

Water was added and the mixture steam distilled. The organic layer was separated and the water layer extracted four times with 30-ml. portions of petroleum ether. The combined organic material was dried over calcium chloride, filtered and fractionated. The 2,3,4,5-tetrachlorothiophene weighed 7 g., mixed m.p. 29°.

Reaction of 2,2,3,4,5,5-Hexachlorothiophene, IV, with Zinc.—A suspension of 150 g. of 90% zinc dust in 500 ml. of water was heated to 95°, and 250 g. of IV added over a one and one-quarter hour period. The unreacted metal was removed by filtration and the organic layer separated. The water layer was extracted with ether and yielded 21 g. of product. The organic material was combined and the ether distilled. The distilled 2,5-dichlorothiophene weighed 85 g.; b.p. 160–163°; n_D^{20} 1.5624.

Acknowledgment.—The authors are grateful to Dr. D. E. Badertscher and Dr. C. C. Price for their advice and interest in this problem, to Miss Emily Burns who carried out a great many of the laboratory experiments, and to Mr. J. G. Ehlers for infrared spectrographic analyses.

Summary

Thiophene reacts with chlorine to produce both addition and substitution products in proportions dependent upon the reaction conditions and the ratio of chlorine to thiophene.

Chlorine addition products were isolated. These are identified as α -2,3,4,5-tetrachlorothiophene, β -2,3,4,5-tetrachlorothiophene, 2,2,3,4,5-pentachlorothiophene and 2,2,3,4,5,5-hexachlorothiophene. The compounds are white crystalline materials stable at room temperature.

Pyrolysis of α -tetrachlorothiophene and of pentachlorothiophene gave mixtures of dichlorothiophenes and trichlorothiophenes, respectively, varying in composition from the chlorothiophenes formed by dehydrohalogenation with ethanolic potassium hydroxide.

PAULSBORO, N. J.

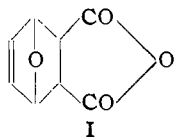
RECEIVED JULY 28, 1947

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

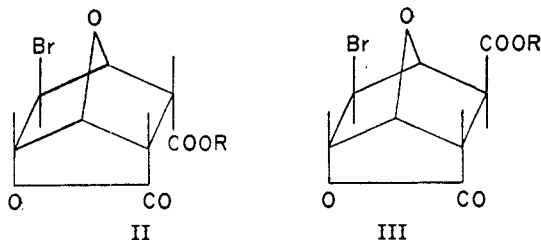
The Reaction of Furan with Maleic Anhydride¹

BY R. B. WOODWARD AND HAROLD BAER

In an attempt to synthesize cantharidine or cantharidine-like compounds, Diels and Alder² undertook the study of the reaction of furan with maleic anhydride. The two substances reacted in ether solution to give a crystalline adduct, m.p. 125°, which was shown to have the structure (I).



Subsequently, the same authors³ observed that an aqueous solution of maleic acid dissolved furan on long shaking. When the resultant solution was treated with bromine a substance, $C_8H_7O_6Br$, m.p. 205°, was precipitated, to which the structure (II, R = H) was assigned. This bromolactonic acid was converted by diazomethane to a monomethyl ester (II, R = Me), m.p. 175°. Hydrobromic acid at 100° converted (II) to an isomer (III, R = H), from which an ester (III, R = Me),

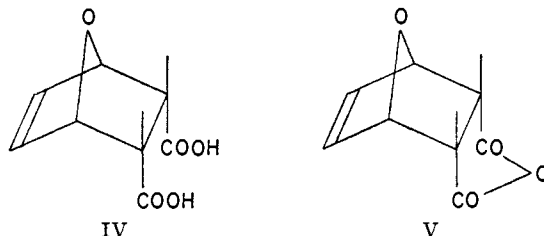


(1) This paper is the third in a series of studies on diene addition reactions. For II, see Woodward and Baer, *THIS JOURNAL*, **66**, 645 (1944).

(2) Diels and Alder, *Ber.*, **62**, 557 (1929).

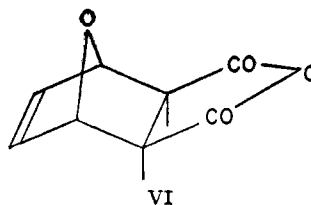
(3) Diels and Alder, *Ann.*, **490**, 243 (1931).

m.p. 168°, was obtained, while the same agent, at 160–170°, converted (II) to *o*-phthalic acid. These observations indicated that the solution of furan in aqueous maleic acid contained *endo-cis*-1,4-endoxo- Δ^4 -cyclohexene-2,3-dicarboxylic acid (IV). It is significant that the German authors presented no evidence of the actual isolation from the solution of an adduct. *On the assumption that*



the acid obtained by the hydrolysis of the crystalline anhydride (I) was identical with the acid contained in the aqueous solution of furan in maleic acid, Diels and Alder assigned the structure (V) to the adduct, m.p. 125°.

In this communication, it is shown that that assumption was incorrect and that, in fact, the product of the addition of maleic anhydride to furan is *exo-cis*-3,6-endoxo- Δ^4 -tetrahydrophthalic anhydride (VI). When the anhydride, m.p.



125°, is dissolved in water or dilute base and the resultant solution is treated with bromine, a new colorless crystalline substance $C_8H_7O_6Br$, m.p. 153° (d.), is precipitated,⁴ in the latter case after acidification with hydrochloric acid. Careful evaporation of the mother liquor from the reaction yields a dibromide of the adduct acid, $C_8H_7O_6Br_2$, m.p. 155°. This substance, which was converted by catalytic esterification to a dimethyl ester, $C_{10}H_{12}O_8Br$, m.p. 116°, is of no great interest and needs no further comment.

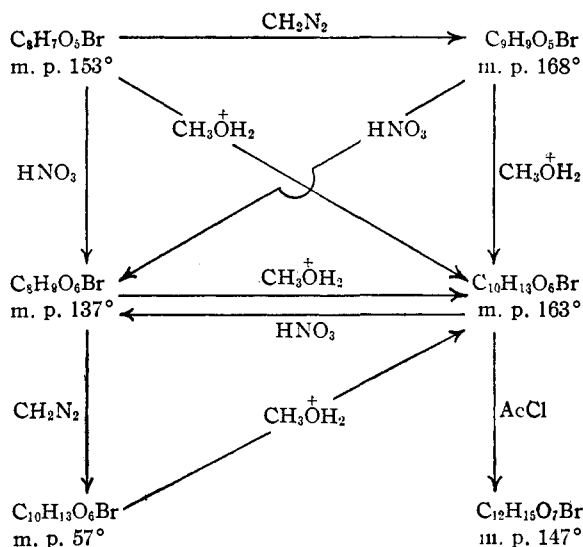
Esterification of the new monobromo compound, m.p. 153°, with diazomethane gives a monomethyl ester, $C_9H_9O_6Br$, m.p. 168° (dec.) which is not identical with either of the isomeric esters, m.p. 175° and 168°, of Diels and Alder (*vide supra*) as evidenced by mixed melting point determinations and, further, by the striking differences between the chemical properties of the new ester, as contrasted with those of the previously described isomers. The latter melt without decomposition to clear liquids, which resolidify on cooling; they are stable to dilute alkalis, and to alkaline permanganate, and do not reduce Fehling solution or Tollens reagent. By contrast, the new ester melts with complete decomposition, it decolorizes cold aqueous permanganate instantly, reduces Tollens and Fehling solution readily when warmed slightly, and it is rapidly destroyed, with the formation of dark-colored intractable material, by the action of cold dilute weak bases or by short warming with dilute acids. Base liberates bromide ion instantaneously from the new ester, but, significantly, alcoholic silver nitrate fails to yield a precipitate of silver bromide.

Catalytic esterification, with methanol and sulfuric acid, converts either the monobromo compound, $C_8H_7O_6Br$, or the new ester, m.p. 168°, into a new substance, $C_{10}H_{13}O_6Br$, m.p. 163° (d.), from which an acetyl derivative, $C_{12}H_{15}O_7Br$, m.p. 147°, may be obtained. Any of the three substances, when boiled with dilute nitric acid,⁵ is converted to an acid, $C_8H_9O_6Br$, m.p. 137° (d.). This acid is transformed by the action of methanol and sulfuric acid to the compound $C_{10}H_{13}O_6Br$, m.p. 163°, but by the action of diazomethane, an isomeric substance, $C_{10}H_{13}O_6Br$, m.p. 57° (dec.) is obtained. The new compound is inordinately unstable. It decomposes spontaneously within an hour, and it is the first substance of this series to yield a precipitate of silver bromide with alcoholic silver nitrate. Methanol containing sulfuric acid converts the 57° compound into its isomer, m.p. 163°. The accompanying chart will clarify this somewhat involved series of changes.

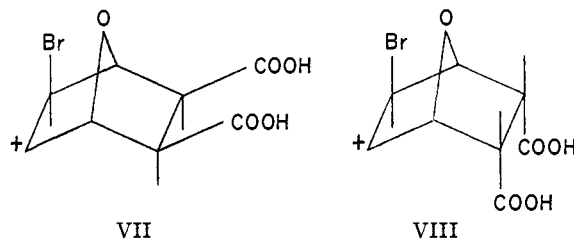
These transformations are explicable only on the basis that the original adduct (I), m.p. 125°,

(4) Observation of Mrs. Virginia (Williams) Eager.

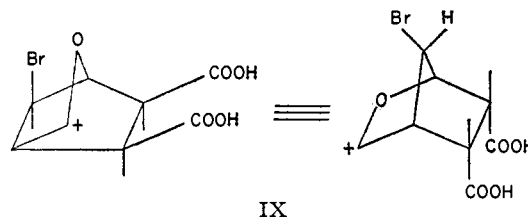
(5) Nitric acid only, of all acids tried, is effective, presumably because it oxidizes the decomposition products which are usually formed in reactions involving these very sensitive substances, and permits ready isolation of the desired product from reaction mixtures free of otherwise inseparable contaminants.



has the *exo-cis* configuration (VII). Attack at the double bond by bromine produces a carbonium ion (VII) or its equivalent. Unlike the corre-

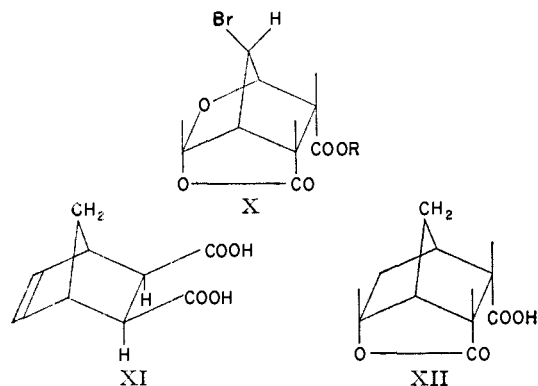


sponding *endo-cis* ion (VIII), which can undergo spontaneous stabilization by lactonization, to give (II, R = H), VII is incapable of direct lactonization, since the oxygen bridge blocks union between the positively charged carbon atom and an oxygen of the carboxyl group. However, after a normal Wagner-Meerwein rearrangement to (IX), the hitherto inaccessible carboxyl group may participate in lactonization, with the formation of (X, R = H); this expression represents the monobromo compound $C_8H_7O_6Br$, m.p. 153°, of the new series. This change is comparable to that involved in the transformation of *exo-cis*- Δ^6 -bicyclo-



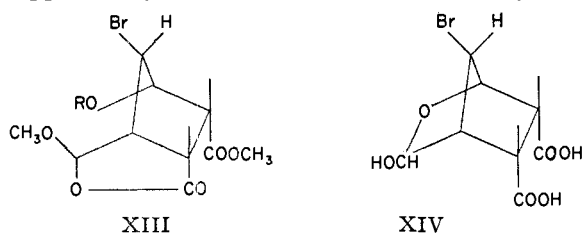
[1,2,2]-heptene-2,3-dicarboxylic acid (XI) into the lactone (XII) on treatment with acid.⁶ In our case, the circumstances are even more favorable for rearrangement, since the oxygen atom tends to stabilize the rearranged ion, through contributions

(6) Alder and Stein, *Ann.*, **514**, 1 (1934).

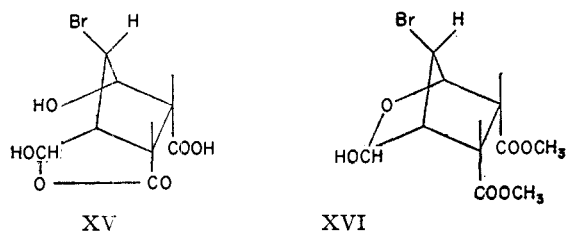


of the type $\text{—}\overset{+}{\text{C}}=\overset{-}{\text{O}}\text{—}$. The presence in the rearranged ion of a carboxyl group in a position in which it may participate in lactonization undoubtedly provides additional driving force for the rearrangement; on the other hand the similar rearrangement in the hydration of dicyclopentadiene⁷ indicates that this factor is not a necessary one. The occurrence of a Wagner-Meerwein rearrangement during bromination is not unexpected in the light of current views on the mechanism of halogenation⁸ and, in any event, has been observed in other cases, *e.g.* in the reaction of pinene with bromine to give 2,6-dibromo-camphane.⁹

The structure (X, R = H) is compatible with all of the observed reactions of the 153° compound. The formulation of the mono-ester, m.p. 168°, as (X, R = CH₃) follows directly, while the compound C₁₀H₁₃O₆Br, m.p. 163°, may be represented as the pseudo-ester (XIII, R = H), a formulation supported by the formation of a mono-acetyl-



derivative (XIII, R = CH₃CO—). The acid, C₈H₉O₆Br, m.p. 137°, is (XIV) (or its ring-chain tautomer, XV), and finally, the isomeric substance C₁₀H₁₃O₆Br, m.p. 57° is the normal diester (XVI).



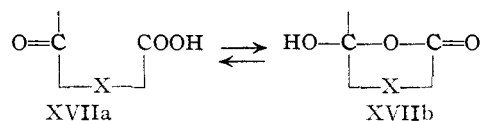
The formation of the isomeric esters, C₁₀H₁₃O₆Br, provides proof of the presence of a (potential)

(7) Bartlett and Schneider, *THIS JOURNAL*, **68**, 7 (1946).

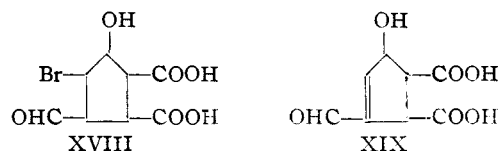
(8) Roberts and Kimball, *ibid.*, **69**, 947 (1937).

(9) Aschan, *Ber.*, **61**, 42 (1928).

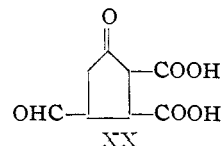
carbonyl group in this series, and in particular, the formation of the pseudo-ester (XIII, R = H) and the normal ester (XVI) respectively under catalytic esterification conditions and through the action of diazomethane, is consonant with the usual properties of substances capable of participation in ring-chain equilibria of the type $\text{XVIIa} \rightleftharpoons \text{XVIIb}$,¹⁰



The great sensitivity of the entire series arises from the circumstance that all of the substances are derived from the cyclopentane aldehyde (XVIII); once the lactone ring of any of the compounds is opened (say by alkali) with liberation of



the free aldehyde group, the β -halogen atom is eliminated with extreme ease. The resultant unsaturated aldehyde (XIX), itself very probably an unstable substance, may readily isomerize¹¹ to



XX, which possesses manifold possibilities for auto-condensation.¹²

The ready elimination of bromide ion, and possibly also the potential aldehyde group, accounts for the facile oxidation by dilute permanganate solution, while the latter feature is responsible for the observed reducing action toward warm Fehling solution and Tollens reagent. In that connection, it is significant that while the substances are immediately oxidized by permanganate in the presence of the merest trace of base, dilute acid suppresses the reduction of that agent considerably; the somewhat greater stability of the acids of the series as compared with the esters is another consequence of the same effect. Finally, the fact that the ester of m.p. 57° is by far the most unstable compound of the entire series is a consequence of the fact that in it the potential aldehyde group is masked only as a simple hemiacetal function; mere prototropic change is necessary to initiate the series of degenerative reactions, while in

(10) *Cf. i. a., Meyer, Monatsh.*, **26**, 1295 (1905); Blaise and Courtot, *Bull. soc. chim.*, [3] **35**, 999 (1906).

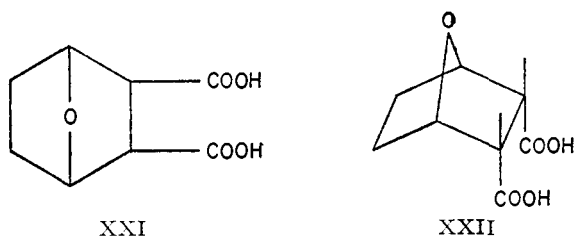
(11) *Cf. Woodward and Blout, THIS JOURNAL*, **65**, 562 (1943).

(12) *Cf. the behavior of levulinic aldehyde, a simple analog of XX. When the acetal of the aldehyde is warmed with dilute acids the free aldehyde is liberated; attempts to neutralize the solutions with sodium carbonate result in very rapid and complete destruction of the substance [Harries, Ber., 81, 37 (1898)].*

the other compounds, a more difficult reaction, initiated by an external reagent, must take place prior to decomposition.

In addition to its ready elimination in the presence of base, the bromine atom in these compounds is remarkable in two further ways. The stability to alcoholic silver nitrate is traceable to the circumstance that while the bi-(or tri)-cyclic ring system is retained, stabilization of the carbonium ion intermediate which might otherwise result from the attack of silver ion is impossible. Finally, the bromine atom in (X) and its derivatives is stable toward zinc under conditions which normally transform dibromides and bromohydrin derivatives into olefins. However, it is known that this reaction is highly stereospecific, in that *trans* elimination takes place exclusively.¹³ For instance, *dl*-2,3-dibromobutane gives only *cis*-butene-2, while *meso*-2,3-dibromobutane gives only the *trans*-olefin. No data are available on the reaction of zinc with a cyclic dibromide or bromohydrin derivative of known *cis*-configuration, but the above facts strongly indicate that the reaction, in such a case, in which the groups to be eliminated cannot assume a *trans* position with respect to one another, will proceed with difficulty, or not at all. Now in the formation of X, it is most probable that the initial attack of the bromine on the adduct (VI) takes place on the *exo* side¹⁴; consequently the bromine atom in (X), and the substances derived from it, will be *cis* to the oxygen attached to the contiguous carbon atom, and the sluggishness toward zinc may be accepted as confirmatory of the assigned structures.

We turn now to a consideration of the configurations of the acids of the structure XXI. Three stereoisomeric forms, *viz.*, *endo-cis* (XXII),

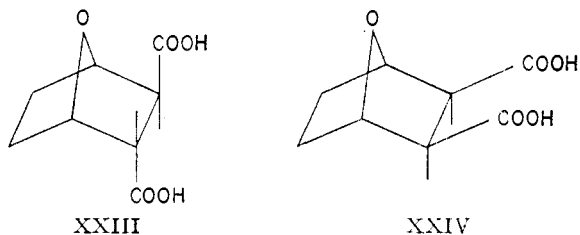


trans (XXIII) and *exo-cis* (XXIV), are possible. Alder and Backendorf, starting from the furan-maleic anhydride adduct (I or VI) have prepared three acids of the structure XXI, and on the basis of the assignment of the erroneous configuration (V) to the original adduct, deduced the configuration of the three saturated acids.¹⁵ It is now clear that the previous configurational assignments, except for that of the intermediary *trans* acid, are invalid and must be revised. In Table I, the correct con-

(13) Young and Lucas, *THIS JOURNAL*, **52**, 1970 (1930); Young and Winstein, *ibid.*, **58**, 103 (1936); Wilson and Lucas, *ibid.*, **58**, 2396 (1936).

(14) Cf. Alder and Stein, *Ann.*, **515**, 185 (1935); **525**, 183 (1936).

(15) Alder and Backendorf, *ibid.*, **535**, 113 (1938).



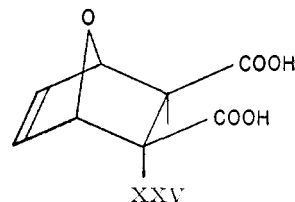
figurations are presented. In this connection it is noteworthy that the German workers were led to believe that in the *endoxocyclohexane* series, the

TABLE I
CONFIGURATIONS OF THE 3,6-*endoxocyclohexane* ACIDS AND ANHYDRIDES

	Acid	M. p., °C.	Anhydride
<i>exo-cis</i> (XXIV)	122-123	116-117	
<i>trans</i> (XXIII)	180	
<i>endo-cis</i> (XXII)	169-170	158-159	

melting point regularities observed in other (*e.g.* the [1,2,2]bicycloheptane) series were reversed, and that further, addition reactions (*e.g.*, hydrogenation), which normally occur with addition from the *exo* side,¹⁶ also took an abnormal course, with *endo* addition. It is now clear that both the melting point regularities and the *exo* addition rule are obeyed in the *endoxocyclohexane* series, and that the only reversal necessary is that which we have made in the configurational assignments.

The work described here demonstrates that the reaction of furan with dienophiles is similar to that of the fulvenes previously studied¹ in this Laboratory in that both *exo* and *endo* adducts may be formed, depending on the reaction conditions, and, in this particular case, on the nature of the addend. We are not prepared to discuss at this point the theoretical implications of the present work, but in any future discussion, the following points must be borne in mind. In the furan series, both addition reactions are readily reversible. Further, the order of stabilities of the isomers is the same as that in the fulvene case, as evidenced by the fact that while the *exo-cis* acid (XXV), obtained from the anhydride (VI), can be purified by recrystallization from warm water, all attempts so far made to isolate the *endo-cis*



acid (IV) from its solutions have failed; since maleic acid is the only solid product obtained it

(16) It is worthy of note that the prevalence of *exo* addition in the catalytic hydrogenation of these bicyclic substances provides an excellent example of the operation of the catalyst hindrance effects postulated by Linstead, *et al.*, *THIS JOURNAL*, **64**, 1985 (1942).

appears that the furan-maleic acid reaction is extraordinarily readily reversible, with the result that attempts at removal of solvent, or extraction, result preferentially in removal of furan, by volatilization or extraction, with continuous displacement of the equilibrium until no adduct remains.

Experimental

Furan-Maleic Anhydride Adduct.—This substance was prepared according to the directions of Diels and Alder.² It is impractical to recrystallize the adduct because of the ease with which it dissociates in warm solvents.

Bromolactonic Acid (X, R = H).—Thirty-six grams of the furan-maleic anhydride adduct was dissolved in a solution containing 19 g. of sodium hydroxide in 600 ml. of water. The solution was cooled to about 8°, and bromine was added dropwise with constant stirring until a faint color persisted. Acidification with hydrochloric acid produced 49.5 g. of a white needle-like crystalline substance whose melting point was 153° (dec.) after recrystallization from water (not warmer than 40°). It is necessary to place the melting point capillary in the bath not more than 10° below the decomposition point or reproducible results cannot be obtained.

Anal. Calcd. for C₈H₇O₅Br: C, 36.5; H, 2.66. Found: C, 36.6, 36.3; H, 2.73, 2.70.

Concentration of the mother liquor *in vacuo* yielded 5.5 g. of the normal dibromide, m. p. 155° (from water).

Anal. Calcd. for C₈H₆OBr(COOH)₂: C, 27.9; H, 2.33; neut. equiv., 172. Found: C, 29.2, H, 2.79; neut. equiv., 170, 172.

Esterification of the dibromo acid (500 mg.) with 10 ml. of absolute methanol containing a few drops of fuming sulfuric acid (30%) yielded the dimethyl ester which, after two recrystallizations from water melted at 115.9–116.3°.

Anal. Calcd. for C₁₀H₁₂O₅Br₂: C, 32.3; H, 3.23. Found: C, 32.6; H, 3.51.

In order to obtain a maximum yield of the 153° compound it is necessary to add the bromine slowly and with rapid stirring as will be illustrated by Table II. The yield of dibromide is variable and of little significance because of the difficulty encountered in its isolation.

TABLE II

Adduct, g.	153° cpd.	Dibromide (155°)
9.2	8.2	2.2
30	28	7.3
36 rapid stirring	49.5	5.5

The 153° compound may also be obtained by dissolving the adduct directly in warm water (40–50°) and after cooling to 0° adding bromine until a slight color persists; the product, which has precipitated from the solution, is filtered off. In two typical experiments the weight of 153° compound obtained was approximately equal to that of the adduct used, and *ca.* one third as much dibromide was isolated.

If a small quantity of the 153° compound is dissolved in water and neutral or acid potassium permanganate added, no oxidation is observed. The addition of the slightest excess of carbonate results in instant decoloration of the solution.

Attempts at solution in caustic alkali or soda result in complete destruction of the compound if warmed; if the solution is kept cold, no decomposition is apparent until the solution is acidified, when a brown, amorphous solid is precipitated.

Schiff reagent fails to react but both Tollens solution and Fehling reagent give positive tests if the solution is warmed gently on the steam-bath. The addition of silver nitrate solution to a hot aqueous solution of the 153° compound produces an immediate precipitate of silver bromide; in alcoholic solution no reaction is observed.

Half-methyl Ester (X, R = CH₃).⁴—Diazomethane is distilled onto an ether suspension of the 153° acid (1 g.). After the reaction has ceased, the ether is boiled off and the solid that remains is recrystallized from methanol: 0.75 g. of fine, cotton-like needles, m. p. 167–168° (d.).

Anal. Calcd. for C₉H₉O₅Br: C, 39.1; H, 3.25. Found: C, 39.1, C, 39.1; H, 3.31, H, 3.39.

This substance is moderately stable to weakly acid permanganate solutions but once again, the addition of the merest trace of alkali results in instant decolorization of the permanganate.

This ester cannot be dissolved either in alkali or dilute sulfuric, hydrochloric, or acetic acids without complete decomposition. The reaction with nitric acid will be described under the preparation of the 137° compound.

If, however, nitrogen is bubbled through a saturated barium hydroxide solution and then the 168° ester rapidly added, the residue remaining, after warming for a half-hour to 50°, is mainly barium carbonate. While no organic product could be isolated from the solution, this result would indicate the presence of a β-keto acid in the solution which presumably resulted from the action of the base on the 168° ester. This observation may be considered as evidence for the change XVIII → XIX.

Pseudoester (XIII, R = H).—Into 10 ml. of methanol, containing a few drops of 30% fuming sulfuric acid, is placed 500 mg. of the 153° acid. After heating under reflux for three hours the solution is poured onto ice, whereupon the ester crystallizes (yield 300 mg.). After recrystallization from methanol the ester is obtained as plates, m. p. 163° (d.).

Anal. Calcd. for C₁₀H₁₃O₅Br: C, 38.9; H, 4.21. Found: C, 38.3, 38.3; H, 4.18, 4.14.

By making use of the above procedure the 168° ester (500 mg.) may be converted to the 163° ester (350 mg.); the 57° ester (*vide infra*) is also converted to the 163° ester by this procedure.

This ester is sensitive to alkali and alkaline potassium permanganate but relatively stable to acid and neutral permanganate.

Heating the 163° ester in methanol with zinc for twenty-four hours resulted in no change.

Acetyl Derivative (XIII, R = CH₃CO⁻).—The 163° ester is dissolved in acetyl chloride and the solution heated under reflux for one hour. The solution was decomposed on ice and cooled in an ice-bath overnight: needles were obtained which, on recrystallization from methanol, melted at 146.5–147°.

Anal. Calcd. for C₁₂H₁₅O₇Br: C, 41.0; H, 4.27. Found: C, 41.1; H, 4.54.

Acid (XIV or XV).—Two grams of the 163° ester is added to a mixture of 10 ml. of concentrated nitric acid and 20 ml. of water and the mixture warmed in a water-bath (50°) with constant stirring until solution is complete. After warming for one more hour the solution is concentrated, by distillation *in vacuo*, and then cooled; the precipitated acid (600 mg.) is twice recrystallized from water and obtained as needles, m. p. 136–137° (d.) (this is not a true melting point and consequently varies somewhat with the rate of heating).

Anal. Calcd. for C₈H₉O₅Br: C, 34.1; H, 3.20. Found: C, 34.2, 34.0; H, 3.28, 3.56.

The same acid is obtained by treatment of either the 168° ester or the 158° acid in an analogous manner. From 1.4 g. of the 168° compound one obtains 450 mg. of acid.

Alkaline potassium permanganate attacks this substance with vigor. The Schiff test is negative but positive Tollens and Fehling tests are obtained.

This acid is readily converted to the 163° ester. To a solution of 300 mg. of acid in 10 ml. of methanol is added a few drops of fuming sulfuric acid (30%) and the whole heated under reflux for several hours. Decomposition of the solution on ice produces the characteristic silky plates of the 163° ester, m.p. 160° (d.).

Normal Ester (XVI).—Onto a suspension of 400 mg. of the 137° acid in ether diazomethane is distilled; the mixture is permitted to stand in ice until the evolution of nitrogen ceases. Removal of most of the ether on the steam-bath followed by cooling in ice results in the formation of 300 mg. of solid ester. Recrystallization from ether containing a little methanol produces clusters of transparent needles, m. p. 57° (dec.). This ester is extremely unstable, decomposing slowly in the cold room (5°) and very rapidly at room temperature (about an hour).

Anal. Calcd. for $C_{10}H_{13}O_6Br$: C, 38.9; H, 4.21; Br, 25.9. Found: C, 38.9; H, 4.43; Br, 26.3.

The Schiff test on this ester is negative but positive Fehling and Tollens tests are very readily obtained on only slight warming. Silver nitrate in alcoholic solution reacts

slowly in the cold but rapidly on warming to produce a copious quantity of silver bromide.

Acid potassium permanganate does not effect a rapid oxidation but in an alkaline solution this reagent is instantly decolorized.

Summary

The reaction between furan and maleic acid in water, and that between furan and maleic anhydride in ether, take different stereochemical courses. In the former case, an *endo-cis* adduct is formed, while in the latter, an *exo-cis* product is obtained.

CAMBRIDGE, MASS.

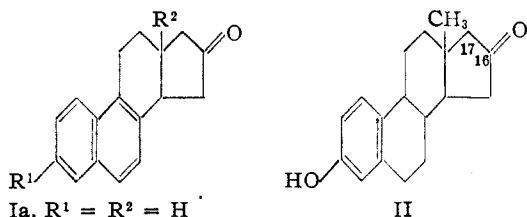
RECEIVED SEPTEMBER 23, 1947

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

The Synthesis of 1,3,5-Estratrien-3-ol-16-one, A Structural Isomer of Estrone¹

BY A. L. WILDS AND THOMAS L. JOHNSON^{2,3}

Several years ago⁴ a method of synthesis was developed for the ketone Ia, which possesses the basic ring system of the female sex hormones but with the ketone group at the 16 rather than the 17-position, and lacking the angular methyl and 3-hydroxyl groups. More recently⁵ this synthetic approach was modified to permit incorporation of



Ia, $R^1 = R^2 = H$
 Ib, $R^1 = H$; $R^2 = CH_3$
 Ic, $R^1 = OH$; $R^2 = CH_3$

the angular methyl group as in Ib, and extended⁶ to the synthesis of Ic, a structural isomer of equilenin. The present paper is concerned with the synthesis of 1,3,5-estratrien-3-ol-16-one (II), which is a structural isomer of estrone having the carbonyl group shifted to the 16-position.

For this extension to compounds having ring B hydrogenated the key intermediate was the ketone VII,⁷ for which an improved synthesis was developed by Bachmann, Kushner and Stevenson.⁸

In the present work the over-all yield in the conversion of the substituted malonic ester III to V

could be raised from 28 to 45% by eliminating distillation of the intermediate keto ester IV and carrying out the cyclization with anhydrous hydrogen fluoride.⁹ The remaining steps involving reduction of the dibasic acid to VI, conversion to the methyl ester, Dieckmann cyclization and methylation of the cyclic β -keto ester, followed by hydrolysis and decarboxylation, proceeded well to give mainly the crystalline isomeride of the octahydro ketone VII. Similar treatment of V led to the related hexahydro ketone VIII.⁸ In each case the over-all yield of ketone from dibasic acid was 75–78%, or about 6.5 and 7.4%, respectively, for the 14–15 step synthesis from *m*-aminophenol.

In the earlier synthesis of the desoxy tetracyclic ketone Ib,⁵ an acetic acid residue was introduced into the 2-position of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene by preparing the sodium enolate of the ketone with sodium amide and alkylating with methyl bromoacetate. Preliminary attempts to apply this procedure to the methoxy ketones VII or VIII (on a 0.5 g. scale) led to oily acidic mixtures after hydrolysis, from which no pure crystalline products could be isolated. Further work in the tetrahydro desoxy series showed that the original procedure, although quite satisfactory on a moderately large scale (71% yield on a 20 g. scale) was poor for small scale experiments (35–39% on a 0.5 g. scale). Triphenylmethylsodium, however, proved to be satisfactory as an enolizing agent even on a small scale, and when the optimum conditions for the reaction were developed it was possible to prepare the crystalline acetic acid derivatives IXa and Xa in 55–59% yields from the methoxy ketones VII and VIII.

With the hexahydroketone VIII the most probable position of alkylation was the 2-position.

(9) Adkins and Hager have found this to be an excellent reagent for effecting the cyclization of somewhat analogous β -keto esters; Glenn F. Hager, Ph.D. Thesis, University of Wisconsin, 1943.

(1) Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(2) Eli Lilly Research Fellow, 1945–1946.

(3) Present address: Sterling-Winthrop Research Institute, Rensselaer, N. Y.

(4) Wilds, *THIS JOURNAL*, **64**, 1421 (1942).

(5) Wilds and Beck, *ibid.*, **66**, 1688 (1944).

(6) Wilds and Close, *ibid.*, **69**, 3079 (1947).

(7) Robinson and Walker, *J. Chem. Soc.*, 183 (1938).

(8) Bachmann, Kushner and Stevenson, *THIS JOURNAL*, **64**, 974 (1942).