NUCLEAR SUBSTITUTION AND ORIENTATION OF FURAN TYPES

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I. INTRODUCTION

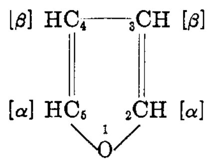
Furan compounds have been known for many years. Furoic or pyromucic acid was probably first obtained about one hundred and fifty years ago, in 1780, by pyrolysis of mucic acid (1). Furfural or 2-furaldehyde, the best known furan compound, was discovered accidentally in 1832 (2), and its isomer (3-furaldehyde) was synthesized almost exactly one hundred years later (3). From the point of view of an evenly distributed chronological series of events, it is interesting to note that thiophene, which bears a marked resemblance to furan and has been designated as thiofuran, was discovered, also by accident, fifty years ago (4).

Despite this relatively long history of furan compounds, there is an astonishing paucity of information on nuclear substitution reactions of furan. The outstanding exceptions are the classical investigations by Hill and coworkers and by Marquis. Their studies, like those of other earlier workers, were confined rather largely to stable compounds like furoic acid. The occasional and infrequent early experiments on nuclear substitutions of less stable compounds like furfural and furfuryl alcohol were discouraging because the more important or more generally used substitution reactions, such as halogenation, nitration, and sulfonation, involve the obvious use or formation of mineral acids, and such acids are the *bête noire* of sensitive furan compounds. The ready formation of apparently intractable oils, resins, tars, and chars may account, in part, for the sporadic nuclear substitution investigations, which culminated in a feeling on the part of some that such reactions with labile furan types were extremely difficult and virtually impossible. Latterly, it has been shown that these reactions are still somewhat difficult but not impossible, and that the furan nucleus has been somewhat maligned insofar as its sensitivity to acids is concerned (5). It must be remembered that the stability or integrity of the furan nucleus, like that of other heterocycles or benzene, is determined largely by the number, kind, and distribution of nuclear substituents. The range of stability of furan compounds extends from types which undergo spontaneous and prompt and complete decomposition, to compounds which have an extraordinary resistance to very drastic reagents and conditions.

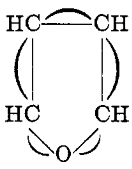
Recent studies now make it possible to discuss with some confidence the constitution of many nuclear substituted furans and to formulate some generalizations in regard to orientation.

II. CONSTITUTION OF FURAN

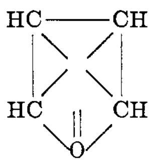
The determination of the position of substituents and the formulation of orientation rules are inherently associated with the structure of furan. All that is now known with definiteness is that furan is a cycle of one oxygen and four carbon atoms, and that this heterocycle has four hydrogen atoms. The formula generally used today (6) is that with two pairs of double bonds, between carbon atoms 2, 3 and 4, 5, respectively (I).



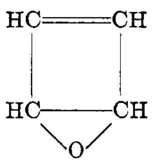
I



II



III



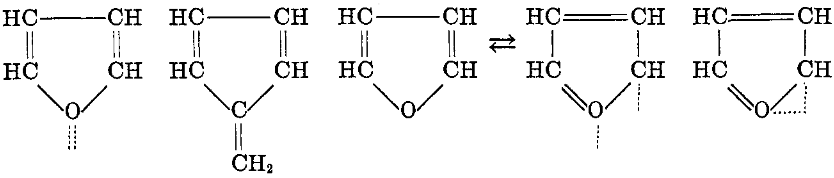
IV

Furan compounds, in general, have aromatic properties much like those of the analogous compounds of benzene. There is no present exact information on the distribution of the fourth valence of each carbon atom in benzene. Likewise, we do not know the distribution of the fourth valence of each carbon atom in furan, and in correlations of furan with benzene there can be several formulas for furan, such as the one (II) involving partial valences after a formula proposed for thiophene (7a), a centric formula (III), and others, each of which is amenable to amplification on the basis of electronic structures (8). In addition, there is an ethylene oxide structure (IV) which was proposed by Baeyer (9) subsequent to his original formula (I).

Just as it is now impossible to determine which of the several formulas or equilibrium mixture formulas of benzene is correct, so we cannot say which of the formulas of furan (suggested on the basis of analogies with benzene) is correct. The ethylene oxide formula (IV) belongs structurally to a somewhat different category. It does lend itself to an interpretation of many of the reactions of furan and derivatives, particularly the oxidation reactions leading to the formation of maleic and fumaric acid derivatives. However, it presupposes a chemical behavior for which there is no experimental support (10). The physical properties or their interpretation (on which there is no unanimous agreement) appear to favor formula I (or some simple modification of it) rather than formula IV (8, 11). Notwithstanding, the ethylene oxide formula merits retention, for the present, as a possible phase that is readily interconvertible with the diolefin (I) or other forms of furan.

A satisfactory formula for furan should take cognizance, among other things, of the tendency to form oxonium compounds (12, 15); the great ease of a combination of addition-substitution reactions (13); the highly chromophoric properties of the nucleus

(14); the marked tendency for α-substitution; and the apparent conjugated system that underlies 1,4-addition (15, 16, 17, 49). Formula V, with two partial or latent valences emerging from the oxygen, takes into consideration some of these properties of furan (16).

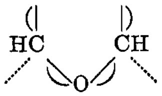


V VI VII VIII IX

This represents two crossed conjugated systems like those present in the highly active and highly colored fulvenes (VI), quinones, and related types.

Formulas VII and VIII are merely a modification (16) of Kekulé's revised formula for benzene, in which there is a shifting or oscillation of double bonds to give an active form (VIII), which by a combination of the dotted valences gives rise to a type like formula IX. The particular merits of the active form (VIII or IX) are a certain usefulness in interpreting both α-substitution and oxidation products. A related oscillation of linkages may, obviously, be used to show that the ethylene oxide form is in equilibrium with the diolefin form.

All of these formulas have explicit or modified conjugated systems, and some sort of conjugation appears desirable or necessary to account for an apparently general tendency of furan compounds to undergo 1,4-addition, either in a preliminary step to α-substitution, oxidation, etc., or in a more immediate transformation, as in the addition of maleic anhydride (17). In this connection, there is another possible formula, X, patterned after a Thiele partial valence idea applied to thiophene (7b).



X

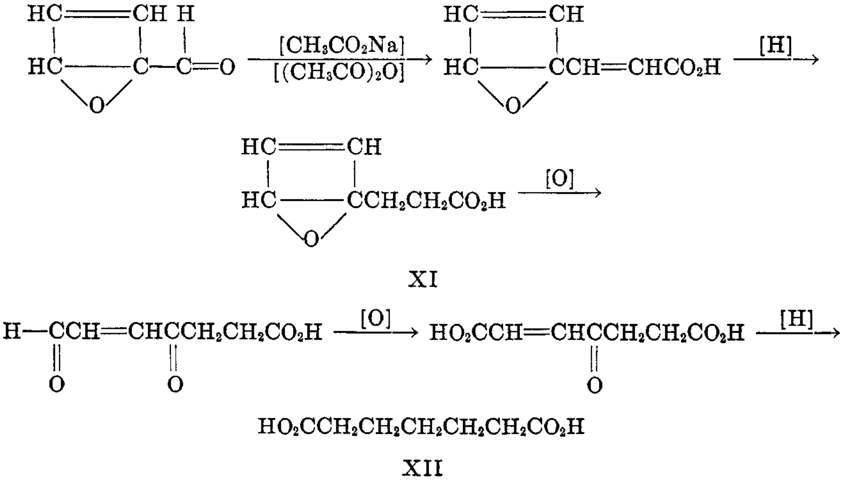
With this formula, the usual saturation of partial valences as represented in formula II does not maintain, because the assumed lesser partial valences of oxygen (with reference to the α-carbons) do not suffice to completely saturate the adjacent carbon atoms. As a consequence, the residuum of affinity on each of the α-carbons may be used to explain the higher activity of these elements as points of attack for 1,4-addition and α-substitution.

III. MONO-α-SUBSTITUTED FURANS

1. Proof of structure of furfural and some other mono-α-substituted furans

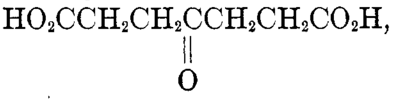
Furfural is the most important furan compound. It comes by this distinction for several reasons. First, it is technically available in tremendous quantities annually and at relatively low cost. Second, more studies have centered about this aldehyde than any other furan compound. Third, and of immediate pertinent interest, its constitution was established early and furfural is also readily converted, by reliable reactions, to other pivotally important furan types substituted in an α-position.

The following sequence of reactions was used by Baeyer (18a) to establish the structure of furfural, and particularly the position of the aldehydic group.



XI

XII

The furylacrylic acid (XI) formed by a Perkin condensation from furfural must have a —$CH{=}CHCO_2H$ grouping, and the succession of reactions culminating in pimelic acid (XII)—a straight chain compound—establishes the acrylic acid group on an α-carbon atom. If the —$CH{=}CHCO_2H$ group were on a β-carbon atom the ultimate product after ring opening would, of necessity, be a branched chain compound. The sequence of reactions as given may or may not have any bearing on the constitution of the furan nucleus. As noted, Baeyer interpreted the reactions to prove the ethylene oxide formula for furan. It is interesting to observe that Marckwald (18b) used a closely related series of reactions to disprove the ethylene oxide formula and to support the diolefin formula (I). Starting with furylacrylic acid obtained from furfural, he opened the ring with an alcoholic solution of hydrochloric acid to get  $HO_2CCH_2CH_2\underset{\underset{O}{\|}}{C}CH_2CH_2CO_2H$, which gave pimelic acid on reduction. In any event, both Baeyer's and Marckwald's reactions show furfural to be an α-substituted furan.

Having established that furfural is an α-substituted furan, it follows that many furan types readily derived from it, by essentially reliable reactions, also have the substituent in the α-position. 2-Methylfuran or sylvan (a compound obtainable from the distillation of wood oils) and furfural are interconvertible, nitrosyl chloride oxidizing the methyl to an aldehydic group, and hydrazine hydrate reducing the aldehyde to sylvan. The Cannizzaro reaction yields 2-furfuryl alcohol (2-$C_4H_3OCH_2OH$) and 2-furoic acid (2-$C_4H_3OCO_2H$), and these compounds, together with furfural and sylvan, are mutually convertible by standard reactions. Of more immediate interest, however, is the relation of these compounds to those obtainable by direct nuclear substitution.

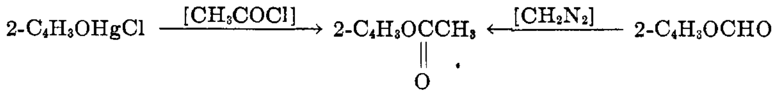
As an illustration, mercuration of furan by mercuric chloride and sodium acetate gives a chloromercurifuran that is a point of departure for the following transformations, which establish, among other things, the α-location of the chloromercuri group:

$$C_4H_4O \rightarrow C_4H_3OHgCl \xrightarrow{[I]} C_4H_3OI \xrightarrow{[Mg]} C_4H_3OMgI \xrightarrow{[CO_2]} 2\text{-}C_4H_3OCO_2H$$

The 2-furylmagnesium iodide has also been converted to other compounds, such as 2-furfuryl alcohol and furfural (10, 19). Furthermore, a bromofuran obtained by decarboxylation of a bromo-2-furoic acid is likewise shown to have its bromine in the α-position, for it forms a Grignard reagent, with greater difficulty, and this RMgBr compound on carbonation gives 2-furoic acid (20).

Two other important substitution reactions are nitration and sulfonation. Furan can be directly nitrated under certain conditions to give a nitrofuran (21). The position of the nitro group has not been unequivocally established, and has been allocated by some to the β-position and by others to the α-position. It is altogether probable that the nitro group is in the α-position, and this will be considered subsequently. It should be stated, forthwith, that the reduction product, 2-aminofuran, has not been isolated, despite many repeated trials. Even if it should be prepared, it is altogether probable, by analogy with substituted α-aminofurans, that it would not give a diazonium or a conveniently workable diazonium compound. This is regrettable, for it at once cuts off an avenue of approach to many α-substituted furans which would be highly serviceable in the proof of structure of nitrofuran and other furan derivatives. Furan has not as yet been directly sulfonated. However, 2-furansulfonic acid and its derivatives have been prepared by indirect methods (22).

The Friedel-Crafts reaction is another nuclear substitution reaction, and the Gattermann-Koch modification using hydrogen cyanide and hydrogen chloride converts furan to furfural (23). Furan and acetyl chloride or acetic anhydride (with condensing agents like aluminum chloride, ferric chloride, stannic chloride, and zinc chloride) give furyl methyl ketone, $C_4H_3OCOCH_3$ which is also obtainable from beech wood. The acetyl group has been shown to be in the α-position, both by the following transformations,



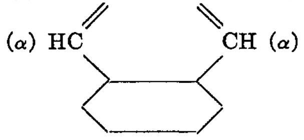
$$2\text{-}C_4H_3OHgCl \xrightarrow{[CH_3COCl]} 2\text{-}C_4H_3O\underset{\displaystyle \overset{\|}{O}}{C}CH_3 \xleftarrow{[CH_2N_2]} 2\text{-}C_4H_3OCHO\,.$$

and by the hydrolysis of ethyl furoylacetate (24), which is prepared from 2-furfural.

Another nuclear substitution reaction shown by some aromatic cycles is the replacement of hydrogen by a metal like sodium. Here, too, substitution occurs in the α-position (25).

$$C_4H_4O \xrightarrow{[C_2H_5Na]} C_4H_3ONa \xrightarrow{[CO_2]} 2\text{-}C_4H_3OCO_2H$$

Finally, it should be observed that the host of compounds derived from furfural by addition and condensation reactions involving the functional group are, like furfural, substituted in the α-position. The same applies to the transformation products derived from the reactions of other α-functional groups. A sweeping generalization of this kind is always made with the reservation that so-called reliable reagents are used and that rearrangements are excluded. It is possible that rearrangement reactions observed with some aromatic compounds will also occur with furan types, despite the pronounced tendency of substituents to enter the α-position. This would apply not only to drastic fusion reactions, but also to a rearrangement like that of α-naphthalenesulfonic acid to β-naphthalenesulfonic acid. Naphthalene is purposely selected because it appears from current studies that one of the nuclei of naphthalene may have more than a formal relationship with furan, as evidenced by some characteristic reactions of furan. A generic correlation appears in the following formula for naphthalene in which the furan oxygen has been replaced by an *ortho*-phenylene group, with the result that the α- and β-positions of furan are those of one of the nuclei in naphthalene.



No monosubstituted furan with the substituent in a β-position has been isolated from a reaction involving direct nuclear substitution. It would be unwise to say that none such has been formed, because the yields of α-substitution products rarely exceed 50 per cent and some β-isomer may have escaped detection.

2. Identity of the two α-positions in furan

It might be concluded that the two α-positions in furan are identical, because an apparently homogeneous mono-α-substituted furan is isolated in all reactions so far investigated involving the introduction, by either direct or indirect means, of a nuclear substituent. However, there exists the possibility that one of the α-hydrogen atoms may be more highly or exclusively disposed to replacement and so give rise to the same compound, even though the other α-position were unlike it. That this is not the case is evident from the following sequence of reactions (36), which are like those mentioned later for the proof of equivalence of the β-positions.

$$2,5\text{-}C_4H_2O(CO_2C_2H_5)(CO_2H) \rightarrow 2,5\text{-}C_4H_2O(CO_2C_2H_5)(COCl) \xrightarrow{[H]}$$

$$2,5\text{-}C_4H_2O(CO_2C_2H_5)(CHO) \xrightarrow{[HOH]} 2,5\text{-}C_4H_2O(CO_2H)(CHO) \xrightarrow{[-CO_2]}$$

$$5\text{-}C_4H_3OCHO \xrightarrow{[O]} 5\text{-}C_4H_3OCO_2H$$

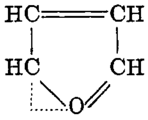
The 5- or α-furoic acid obtained in the above manner from the ester-acid is identical with that obtained from the following reactions in which the carboxyl group of the ester-acid is first removed, and not the carbethoxy group which was first removed above.

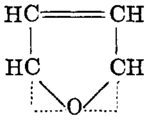
$$2,5\text{-}C_4H_2O(CO_2C_2H_5)\ (CO_2H) \xrightarrow{[-CO_2]}$$

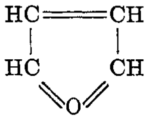
$$2\text{-}C_4H_3O(CO_2C_2H_5) \xrightarrow{[HOH]} 2\text{-}C_4H_3OCO_2H$$

The usual assumption is made here, namely, that the relatively stable carbon-carbon linkage suffices to fix the several α-substituents so that there is no rearrangement from one α-position to the other. Other reactions are available to establish the equivalence of the α-positions. One of these mentioned at the beginning of the next section involves a Grignard reagent (20), and another is the conversion of 5-hydroxymethyl-2-furfural (66c) to 5-hydroxymethyl-2-methylfuran (66a).

The fact that the two α-positions (and the two β-positions, as will be shown subsequently (p. 338)) are identical, militates against formulas VIII and IX for furan, unless it be assumed that these are active states of transitory existence. With oscillating bonds, another phase would have the dotted valences on the oxygen and carbon atom 5, so that such a formula (XIII) would also be in equilibrium with formula VII. The difficulty can also be circumvented


XIII


XIV

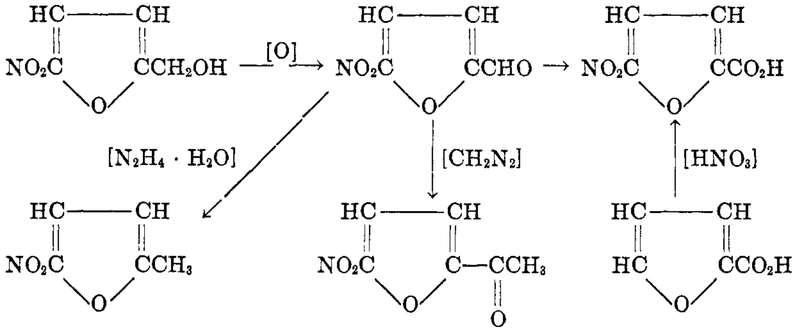

XV

by writing formula IX in the symmetrical form shown by formula XIV or XV.

IV. DI-α-SUBSTITUTED FURANS

The determination of the position assumed by an element or group introduced into the nucleus of a mono-α-substituted furan is, generally, a relatively simple matter. It owes its simplicity, in part, to the fact that the second substituent tends to occupy the other α-position. Accordingly, it is generally sufficient to remove the original α-substituent, and then establish the identity of the remaining monosubstituted furan with a known α-substituted furan. As an illustration, we might select the bromination of 2-furoic acid. One of the products of this reaction is a monobromo-2-furoic acid which on decarboxylation gives a bromofuran. The bromine in this monobromofuran must be in an α-position because the Grignard reagent prepared from it gives 2-furoic acid on carbonation (20).

It is, of course, unnecessary to remove one of the α-substituents to locate the position of the other substituent. What has been done most frequently is to refer new disubstituted furans to one whose constitution is well known. A poor illustration, because the nitro group in furan has not been established decisively, is the nitration of some α-substituted furans. We select this not only because of the considerable work done on nitration, but more particularly because it illustrates the pronounced tendency of the second group to assume an α-position, irrespective of the nature of the substituent already present. 2-Furoic acid, ethyl 2-furoate, 2-furfural, 2-furfural diacetate, 2-furfuryl acetate, 2-furfurylchloride, 2-furfuryl methyl ether, 2-furyl methyl ketone, and 2-methylfuran, on nitration, direct the nitro group to the other α-position. The following reactions illustrate how the position of the nitro group in some of these compounds has been located.



The tendency of the second substituent to occupy the other α-position is strikingly unlike orientation in the benzene series, where the group already present markedly influences the position taken by the new substituent.

There is not, at this time, any fully established case where the entering group in an α-substituted furan assumes a position other than α. The sole possible exception is the nitration of 2-methylfuran, which gives chiefly the expected 2-methyl-5-nitrofuran as well as a very small quantity of what may possibly be 2-methyl-3-nitrofuran (26). This has not yet been isolated in a pure condition. In some cases, as in the nitration of ethyl 2-furoate, an exhaustive search has failed to reveal any nitro-ester other than ethyl 5-nitro-2-furoate. It is reasonable to expect that a β-isomer may be found among the substitution products of furans having as the α-substituent a group, which in benzene, facilitates nuclear substitution. Groups of this kind are the amino, acetamino, hydroxyl, and alkoxyl groups.

A second way of preparing di-α-substituted furans is to start with a known di-α-compound and to replace completely one of the groups by a new substituent, as in the action of nitric acid on 5-methyl-2-furoic acid.

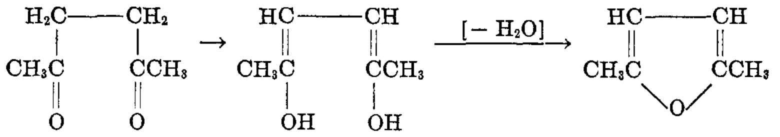
$$2,5\text{-}C_4H_2O(CO_2H)(CH_3) \xrightarrow{[HNO_3]} 2,5\text{-}C_4H_2O(NO_2)(CH_3)$$

The assumption that the nitro group has occupied the position of one of the carboxyl groups may be gratuitous in certain cases for several reasons, and chiefly because of the pronounced tendency of many furoic acids to undergo decarboxylation. That is, the nitro group might have entered a β-position prior to or simultaneous with the removal of the carboxyl group. If such replacement reactions are to be used with confidence for determining the position of substituents it would seem desirable to establish first, with a series of known compounds, the reliability of the replacement. Obviously, even with a high degree of success with known compounds, there is the ubiquitous hazard that the unknown compound might not respond in a normal manner.

This inherent weakness is not confined to reactions involving the complete replacement of one group by another. This special type of metathetical reaction is mentioned for two reasons. First, transpositions of groups have been observed with substitution reactions in the benzene series (27). Second, the marked tendency of furancarboxylic acids to decarboxylate and of α-sulfonic groups to be removed invites especial caution in interpreting replacement reactions involving the carboxyl and sulfonic groups. Even with replacement reactions involving but part of a substituent there is the ever-present danger of rearrangement, but experience indicates that there is a generally lesser risk involved in such cases when essentially reliable reactions are selected. It is reasonable to inquire why no question has been raised concerning the proof of structure of furan compounds by means of the Grignard reagent. Recent studies have shown that RMgX compounds having the —MgX group as part of an allylic system do undergo rearrangements with some reactants like formaldehyde and ethyl chlorocarbonate. Actually, the ethylene oxide form of furan (IV) does have a modified allylic system (10). However, when 2-furylmagnesium iodide was treated with formaldehyde and ethyl chlorocarbonate, for the express purpose of discovering rearrangement products, it was observed that the reactions proceeded normally.

A third method for the preparation and the proof of structure of di-α-substituted furans involves their synthesis from non-furanic compounds by ring closure. 2,5-Furandicarboxylic (dehydromucic) acid is now best prepared by the dehydration of mucic acid. 5-Methyl-2-furfural and 5-hydroxymethyl-2-furfural are procurable from carbohydrates. The structures of such furans follow from the constitution of the initial compounds. Conversely, the structures of the starting compounds have confirmation (in most of these cases it is essentially superfluous) in the furan products whose constitutions have been fixed by other means. Finally, there are some naturally occurring furan compounds, the number of which is increasing with newer studies in this field. Some of these furan compounds are apparently present as such in plants and may not owe their origin to ring closure incidental to isolation.

Many substituted furans can be synthesized by ring closure reactions, leading particularly to the formation of alkylfuroic acids. A simple ring closure is observable with γ-dicarbonyl compounds through the intermediate di-enols. An illustration is the formation of 2,5-dimethylfuran from acetonylacetone.

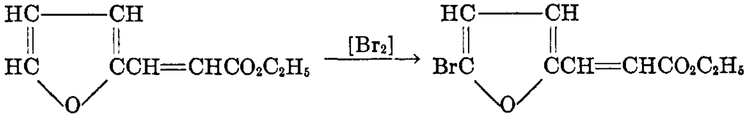


This settles the positions of the two methyl groups, and the 2,5-dimethylfuran so formed can then be used as a reference compound as, for example, in determining the position of the chloromercuri group introduced by the mercuration of 2-methylfuran:

$$2\text{-}C_4H_3OCH_3 \rightarrow 2,5\text{-}C_4H_2O(CH_3)(HgCl) \rightarrow 2,5\text{-}C_4H_2O(CH_3)(I) \rightarrow$$

$$2,5\text{-}C_4H_2O(CH_3)(MgI) \xrightarrow{[(CH_3)_2SO_4]} 2,5\text{-}C_4H_2O(CH_3)_2$$

The tendency for mono-α-substituted furans to direct the entering group to the other α-position is so highly developed that in some cases where the reactant might be expected to add to a laterally unsaturated α-substituent already present, no such addition occurs. Instead, there is substitution on the other α-carbon atom. An illustration is the reaction of bromine with ethyl 2-furylacrylate:



Related to this is a tendency for nuclear rather than lateral substitution, and the following mechanism (28) has been shown to be incorrect (5).

$$2\text{-}C_4H_3OCH{=}C(CN)CO_2C_2H_5 \xrightarrow{[Br_2]} 2\text{-}C_4H_3OCBr{=}C(CN)CO_2C_2H_5$$

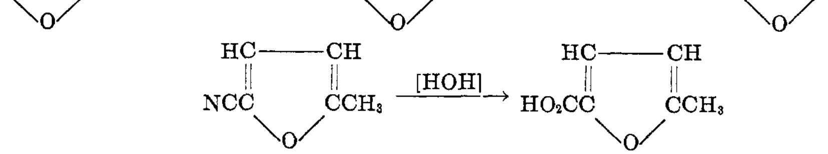
That the bromine actually entered the nucleus to give ethyl α-cyano-β-(5-bromofuryl)acrylate was proved by showing the identity of the bromination product with the compound obtained by the condensation of 5-bromo-2-furfural with ethyl α-cyanoacetate. The great inclination of furan to undergo substitution is also indicated in reactions involving a compound like 2-furyl phenyl ketone, $C_4H_3O\underset{\underset{O}{\|}}{C}C_6H_5$. Nitration of this ketone gives 5-nitro-2-furyl phenyl ketone (29). This illustrates that the furan nucleus undergoes substitution more readily than the phenyl nucleus, and is part of accumulating evidence which leads one of us (H.G.) to the opinion that furan has superaromatic properties (13).

The reaction between α-substituted furans and a reagent which can effect nuclear substitution does not always lead to the formation of di-α-substituted furans. Two illustrations may suffice. First, the action of bromine on 2-furylethylene, $C_4H_3OCH{=}CH_2$, results in preliminary lateral addition to give the dibromide, $C_4H_3OCHBrCH_2Br$ (12a). Second, the bromination of 2-furyl methyl ketone gives a laterally substituted ketone, $C_4H_3O\underset{\underset{O}{\|}}{C}CH_2Br$

(22). These reactions might have been predicted. In the case of the ketone we are probably concerned with preliminary addition of bromine to the highly active olefin linkage arising from enolization. However, because of the active linkages in the furan nucleus, which are essentially modified enols or enol ethers, it would not be surprising to find among the reaction products some of the nuclear substituted product. In this connection, the nitration of 2-furyl methyl ketone gives 5-nitro-2-furyl methyl ketone (30), the constitution of which was established by the action of diazomethane on 5-nitro-2-furfural (22).

There is another exception to the general rule that an α-substituted furan favors ready substitution on the other α-carbon. Nitrofuran, which very probably has the nitro group in an α-position, does not react with bromine to give 5-bromo-2-nitrofuran. Instead, the nitrofuran is recovered largely, under conditions where other α-furans undergo prompt nuclear substitution. It is altogether reasonable to expect that with slightly forced conditions bromination will take place. In this connection, it is interesting to note that nitration of 2,5-diiodofuran gives 5-iodo-2-nitrofuran in low yields.

Two special methods for the preparation of disubstituted furans should be mentioned. One of these involves the removal of substituents either from a tri- or a tetra-substituted furan or from a tetra-substituted tetrahydrofuran. These methods of substitution by the removal of groups from a polysubstituted compound lead very often to the formation of β-substituted furans, which are considered later. The other special synthesis involves rearrangement of a monosubstituted furan. The mechanism of this rearrangement is still being investigated, but the essential changes may be the following (31) when 2-furfuryl chloride is treated with aqueous sodium cyanide to give 5-methyl-2-furoic acid on hydrolysis:



A related rearrangement (25) may occur when 2-methylfuran is treated either with ethylsodium or with phenylsodium to give an organosodium compound which on carbonation yields 5-methyl-2-furoic acid:

$$2\text{-}C_4H_3OCH_3 \xrightarrow[{[C_6H_5Na]}]{{[C_2H_5Na]} \atop \text{or}} 2\text{-}C_4H_3OCH_2Na \rightarrow 2,5\text{-}C_4H_2O(CH_3)CO_2H$$

In this case, there may have been no lateral substitution. Instead, the organosodium compound might have formed by direct replacement of the nuclear α-hydrogen, or by a 1,2- or a 1,4-addition followed by rearrangement. The only present evidence is a possibly not too compelling analogy with methylbenzenes which undergo lateral substitution so that toluene, for example, gives benzylsodium.

V. α, α, β-TRISUBSTITUTED FURANS

It is apparent that the positions of mono-α- and di-α-substituted furans can be determined without difficulty. As a matter of fact, the tendency for substituents to occupy the α-positions is so exaggerated that one can confidently predict, with new substitution reactions, that the entering group will go to an available α-position. However, an entirely new picture presents itself with substitution reactions of di-α-furans. First, with some di-α-substituted furans having groups which in benzene orient generally to the *meta*-position, further substitution is extremely difficult and perhaps impossible. Some random illustrations are 2,5-furandicarboxylic acid (32, 33, 5), ethyl 5-nitro-2-furoate, 5-sulfo-2-furoic acid (34), and 5-nitro-2-furfural (5).

Second, with symmetrical compounds like 2,5-dimethylfuran, where the substituents do not prevent β-substitution (35), there is no problem on orientation because of the identity of the two β-positions. Such identity has been established by the following sequence of reactions (36).

$$2,5,3,4\text{-}C_4O(CH_3)_2(CO_2H)(CO_2C_2H_5) \xrightarrow{[SOCl_2]} 2,5,3,4\text{-}C_4O(CH_3)_2(COCl)(CO_2C_2H_5) \xrightarrow{[H]}$$

$$2,5,3,4\text{-}C_4O(CH_3)_2(CHO)(CO_2C_2H_5) \xrightarrow{[HOH]} 2,5,3,4\text{-}C_4O(CH_3)_2(CHO)(CO_2H) \xrightarrow{[-\,CO_2]}$$

$$2,5,3\text{-}C_4HO(CH_3)_2CHO \xrightarrow{[O]} 2,5,3\text{-}C_4HO(CH_3)_2CO_2H$$

The 2,5-dimethyl-3-furoic acid obtained in this manner, by removing the carbethoxy group, is identical with the acid secured by removing the carboxyl group of the ester-acid:

$$2,5,3,4\text{-}C_4O(CH_3)_2(CO_2H)(CO_2C_2H_5) \xrightarrow{[-\,CO_2]} 2,5,4\text{-}C_4HO(CH_3)_2(CO_2C_2H_5) \xrightarrow{[HOH]} 2,5,4\text{-}C_4HO(CH_3)_2CO_2H$$

Third, with compounds having two unlike α-substituents which do not prevent substitution of one of the β-hydrogens, there is a possibility of obtaining two isomeric α,α,β-trisubstitued furans. The proof of structure of either of these isomers is, at the present stage of development of furan chemistry, a difficult problem. Indeed, we do not have a single case of this kind for which the positions of the substituents have been positively demonstrated. This glaring weakness in orientation has naturally invited a consideration of a miscellany of methods, direct and indirect, for determining the position of substituents and so arriving at some rule of orientation.

1. General methods for determining the position of substituents in polysubstituted furans

(1) *Analogies with related heterocycles.* There is, at least, a formal relationship between furan and other heterocycles like thiophene, pyrrole, oxazole, thiazole, pyrazole, etc. These types have properties which have something in common with benzene. Of the several heterocycles, the one which appears to bear the most marked resemblance to furan is thiophene.[1] Thiophene is a more stable nucleus than furan, and partly for this reason Victor Meyer, in particular, in a classical series of investigations, explored deeply the substitution reactions of this sulfur analog of furan. Subsequently, these studies were amplified by numerous investigators, especially Steinkopf, so that to-day we have a large body of factual material on thiophene and its derivatives. With this as a background and with the known resemblances between thiophene and furan, it seems reasonable to expect and to obtain much assistance by making analogies with thiophene compounds.

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[1] See, however, Reichstein (Helv. Chim. Acta **13**, 349 (1930)) for the correlation of furan with pyrrole.

Two factors operate to obstruct seriously such aid. First, there are essential differences between furan and thiophene. Second, and this is of critical importance, the position of substituents and the rules of orientation in the thiophene series have not been satisfactorily established (37). In fact, it appears that the assigned positions of thiophene substituents, in some cases, are incorrect. As a consequence, it is not unlikely that analogies, if such are to be made, will have to be reversed, and that the position of substituents in thiophene will be indicated by reference to related furan compounds, when these shall have had their structures determined with certainty.

(2) Use of physical properties. Furan can be considered as derived from benzene by the replacement of a vinylene group, —CH=CH—, by oxygen. On such a basis, the α- or 2,5-positions correspond to the *para*-positions in benzene; the 2,4-or 3,5-positions are *meta*; and the 2,3- or 4,5-positions are *ortho*. Not much has been said, with a scheme of this kind, of the 3,4-positions. It appears, on the basis of some current chemical reactions, that the 3,4-positions may be more like the *ortho*-positions in benzene, than are the 2,3- or 4,5-positions. By the use of such analogies, confirmatory evidence has been adduced, with varying success, for the structures of some polysubstituted furans (38). This method will probably have a restricted application for two reasons. First, there are no clear cut correlations in the benzene series between physical constants and the position of substituents. Second, there are not now available a sufficient number of completed isomeric series of polysubstituted furans to test the validity of the method. It is pertinent in this connection to direct attention to like analogies which have been drawn between thiophene and benzene. The physical properties of a number of benzene compounds correspond, to an astonishing degree, with those of related thiophene compounds. So great is this concordance, that it is extremely difficult to separate related benzene and thiophene compounds by physical methods such as fractional distillation. However, this marked resemblance of the two classes of compounds has been somewhat exaggerated, and does not extend very deeply in the two series (39). It is possible that other physi-

cal properties, such as refractive indices and absorption spectra, may be of assistance in indicating the position of substituents, particularly the differentiation of α- and β-substituted furans (40). However, current studies on β-substituted furans show that on the basis of melting points there is not much regularity between α- and β-substituted furans. Preliminary studies on dissociation constants and rates of reaction appear more promising.

(3) *Use of physiological properties.* There is unquestionably a correlation between chemical constitution and physiological action with related furan, thiophene, and benzene types (41). However, it would be inadvisable, at this stage, to place too much confidence in such correlations as they concern the definite allocation of substituents.

(4) *Absolute and relative methods of orientation.* Two fundamental processes have been used with signal success in benzene chemistry in determining the position of substituents. The first is the classical plan used so effectively by Körner to fix the position of substituents by what is commonly designated as an absolute method. The position of groups in disubstituted benzenes was established on a mathematical basis, with the warranted assumption of the symmetry of benzene. That dibromobenzene, for example, which gives two isomeric tribromobenzenes, has the initial bromine atoms in the *ortho*-position; three isomers can be formed from the *meta*-dibromobenzene; and but one trisubstituted benzene results from the *para*-compound. In this manner, the structures of pivotally important types became available as reference compounds. The second method consists merely in the interconversion of unknown compounds, by means of so-called reliable reactions, and the reference compounds.

Unfortunately, these methods can be used only partially in furan chemistry, and this makes the determination of the position of substituents in furans a more difficult problem. In the first place, we have seen that not all possible isomers are formed in furan substitutions. At least, no significant or workable quantities of isomers have so far been isolated. Second, even if all possible isomers were formed and to such an extent that an appreciable quantity of each could be isolated, the absolute method would be of practically no value. This is evident by comparing the four replaceable hydrogen atoms of furan with the six hydrogen atoms of benzene. As an illustration of one possibility, we might consider the six isomeric disubstituted furans having two unlike substituents. Each of these disubstituted furans could give, on the introduction of a third substituent, two, and only two, trisubstituted furans. Such information, even if it were procurable directly, is essentially valueless because the absolute method mentioned depends on differing numbers of isomers. There is still a residuum of usefulness if the third substituent introduced is like one of those already present. In such a case, each of three pairs of isomeric disubstituted furans would give the same trisubstituted furan. This information is of some assistance, but it does not of itself directly establish the structure of any one of the disubstituted furans. On the other hand, if the third substituent introduced were unlike the two initially present the number of isomeric trisubstituted furans formed would be valueless, inasmuch as twelve isomeric trisubstituted furans are possible.

It is, of course, not necessary to obtain reference compounds solely by isolating all isomeric polysubstituted compounds. The basic compounds can be had by indirect methods. Some reference compounds, however few in number, are urgently desirable or necessary, and there is a particular need for such compounds having two nuclear substituents. Theoretically, there are four isomeric disubstituted furans, in which the substituents are alike, and six isomers when the substituents are unlike. The extreme paucity of reference compounds becomes obvious when we learn that there is not one complete series of disubstituted furans having two like substituents. The first complete series of isomeric disubstituted furans having two unlike groups has just been completed with the synthesis of the sixth methylfuroic acid (42).

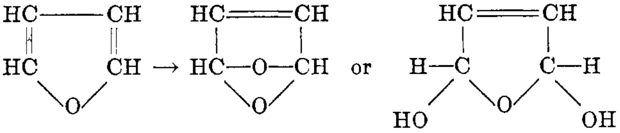
The solution of the problem concerned with the determination of the position of furan substituents is facilitated but not readily completed even with the acquisition of several reference types. This additional obstacle, essentially peculiar to furan, is due to the difficulty, and in some cases the impossibility, of effecting transformations of furan substituents in an effort to correlate unknown compounds with the reference compounds. Two illustrations might be cited. First, it is at present practically impossible to convert an α-amino group to a workable diazonium group (30). A like difficulty was initially observed in the thiophene series (43). This means that little can be done to relate an α-nitro group, through the amino and diazonium compounds, to the many groups formed with ease from benzenediazonium compounds. Second, an otherwise active halogen like iodine when substituted in a β-position is extraordinarily inert (44), and is, in fact, the only known iodine atom attached to a doubly bonded carbon atom which has not reacted with magnesium to form a Grignard reagent (45).

Whatever present difficulties may delay the utilization of the absolute and relative methods, it is needless to observe that these methods will have their greatest appeal to organic chemists because they rest on a most secure foundation. No other method will give comparable confidence in the position of substituents, for the whole fabric of organic chemistry, aliphatic and aromatic, comes by its strength through an intimate and fine interweaving of transformations that eventuates in compounds of known structure. Only in this way do we learn definitely of unreliable reactions and rearrangements, and only after such a pattern has been created can we fully utilize physical methods like absorption spectra which depend so largely on comparisons of unknown compounds with known compounds whose structure has been established by essentially chemical methods.

(5) *Reduction.* The proof of the position of substituents by reduction appears to be of limited usefulness. Catalytic reduction, for example, may affect the substituents, may add to give a di- or tetra-hydrofuran, or may open the ring to give an aliphatic hydroxy compound (46). Adams and coworkers have successfully used their catalyst in conjunction with promoters like ferrous chloride to confine reduction, in a large degree, to selected functional groups. However, even if it were possible to have convenient access to particular promoters which would

smoothly cleave the furan nucleus to open chain compounds, there would still be the problem of determining the structure of such scission products where they are unknown. Catalytic reduction is the best way, incidentally, of effecting some reactions (47), particularly the conversion of ethyl 5-nitrofuroate to ethyl 5-aminofuroate (30, 48). The method has also been tried to determine the intermediate nitration product of methyl furoate (49).

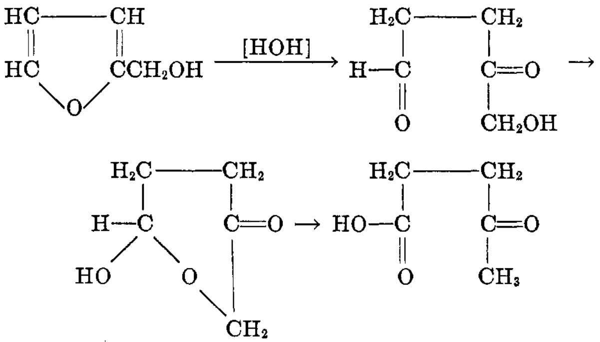
(6) *Oxidation.* Hill and coworkers have made most effective use of oxidation in determining the position of substituents (50). The isolation, by early workers, of maleic and fumaric acids probably was a decisive factor in commending the ethylene oxide formula (IV) for furan, because the double bond between carbon atoms 3 and 4 corresponds with its position in maleic and fumaric acids. However, such evidence is hardly conclusive, because the diolefin formula might add oxygen or hydroxyl groups by 1,4-addition to give rise to a double bond between carbon atoms 3 and 4:



Whatever the mechanism of oxidation, the method is of circumscribed utility. A polysubstituted furan having, for example, two bromine atoms in the β-positions will give a dibromomaleic acid, thereby establishing the presence of a bromine on each β-carbon. With a polysubstituted furan having one bromine on a β-carbon, monobromomaleic acid will result. But this is of little significance, for it does not inform us on which β-carbon the bromine was originally located. With other β-substituents, like the nitro or carboxylic group, the method may be limited either because of the non-availability of the correspondingly substituted maleic or fumaric acids or because of secondary transformations. Oxidation has been used with varying degrees of success in reactions not involving rupture of the nucleus, to convert methyl and other groups to known carboxylic acids (51). Such oxidations are of increasing value because of the availability of methylfurans by ring closure reactions. Ozonization (18c) can be used effectively with some phenylated furans, but difficulties will probably be encountered with others. Incidentally, ozonization might be of service with methylated furans to throw light on possible oscillating double bond formulas like VII, VIII, and IX (52).

(7) *Ring scission with acids and alkalies.* Furan compounds are notoriously sensitive to acids, but, as was mentioned in the introduction, a part of this reputation is undeserved. There is no question concerning such high sensitivity with simple furan types, particularly those having groups which are strongly *ortho-para* directing in the benzene series. The mechanism of such reactions has not been adequately established in many cases. Undoubtedly, ring scission occurs and the resins which are all too frequently encountered in substitution studies of furan compounds with acidic reagents may be due to polymerization of intermediate compounds, the most important of which is succinic dialdehyde, leading to humus-like substances (53).

Ring scission was used early to establish the constitution of compounds like furylacrylic acid (54). Studies have been made of the scission of 2-furfuryl alcohol to levulinic acid. The following mechanism involves a possible intramolecular Cannizzaro reaction (55a), and another interpretation of this rearrangement was proposed recently (55b).



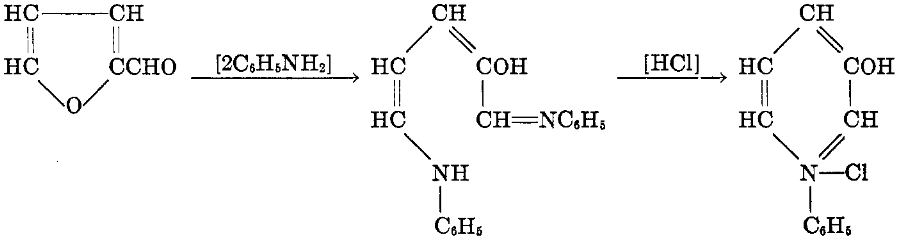
Apparently, such intramolecular migration occurs frequently in ring openings. An elaborate study of 5-hydroxymethyl-2-furfural shows that the splitting to levulinic and formic acids takes place almost quantitatively; but with furfuryl alcohol the yield of levulinic acid is only 30 to 40 per cent, and under the most favorable conditions more than half of the alcohol undergoes resinification (56). Even with the clean splitting of 5-hydroxymethyl-2-furfural, about 10 per cent of humus material forms. It appears, therefore, that the proof of structure by such means will generally involve difficulties.

There are two other conspicuous difficulties. First, even with smooth ring scission, few of the open chain compounds resulting from polysubstituted furans are available for purposes of identification. Second, and this is of even greater import, many polysubstituted furans are extremely resistant to the action of acids. This applies particularly to compounds having negative groups, and just such groups are introduced in common substitution reactions such as nitration and sulfonation. Indeed, the nitro group in 5-nitro-2-furfuryl methyl ether so stabilizes the ring that it is relatively unaffected by hydrogen iodide, and this effect is transmitted laterally to such an extent that the methoxyl group, under these conditions, is also essentially unchanged (57). The stability of the nucleus to the action of strong acids is in evidence with compounds like 2,4-furandicarboxylic acid, even though an α-position is available. This compound is recovered unchanged after attempted bromination, nitration, and sulfonation, under conditions which are effective for nuclear substitution of many furan compounds (58).

As a general rule, the furan nucleus is quite resistant to the action of alkalies. An outstanding exception is the polymerization of 2-methylfuran by alkalies. In this connection, it is interesting to note that organoalkali compounds like ethylsodium and phenylsodium and alkali metals like potassium will replace an α-hydrogen by the alkali metal (25). Furylpotassium is a minor product in the reaction between furan and potassium.

(8) *Ring scission with aniline.* The aniline acetate color test for furfural is one which has been used for a long time for both qualitative (59a) and quantitative estimations (59b). It is shown not only by furfural, but probably by all α-furaldehydes

and by no β-furaldehydes (3). The reaction can be highly complex, depending on experimental conditions (60). However, the significant feature is that the ring is cleaved by aromatic primary amines and then closed by hydrogen chloride to a new heterocycle. The following transformations are typical of the intermediate formation of an hydroxyglutaconic aldehyde derivative, and the ultimate formation of *N*-phenyl-β-hydroxypyridinium chloride.

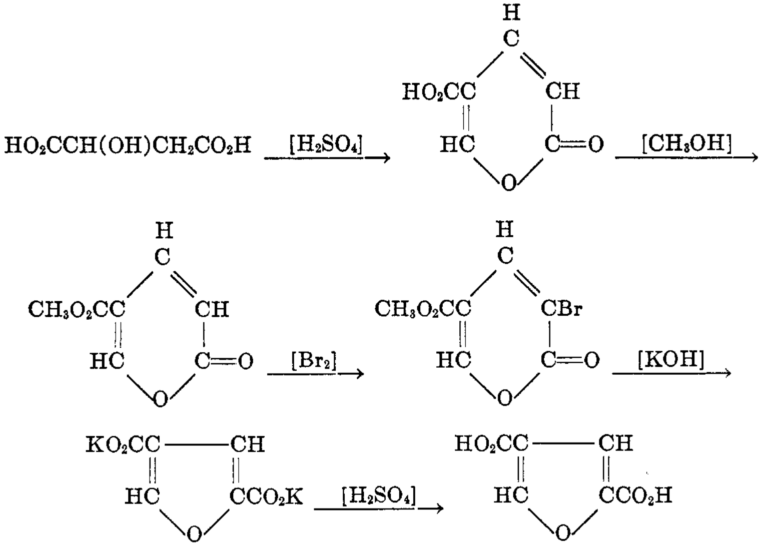


Accordingly, it would be sufficient to cleave a substituted α-furaldehyde with aniline acetate and then close the intermediate to a substituted *N*-phenyl-β-hydroxypyridinium salt of known structure. Unfortunately, the reaction is of little promise and for two reasons. First, there are not now available a sufficient number of the necessary substituted *N*-phenylpyridinium salts for reference purposes. Second, like some other scission reactions, the method fails dismally in some cases because a nuclear substituent is removed. For example, 5-chloro-2-furfural and 5-bromo-2-furfural give the same product with aniline acetate (61).

Aniline and aniline salts will cleave furan compounds other than 2-furfural and its derivatives (62). However, the intermediate derivatives of *N*-phenylpyrrole are of relatively inconsequential value from the point of view of determining the position of substituents, for the simple reason that some of the critical substituents (as with the substituted 2-furfurals) are removed. The removal of the substituent whose position one is trying to fix does not necessarily and always make such experiments abortive. This is so provided that the substituent removed is uniformly in a special position, and such appears to be the case in many reactions where apparently only an α-substituent is removed.

(9) *Ring closure.* The use of ring closure to determine the position of substituents has been used with much greater effect than ring scission methods. Among the simpler compounds we need but recall 2-furfural from pentoses, 5-methyl-2-furfural from methylpentoses, 5-hydroxymethyl-2-furfural from hexoses, 2,5-dimethylfuran from acetonylacetone, and 2,5-furandicarboxylic acid from mucic acid. Many of the necessary reference or standard compounds are being recruited by ring closure methods. For example, five of the six methylfuroic acids which comprise the first complete series of isomeric disubstituted furans were made available by ring closure reactions. The sixth of this series was isolated from a natural product (63), but here, too, it appears altogether reasonable to expect that it owes its formation to ring closure of isoprene types which seem to underlie the formation of many naturally occurring products.

As an illustration of ring closure methods we might select the synthesis of 2,4-furandicarboxylic acid (from which was prepared the sixth methylfuroic acid, 5-methyl-3-furoic acid (42)) because this dibasic acid will be referred to later in connection with β-substituted furans. The initial material is malic acid, which is successively converted to coumalic acid, methyl coumalate, methyl bromocoumalate, and 2,4-furandicarboxylic acid (64a).



Such ring closure syntheses leading to the formation of relatively simple furans are apparently quite reliable, if one might judge from subsequent confirmatory evidence for the structure of these furans. However, there are hazards involved in any broad assignment of the position of substituents to types related to furan and formed by an almost identical ring closure reaction. For example, in many ring closures effected with ammonia there is formed a mixture of substituted furans and substituted pyrroles, but the relative positions of the substituents on these nuclei are not always the same (64b).

The same inherent difficulties in the way of a full utilization of ring scission methods apply to ring closure methods, namely, the requisite substituted open chain compounds are not now available or if available do not lend themselves satisfactorily to the purposes in hand. This is obvious when we realize that substituents are not confined to alkyl and carboxyl groups, but more frequently concern halogens and the nitro and sulfonic acid groups; and just as ring opening of nitro types is complicated by secondary reactions which may reach complete frustration by removal of the group or groups, so ring closure is attendant with corresponding objections. Halogen and phenyl substituted furans can be obtained by ring closure methods, but these polysubstituted furans, such as 2,3,5-triphenyl-4-bromofuran and homologs (65), do not now offer much promise. This is so because the rearrangements leading to their formation are not adequately established in many cases, and, more particularly, because the need is for furans having groups like the nitro and sulfonic groups, and not the phenyl group, which has not been directly substituted in furan types.

(10) *Miscellaneous methods.* Other methods, of less immediate value, suggest themselves. One of these turns on color reactions for α- or β-groups. We have mentioned the aniline acetate color test for 2-furfurals (3). A ferric chloride color test may be useful to differentiate α- from β-furoic acids (66b). A sulfonic acid in the α-position is smoothly replaceable by a nitro group, and this reaction has not been shown with β-sulfonic acids (34, 67). In general, α-substituents are more readily removed or replaced than are the β-substituents. This applies particularly to car-

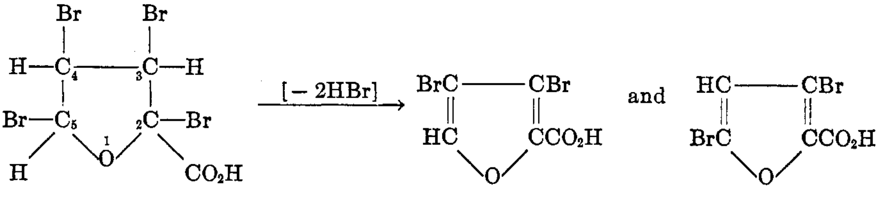
boxylic groups and to the halogens. However, such reactions can be used only in a qualitative way because the differences are largely of degree and not of kind. The resolution of β-substituted furans, after the procedure used by Adams and coworkers with related pyrroles (68), may possibly be applied to determine the position of blocking groups. Intramolecular cyclization is being used, particularly to establish which positions correspond with the *ortho*-positions in benzene (69).

Some of these general methods, or combinations of them, for determining the structures of polysubstituted furans will undoubtedly be used effectively. Their present development, however, is such that we do not have a single fully authenticated case of the directive influence of two different α-substituents on the position assumed by a third substituent. It would, perhaps, be more correct to state we do not know in advance which of the β-positions will be substituted to a greater extent. A modification in a statement of this kind appears necessary, not because there is any clean cut case of the formation of such isomers, but rather because some reaction products may consist of mixtures (20). This is in sharp contrast with furan itself which appears to give no isomeric monosubstitution products on direct substitution, and α-substituted furans which appear to give, rather exclusively, only a di-α-substituted product.

The first significant contributions to the allocation of groups in polysubstituted furans were made by Hill and coworkers (70). Their meticulous experimental work is a model for reliability. However, the positions assigned by them to α,α,β-trisubstituted furans were based rather largely on analogies deduced from the constitution of furan. The structures so assigned may or may not be correct, and there are not now available experimental data on which to base a decisive criticism, favorable or adverse. For purposes of illustration, only the dibromo-2-furoic acids will be considered, because the structures of these compounds were used as a basis for the assignment of constitution to other related trisubstituted furans.

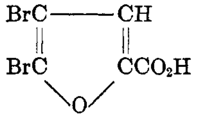
In the bromination of furoic acid a dibromofuroic acid, melting at 167–8°, was obtained, which is identical with one of the two isomeric dibromofuroic acids secured by the action of alcoholic sodium hydroxide on furoic tetrabromide or 2,3,4,5-tetrabromotetrahydro-2-furoic acid (the compound formed by the addition of four atoms of bromine to furoic acid). The same dibromofuroic acid is obtained, as might have been predicted, by the action of bromine on 5-bromo-2-furoic acid (71). The structures of these isomeric dibromofuroic acids, melting at 167–8° and at 191–2°, were established by a study of the oxidation products *and* by a consideration of the total possible number of dibromofuroic acids obtainable from the furoic tetrabromide. The evidence based on oxidation is probably reliable; however, the necessary supplementary evidence based on the maximum number of isomeric dibromofuroic acids is not conclusive.

The addition compound (XVI) is known to lose two molecules of hydrogen bromide by the action of alcoholic sodium hydroxide, and the assumption is made that only two dibromofuroic acids can result. One of these (XVII) is formed as a consequence of the removal of (bromine-2 and hydrogen-3) and by the removal of (bromine-5 and hydrogen-4). The other isomer (XVIII) is formed by the removal of (bromine-2 and hydrogen-3) and by the removal of (bromine-4 and hydrogen-5).

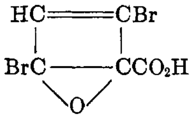


XVI XVII XVIII

The dibromofuroic acid melting at 191–2° gives dibromomaleic (or mucobromic acid) on oxidation, and, accordingly, this isomer has been designated as the 3,4-dibromo-2-furoic acid (XVII). The isomer melting at 167–8° gives monobromofumaric (or monobromomaleic) acid on oxidation, and it has been labelled 3,5-dibromofuroic acid (XVIII). Actually, a third isomeric dibromofuroic acid is possible. Two molecules of hydrogen bromide can be removed by a combination of 1,2- and of 1,4-elimination, (bromine-3 and hydrogen-4) and (bromine-2 and hydrogen-5), respectively, to yield 4,5-dibromo-2-furoic acid (XIX).



XIX



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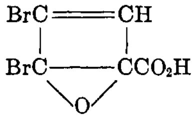

XXI

This, like 3,5-dibromo-2-furoic acid (XVIII), would also be expected to give monobromofumaric (or monobromomaleic) acid on oxidation.

A 1,4-elimination of hydrogen bromide of this kind may not have been seriously entertained because if rigorously applied, on the basis of the ethylene oxide structure for furan, it would not give a dibromofuroic acid which would yield dibromomaleic acid on oxidation. The two isomeric dibromofuroic acids would have the following structures, XX being formed by the removal of hydrogen bromide as (bromine-2 and hydrogen-5) and (hydrogen-3 and bromine-4), and XXI forming as a consequence of the elimination of hydrogen bromide as (bromine-2 and hydrogen-5) and (bromine-3 and hydrogen-4). To repeat, neither formula XX nor formula XXI could account for the formation of dibromomaleic acid, and, therefore, not only was the mechanism which suggested their possibility considered invalid, but also the experimental evidence was adduced as an argument against the ethylene oxide formula for furoic acid (and furan (IV)).

There are now convincing data for 1,4-addition to the furan cycle. Even though the present evidence for 1,4-elimination is not so compelling, it appears altogether reasonable, on other grounds, to expect 1,4-elimination where there is 1,4-addition.[2] As previously stated, the ethylene oxide (IV) and diolefin (I) structures for furan appear to be interconvertible, so that any

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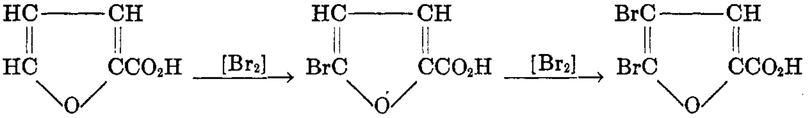
[2] The endocyclic compound formed from furan and maleic anhydride dissociates into its components at its melting point (125°). See Diels and Alder: Ber. **62**, 554 (1929). Such ready 1,4-dissociation or 1,4-elimination may underlie the difficulty of using maleic anhydride generally for the characterization of substituted furans.

indirect evidence for a possible number of isomers based on one of these formulas to the exclusion of the other is correspondingly impaired. It should also be added, that the complex mixture obtained by the action of alcoholic sodium hydroxide on furoic tetrabromide has not been completely analyzed, and it is probable that a thorough separation may reveal the three possible dibromo-2-furoic acids.

Restricting attention to so-called direct substitution, we note that the dibromo-2-furoic acid melting at 167–8° has been obtained by the bromination both of furoic acid and of 5-bromo-2-furoic acid. There is no convincing proof that it is 3,5-dibromo-2-furoic acid (XVIII). Actually, the weakness of the indirect evidence, already presented, and the nuclear substitutions of other related di-α-substituted furans, indicate that the compound is 4,5-dibromo-2-furoic acid, formed by the following sequence of reactions.



It is our belief that the χ-dichlorofuroic acid (70b) may be 3,5-dichloro-2-furoic acid. These conclusions are to be verified experimentally. They are presented in accordance with the tentative hypothesis that, as in the benzene series, the *ortho-para* directing group has a greater orienting influence than the *meta* directing group.[3] On this basis, the acetamino grouping in ethyl 5-acetamino-2-furoate has directed the nitro and bromo groups to the 4-position (48, 30).

This principle has been formulated, together with others on general nitrations of furan compounds (30), partly as a consequence of the nitration of methyl 5-methyl-2-furoate (26).

$$2,5\text{-}C_4H_2O(CO_2CH_3)(CH_3) \xrightarrow{[HNO_3]} 2,4,5\text{-}C_4HO(CO_2CH_3)(NO_2)(CH_3)$$

The evidence for the structure of the methyl 5-methyl-4-nitro-2-furoate is the best we now have for the directing influence of di-

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[3] See Reese (J. Am. Chem. Soc. **54**, 2009 (1932)) for some *o*-, *p*- and *m*-substitution relationships in the benzene series.

α-substituents.[4] However, it falls short of being decisive. The supposed methyl 5-methyl-4-nitro-2-furoate gives on hydrolysis the corresponding acid which when treated with nitric acid undergoes the following reaction.

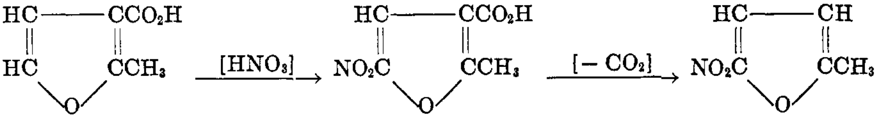
$$2,4,5\text{-}C_4HO(CO_2H)(NO_2)(CH_3) \xrightarrow{[HNO_3]} 2,4,5\text{-}C_4HO(NO_2)_2(CH_3)$$

The correctness of the positions of the two α-substituents comes from the following reaction, which starts with the known, or reasonably well known, 5-methyl-2-nitrofuran. This compound on nitration yields the same dinitromethylfuran obtained by nitration of 5-methyl-4-nitro-2-furoic acid.

$$2,5\text{-}C_4H_2O(NO_2)(CH_3) \rightarrow 2,4,5\text{-}C_4HO(NO_2)_2(CH_3)$$

But these reactions do not determine to which β-position the second nitro group is attached. The evidence advanced for assigning the β-nitro group to the position indicated is based on analogies with the melting point of 2,4-dinitrotoluene. Such support, in want of any other, is of some value, but it hardly is conclusive.

The structures of most trisubstituted furans prepared from disubstituted compounds other than the di-α-derivatives have been established. As an illustration, the nitration of 2-methyl-3-furoic acid gives 2-methyl-5-nitro-3-furoic acid, and the following reactions illustrate its synthesis and the determination of the position of the nitro group (72).



The 2-methyl-5-nitrofuran, formed by decarboxylation, was shown to be identical with specimens of proved constitution.

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[4] It has just been observed (58) that the sulfofuroic acid obtained by sulfonation of 5-bromo-2-furoic acid, followed by removal of the bromine, gives 2,4-furandicarboxylic acid on fusion with sodium formate. This pertinent information warrants confirmation by less drastic methods. Also, it is necessary to establish such orientation with other reactions like the halogenation and nitration of di-α-substituted furans having unlike substituents.

Such substitution is what might have been predicted in view of the availability of an α-position and the overwhelming or complete tendency for groups to enter an α- or 2- or 5-position. In accordance with these principles, other disubstituted furans, like the 2,4- and 3,4-furans, also direct the third substituent to the α- or one of the α-positions. Here, again, we note a profound tendency to minimize or completely frustrate the formation of isomers.

VI. TETRASUBSTITUTED FURANS

Relatively few tetrasubstituted furans are known. Indeed, apparently no furan is known which has four unlike nuclear substituents. There are two chief reasons for the scarcity of such compounds. First, many α,α,β-trisubstituted furans (as well as some α,β,β-trisubstituted furans), particularly those having negative groups, are highly resistant to further nuclear substitution. This hindrance to substitution is more widespread than with disubstituted furans, which in turn greatly exceed in number the monosubstituted furans which substitute either with difficulty or not at all. Current studies may reveal the extent of steric influences. Second, the relatively virgin field of nuclear substitution is as yet untarnished, fortunately, by any desire to synthesize compounds for which there exists no immediate and compelling need.

The tetrasubstituted furans are accessible both by ring closure methods and by direct substitution. The tendency for nuclear substitution is so highly developed in some cases that furan, for example, on mercuration gives a tetrachloromercurifuran (73). As might have been expected, the formation of completely substituted furans from mono- or di- or tri-substituted furans is facilitated by the presence of positive groups and the availability of α-positions.

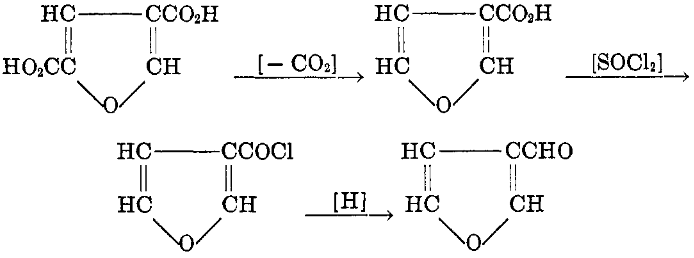
There would be no problem in the proof of structure of tetrasubstituted furans if, obviously, we but knew the structures of the underlying trisubstituted furans. Even such information is unnecessary if more than one of the same group are introduced, as in the synthesis of tetrachloromercurifuran from furan or of

2,5-dimethyl-3,4-dichloromercurifuran from 2,5-dimethylfuran. In short, the only problem revolves about those tetrasubstituted furans prepared directly from trisubstituted furans of as yet undetermined structure.

VII. β-SUBSTITUTED FURANS

The mono-β-substituted furans may belong logically with the mono-α-substituted furans. The reasons for considering them here are: (1) they are not formed by direct nuclear substitution of furan; (2) they comprise a distinctly new series of compounds because it is only very recently that compounds having a methyl, aldehydic, carboxylic, sulfonic, chloromercuri, and other groups in the β-position have been synthesized; and (3) practically nothing is now known of the directing influence of a β-substituted furan. Incidentally, β-substituted thiophenes are more accessible.

The indirect methods for the syntheses of these compounds are as yet, almost exclusively, ring closure procedures giving rise generally to a disubstituted furan from which one of the substituents is subsequently removed. A recent illustration is the synthesis of 3-furaldehyde (3) from 2,4-furandicarboxylic acid, which, as previously mentioned, is prepared from malic acid.



There are two other sources of starting compounds. One of these is natural products; the other is simple furan compounds which, after all, are only a step or two removed from natural products because so many of them are now elaborated from furfural. Belonging to this latter class are the syntheses of β-compounds like 3-iodofuran and 3-chloromercurifuran. The 3-iodofuran has been prepared from tetraiodofuran by stripping three of the iodine atoms by means of aluminum amalgam. The 3-chloromercurifuran can be prepared from 2-furoic acid through what is possibly anhydro-3-hydroxymercuri-2-furoic acid. Incidentally, the preferential decarboxylation of 2,4-furandicarboxylic acid and the preferential removal of the α-iodine atoms from the tetraiodofuran illustrate a rather general phenomenon, namely, the α-substituents undergo more ready removal and replacement than do like substituents in the β-position.

It has been convincingly demonstrated that α-substituted furans, whatever their nature, direct a second substituent to the other α-position. We do not know, at this time, the general orienting effects of β-substituted furans. Only one case has been established and that is the introduction of an aldehydic group into 3-methylfuran (74). Here the methyl group orients to the α-carbon adjacent to it, and the position of the aldehydic group was

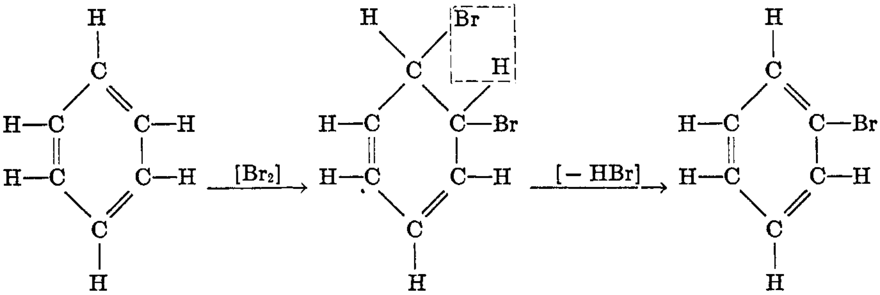
$$3\text{-}C_4H_3O(CH_3) \xrightarrow{[HCN + HCl]} 2,3\text{-}C_4H_2O(CHO)(CH_3)$$

fixed by oxidizing the compound to the known 3-methyl-2-furoic acid. Nitration of 3-furoic acid gives a mononitro-3-furoic acid, identical with that obtained by nitration of ethyl 3-furoate and subsequent hydrolysis (36). The position of the nitro group is not known. However, it is a certainty that the nitro group has entered one of the α-positions. It is of great interest to note that isomeric nitro-3-furoic acids were not isolated, despite the availability of two α-positions. We have here another illustration of the extraordinary tendency of furan compounds to confine nuclear substitutions to a preferred position.

Essentially nothing is known of the directing influence of a di-β-substituted furan having unlike groups. It will be interesting to observe whether the orientation of such types is related to that of di-α-furans having unlike substituents.

VIII. SOME MECHANISMS OF SUBSTITUTION

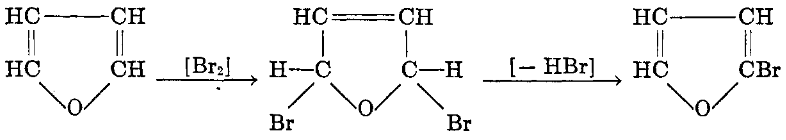
Furan is an aromatic compound and as such it is reasonable to expect that some of the mechanisms proposed for substitution reactions of benzene and its congeners can be extended to include substitutions of furans. Among these mechanisms is one postulating the formation of an intermediate addition compound which subsequently loses a hydrogen from the ring and a part of the addenda to give the ultimate substitution product. The following reaction may be taken by way of illustration of the bromination of benzene.



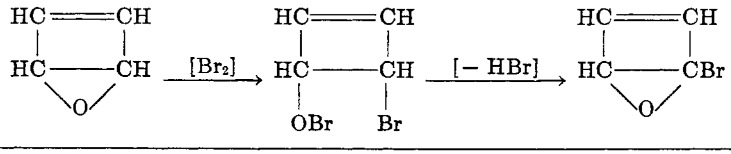
The superaromatic properties of furan, as reflected in part by a marked tendency for smooth and controlled nuclear substitution, may be due to a combination of highly developed addition and readily removable nuclear hydrogen. Such a combination appears necessary for facile substitution (7a, 13). There is no doubt concerning the great tendency of furan compounds to undergo preliminary addition (15, 49, 75). Also, furan has highly mobile α-hydrogen atoms as is attested, among other reactions, by the replacement of such hydrogen by potassium, and also by sodium (with the use of ethylsodium or phenylsodium) (25). The mobility of hydrogen in furan might possibly warrant an interpretation of substitution which turns on preliminary dissociation followed by addition. However, attention will be confined, at this time, to those mechanisms involving preliminary addition succeeded by elimination.

Preliminary addition, leading to α-substitution, may take place in several ways. First, there might be addition to one of the ethylenic linkages in formula I (15, 49). This is an attractive possibility, because the diolefin formula for furan is in reality an ether linkage attached to a double bond, and such combinations (as well as others like the corresponding enols) reflect a marked degree of unsaturation. Furthermore, it is known that aromatic ethers, such as anisole, undergo ready nuclear substitution. Analogies with benzene compounds should perhaps be made with reservation because the hydrogen atoms in anisole which undergo substitution are those on the carbon atoms two- and four- removed from the oxygen. With furan the carbon two-removed from the oxygen is in the β-position, and β-substituted furans are not formed by direct substitution. The analogy with benzene still has some, perhaps considerable, merit, inasmuch as the carbon four-removed from the oxygen is an α-carbon, and substitutions of anisole types take place to a greater extent in the *para*-position or on the carbon four-removed from oxygen.[5] If we grant that 1,2-addition takes place to an olefinic linkage of furan, then 1,2-elimination is necessary to develop the monosubstituted furan. Since 1,2-elimination can occur in two ways, to give rise to an α- and a β-substituted furan, and since only α-substituted furans are formed, it is necessary to stipulate that 1,2-elimination involves only the α-hydrogen (which in furan is more mobile than the β-hydrogen).

Second, there might be 1,4-addition followed by 1,4-elimination (15, 49).



This 1,4-addition may also take place with the ethylene oxide formula (IV) or with the partial valence formula (X). With the ethylene oxide formula a rupture of a carbon-carbon linkage is involved, and such a mode of action may not be unlikely with an endocyclic system. If the ethylene oxide nucleus behaves as it does in independent or isolated systems, then a rupture of a carbon-oxygen linkage is more reasonable,



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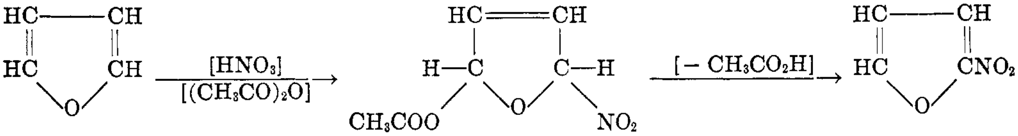
[5] With the ethylene oxide formula for furan, a carbon atom two-removed from oxygen occupies a reactive α-position.

and the postulated intermediate cyclobutene hypobromite may lose hydrogen bromide in the manner indicated.

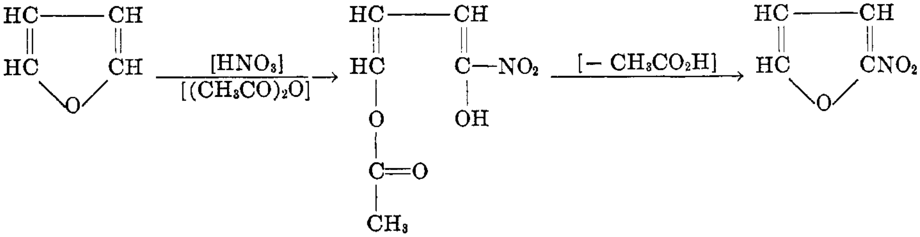
A related 1,4-addition using the diolefin formula has been proposed to account for the nitration (in acetic anhydride) of furan,



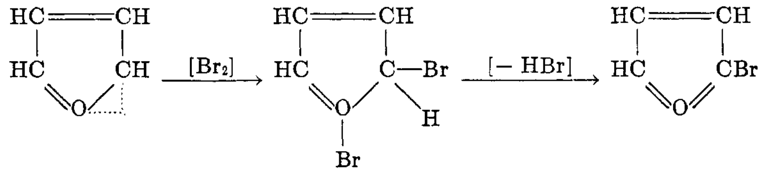
the acetic acid being removed by 1,4-elimination or by 1,2-elimination subsequent to rearrangement (49).

It is well to keep in mind that what we now designate as 1,4-addition and 1,4-elimination may in reality be 1,2-processes which come into play even with explicit conjugated systems. For example, a so-called 1,4-reaction may be a 1,2-reaction, and the allylic grouping so formed may then undergo transformations of three-carbon systems to give as an ultimate product a compound which appears to have been formed by a 1,4-transformation but which actually involves two separate steps, namely, a 1,2-reaction and an allylic rearrangement. A formulation of this kind appears highly unlikely with some furan structures, unless it be stipulated that the allylic rearrangement precedes the elimination; otherwise, we would be confronted with the rearrangement of a substituent from a β- to an α-position in furan, and there is no present evidence for such a change.

Third, ring scission may also occur with the diolefin structure; such a mechanism was proposed to account for the intermediate compound isolated in the nitration of furan (21, 15, 49, 75). The following illustration has been modified to show the nitro group in an α- and not a β-position as was originally proposed (21).

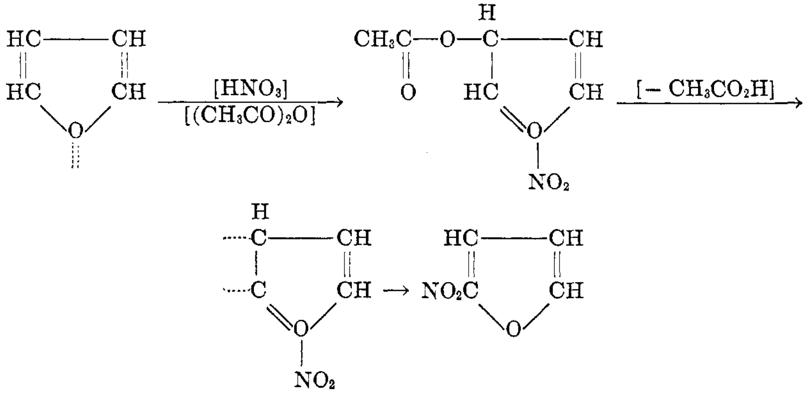


Fourth, there might be 1,2-addition to a carbon-oxygen linkage of one phase (formula IX) of the oscillating formula, without the necessity of ring rupture,

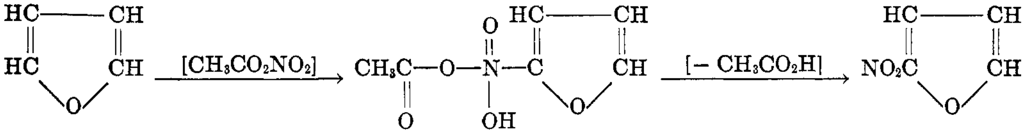


and the resulting compound may then rearrange to the diolefin or ethylene oxide or other forms with which it may be in equilibrium.

Fifth, the oxygen may also be involved, again without ring scission, in a 1,1- or 1,4-addition as well as the 1,2-addition just mentioned. The 1,1-addition to oxygen leads to the formation of oxonium compounds (12a, 15), or possible molecular complexes. The formation of oxonium compounds can be a precursory reaction to the other additions which might ensue by rearrangement or dissociation of the oxonium compound. The fulvene-like structure of furan (V) might be expected to endow the oxygen with a high additive capacity. It should be mentioned, however, that such a structure, when interpreted on the basis of partial valences in crossed conjugated systems, may lead to β-addition or substitution. Such a difficulty, if present, can be circumvented by the expedient of postulating 1,2-removal of the β-substituent with an α-hydrogen, and rearrangement of the addendum on the oxygen to the α-carbon. A like removal is indicated when 1,4-addition occurs to a conjugated system set up by the unsaturation emerging from the oxygen and one of the ethylenic linkages (75):



Sixth, addition might take place without affecting the unsaturation of the furan nucleus. This would involve the essential addition, in nitration, of the furyl group and a mobile α-hydrogen to compounds like acetyl- or diacetyl-nitric or ortho-nitric acids (75). If any merit resides in such a proposal it is the avoidance of a ring-splitting reaction with nitrations carried out in acetic anhydride.



Seventh, with unsaturated lateral groups, like those present in 2-furfural and 2-furylacrylic acid, which are in conjugation with the nucleus, there is a possibility of 1,6- or 1,8-addition (16). Such addition is improbable, particularly in view of the fact that the lateral-nuclear conjugation appears to be ineffective towards reagents which have been used successfully for the characterization of such systems. Completely lateral conjugated systems, like the one in furylacrylic acid, participate in some typical 1,4-additions. However, the exceptions from the related benzene compounds are sufficiently marked to emphasize caution in drawing broad generalizations between the phenyl and furyl series.

It is not now known which, if any, of these addition reactions are involved prior to nuclear α-substitution. No one of them has any convincing experimental support. Some sort of preliminary addition occurs because the addition compounds have been not only isolated, but also converted by various agents, or spontaneously, to the substitution product. If addition does take place, it would be inadvisable to interpret all substitution reactions by a single mode of addition. Actually, it is possible that a selected reaction may occur by different mechanisms. A tentative illustration is the nitration of ethyl 5-acetamino-2-furoate in acetic anhydride. Here the nitro compound is precipitated as such, when the reaction is about one-half completed. When the oily filtrate is added to ice water it solidifies to an unstable intermediate, which when treated with pyridine gives more of the true nitro compound. The formation of intermediates on nitration does not always take place. Perhaps it is more correct to state that such intermediates have hitherto been isolated with nitrofuran (21), nitrofurfural diacetate (76) and methyl nitro-2-furoate (49). Each of these undergoes a smooth endothermic reaction with pyridine or a related agent to give the ultimate nitro-nuclear substitution product after the removal of acetic acid. Such intermediates may or may not come into existence as a consequence of ring scission. On the basis of analogy with the facile splitting of unsaturated ethers by acids, it appears eminently reasonable to retain, together with other mechanisms, the possibility of ring scission until such time as unequivocal contrary evidence is presented. Incidentally, modifications of the several mechanisms may be used to explain polynuclear substitutions. In addition, there is the possibility of a substituent already present undergoing preliminary addition or partial substitution before rearrangement to a polynuclear type.

Inasmuch as the addition reactions postulated are based on different formulas for furan, it is possible that furan is not a single compound, but rather a dynamic equilibrium mixture of several forms. It is, of course, unnecessary to select one formula as the most correct expression. The fourth valence of each carbon can be left in abeyance by designating furan as a pentagon, regular or distorted; or the diolefin structure can be used with such reservations and qualifications as may be necessary to introduce the other formulas for the explanation of specific reactions.

IX. SUMMARY

The following general rules of orientation are derived from present information on nuclear substitution reactions of furan:

(1) Direct nuclear substitution of furan leads to the formation of mono-α-substituted furans, and no isomeric β-substituted furan is formed.

(2) Direct nuclear substitution of a mono-α-substituted furan gives an α,α-disubstituted furan, apparently to the exclusion of any isomeric α,β-disubstituted furan.

(3) Direct nuclear substitution of an α,α-disubstituted furan

yields generally but one α,α,β-trisubstituted furan. When the α-substituents are unlike, the β-position assumed by the third substituent is determined largely by the nature of the groups already present, and probably in essential accordance with the directing influence of groups in the benzene series. For example, 5-bromo-2-furoic acid on sulfonation yields 5-bromo-4-sulfo-2-furoic acid, and not 5-bromo-3-sulfo-2-furoic acid.

(4) Direct nuclear substitution of mono-β-substituted furans, now accessible by indirect methods, involves the replacement of an α-hydrogen. Here, again, the apparent absence of isomers is noteworthy, for despite the availability of two α-positions but one α,β-disubstituted furan results.

Several mechanisms of nuclear substitution are discussed. Furan appears to consist of a dynamic equilibrium of a number of structures rather than of a single formula.

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