. It was advantageous to place a quantity of dry-ice on 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 satisfactory to extract the contents of the flask with ether, wash with dilute hydrochloric acid, then with water, and evaporate the ether after drying over sodium sulfate. In either case, the oil was distilled *in vacuo*. Thirty-nine grams of 2-[β-(*m*-methoxyphenyl)-ethyl]-furan was obtained as a colorless oil, b. p. (10 mm.) 153°, of aromatic odor, which turned yellow on standing. The same change was noticed with 2-(β-phenylethyl)-furan and 2-(γ-phenyl-*n*-propyl)-furan.

(b) (By the Grignard reaction.) Three grams of magnesium was placed in a dry three-necked flask equipped with dropping funnel, reflux condenser, and mercury seal bearing a mechanical stirrer. A few drops of *m*-methoxybenzyl 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*-methoxybenzylmagnesium 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 reaction proceeded. When the addition of 2-furfuryl bromide was complete, a large excess of freshly prepared butylmagnesium bromide was added rapidly and the reaction mixture was allowed to stand for one-half 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 sulfate. On fractionation *in vacuo*, 13 g. of 2-[β-(*m*-methoxyphenyl)-ethyl]-furan was obtained, identical in every respect with that prepared by method (a).

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.3; H, 7.10. Found: C, 77.1; H, 7.1.

2-Furfuryl Bromide.—Forty grams of freshly distilled 2-furfuryl alcohol dissolved in 400 g. of absolute ether was treated in the course of a half hour with 40 g. of pure phosphorus tribromide dissolved in 60 cc. of anhydrous ether. The flask was cooled from time to time by running water. When the addition had been completed, the reaction mixture was allowed to stand for half an hour before decanting from the waxy precipitate of phosphorous acid which covered the walls of the flask. The decanted solution was treated with a solution of 0.1–0.2 mole of butylmagnesium bromide (from 18 g. of butyl bromide and 4.0 g. of magnesium) in 100 cc. anhydrous ether, and used directly in the reaction described above.

3-(β-Phenylethyl)-3,6-endoxo-Δ^4-tetrahydro-*o*-phthalic Anhydride (VII, R = H).—Three grams of pure maleic anhydride (twice recrystallized from chloroform) and 5.4 g. of 2-(β-phenylethyl)-furan dissolved in the smallest amount of anhydrous ether necessary for complete solution were allowed to stand in a well-stoppered flask. In a few days 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 separated, m. p. 73–74°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.2; H, 5.18. Found: C, 71.2; H, 5.3.

If this substance was dissolved in warm ligroin (b. p. 70–90°) and the resulting solution allowed to stand in the icebox, needles separated, which proved to be maleic anhydride, m. p. 57–59°, mixed m. p. 57–59°; orange color on heating with dimethyl- or diethylaniline.

Bromohydroxy Derivative (VIII, R = H).—The addition product (1.0 g.) was dissolved in excess sodium carbonate and the basic solution was exactly neutralized. This solution was shaken vigorously with a slight excess of bromine. Recation took place immediately with the quantitative precipitation of the bromohydroxy acid. After recrystallization from boiling water (Norit) the acid melted at 142–143°, with decomposition.

Anal. Calcd. for $C_{16}H_{15}O_5Br$: C, 52.4; H, 4.18. Found: C, 52.1; H, 4.4.

3 - [β - (*m* - Methoxyphenyl) - ethyl] - 3,6 - endoxo-Δ^4-tetrahydro - *o* - phthalic Anhydride (VII, R = OCH_3) crystallized quantitatively in beautiful transparent rosets when 31.6 g. of 2-[β-(*m*-methoxyphenyl)-ethyl]-furan and 15.3 g. of pure maleic anhydride were dissolved in the least amount of anhydrous ether necessary for complete solution and allowed to stand for three days. After washing with anhydrous ether, drying and crystallizing by the chloroform–petroleum ether procedure, long, transparent needles were obtained, m. p. 78–80°.

Like the unsubstituted addition product, this methoxy derivative gave maleic anhydride on heating in ligroin, gave no color with dimethylaniline until heated, and was unstable to cold dilute alkaline permanganate.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 68.0; H, 5.33. Found: C, 68.0; H, 5.4.

Hydrogenation Experiments.—If 1 g. of 3-(β-phenylethyl)-3,6-endoxo-Δ^4-tetrahydro-*o*-phthalic anhydride 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°.

All attempts to isolate other crystalline products from the reaction, or from numerous runs made in ethyl acetate or inert solvents, failed.

Summary

The synthesis of 2-(β-phenylethyl)-furan and 2-[β-(*m*-methoxyphenyl)-ethyl]-furan has been accomplished.

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

CAMBRIDGE, MASS. RECEIVED MARCH 11, 1940

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ketene Acetals. VI. The Preparation of Ketene Acetals from α-Bromo-orthoesters[1]

BY PHILIP M. WALTERS AND S. M. MCELVAIN

The procedure which has been used in this Laboratory for the preparation of ketene acetals involves the removal of the elements of halogen acid from a halogenated acetal by means of potassium *t*-butoxide

$$XCH_2CH(OEt)_2 + KOC_4H_9(t) \longrightarrow CH_2{=}C(OEt)_2 + KX + t\text{-}C_4H_9OH$$

By this reaction ketene diethylacetal and various halogenated derivatives of it have been prepared.[2] It is obvious that attempts to apply this procedure to the acetals of the higher α-halogenoaldehydes, $R_2CHCHXCH(OEt)_2$, might be unsuccessful due to the preferential loss of halogen acid from the α- and β-carbon atoms with the resultant formation of the acetals of the unsaturated aldehydes.[3]

Another route to the ketene acetal structure that was partially explored when the problem first was undertaken is the elimination of the elements of ethyl hypohalite, EtOX, from an α-halogeno-orthoacetic ester in a manner similar to that used by Boord and co-workers[4] to prepare olefins. A

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(1) Paper V of this series is Barnes, Kundiger and McElvain, THIS JOURNAL, **62**, 1281 (1940).

(2) Beyerstedt and McElvain, *ibid.*, **58**, 529 (1936); **59**, 2266 (1937); Magnani and McElvain, *ibid.*, **60**, 2210 (1938).

(3) In the cases of the acetals of the α-halogeno-propionaldehyde, -butyraldehyde and -isobutyraldehyde the larger numbers of hydrogens on the β-carbon atoms makes the α,β-loss of halogen acid much more probable than that between the α-carbon and the aldehyde carbon atom. However in the case of the acetal of α-halogeno-isovaleraldehyde, $(CH_3)_2CHCHXCH(OEt)_2$, in which there is only one hydrogen on the β-carbon atom it seems that there should be some chance of loss of halogen acid from the α-carbon and the aldehyde carbon atom. But Jones (B.S. Thesis, University of Wisconsin, 1939), working along this line found that each of the above acetals (X is Br) gave the corresponding unsaturated acetal, through an α,β-loss of hydrogen bromide, when treated with potassium *t*-butoxide in *t*-butyl alcohol.

(4) Boord, *et al.*, THIS JOURNAL, **52**, 3396 (1930); **53**, 1505 (1931) **54**, 751 (1932); **55**, 3293, 4930 (1933).