RING-CHAIN TAUTOMERISM

PAUL R. JONES

University of New Hampshire, Durham, New Hampshire

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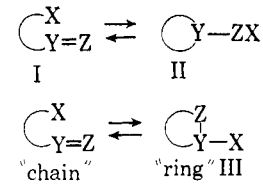
I. INTRODUCTION

The word tautomerism was proposed by Laar (179) in 1886 to describe the mobile equilibrium between two compounds containing weakly bonded hydrogen atoms. According to Lippmann (200), however, the possibility of such a phenomenon was recognized as early as 1754 by Gerhardt in a book on organic chemistry. This classical keto–enol tautomerism has subsequently been restated in terms of modern electronic theory by numerous workers. Considerably later, recognition was given to the possibility of a related reversible isomeric change, ring-chain tautomerism, in which one of the tautomeric forms is cyclic (245). A discussion by Baker of a number of the examples of ring-chain tautomers reported up to 1934 appeared in his book, "Tautomerism" (21).

Because the subject is a broad one, examples of it are likely to appear in the literature of apparently unrelated topics. Indeed, a search through *Chemical Abstracts* under the headings, "tautomerism," "isomerism," "ring," "chain," and "cyclic," has served to uncover only a fraction of the references cited. This survey of ring-chain tautomerism, therefore, is based on a cross section of examples that have been found and others that might be anticipated. There is no intention to make it an exhaustive compilation of all recorded instances of the phenomenon.

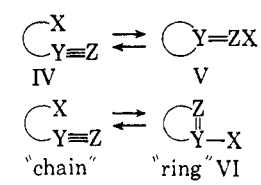
The structural requirements for ring-chain tautomerism can be stated in very general terms with regard to the chain tautomer: It must possess at least two functional groups, one containing a multiple bond and the other capable of effecting an additive reaction at the multiple bond. Thus, in the examples below, if YZ is a function containing a double bond which will react additively with X, the corresponding cyclic tautomer could possess one of the two structures shown, depending on the direction of addition.



I II

"chain" "ring" III

Two similar ring-chain tautomeric equilibria would be possible if the unsaturated function contained a triple bond, Y≡Z.



IV V

"chain" "ring" VI

TABLE OF EXAMPLES OF RING-CHAIN TAUTOMERISM

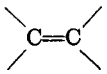
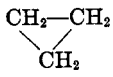
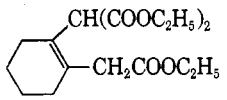
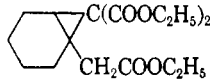
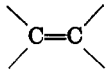
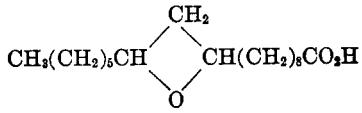
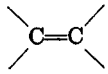
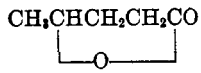
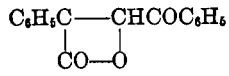
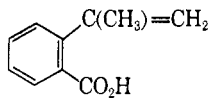
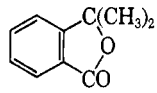
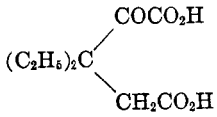
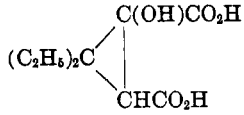
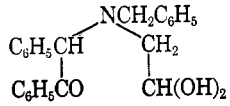
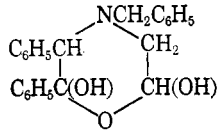
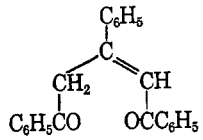
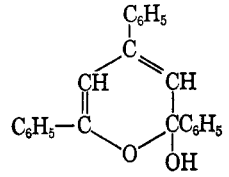
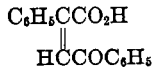
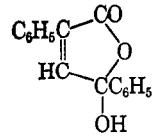
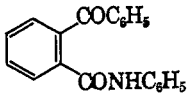
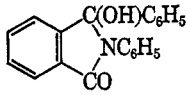
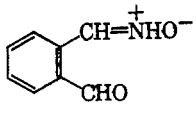
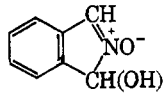
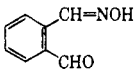
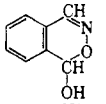
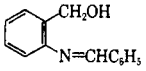
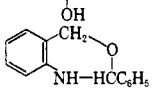
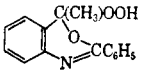
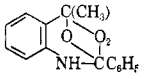
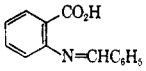
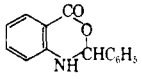
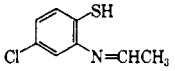
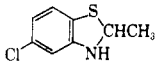
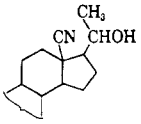
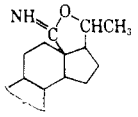
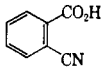
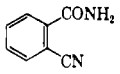
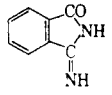
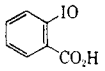
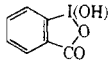
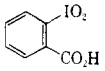
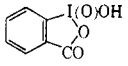
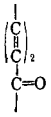
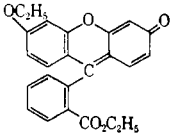
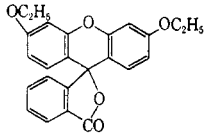
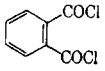
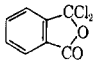
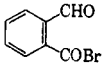
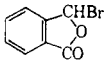
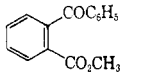
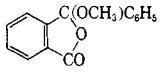
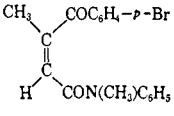
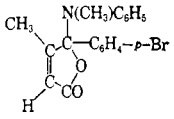
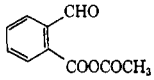
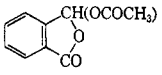
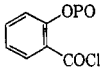
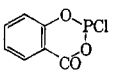
X	YZ	Chain tautomer	Ring tautomer	Reference
I. Electrophilic				
CH		$CH_2{=}CHCH_3$		317
				18
		$(C_2H_5O_2C)_2C{-}CH{=}C(COOC_2H_5)_2$ $(C_2H_5O_2C)_2CHCH{-}CH(COOC_2H_5)_2$		144
			$(C_2H_5O_2C)_2{-}C{-}CHCH(CO_2C_2H_5)_2$ $(C_2H_5O_2C)_2CHCH{-}C(COOC_2H_5)_2$	
—OH		$CH_3(CH_2)_5CH(OH)CH_2CH{=}CH{-}(CH_2)_7CO_2H$		24
—CO_2H		$CH_3CH{=}CHCH_2CO_2H$		45
		$C_6H_5C(CO_2H){=}CHCOC_6H_5$		164
				174
CH	C=O			77
—OH	C=O	$CH_2(OH)CH(OH)CH(OH)CH(OH){-}{-}CH(OH)CHO$	$CH_2(OH){-}CHCH(OH)CH(OH)CH(OH)$ $O{-}CH(OH)$	68
				222
				36
—CO_2H	C=O			51
NH	C=O			329
				117

TABLE OF EXAMPLES OF RING-CHAIN TAUTOMERISM (*Continued*)

X	YZ	Chain tautomer	Ring tautomer	Reference
=NOH	C=O			117
—OH	C=N			340
—OOH				339
—CO_2H				302
—SH				182
—OH	—C≡N			26
—CO_2H				78
NH				49
—CO_2H	—IO			30
	—IO_2			30
—R				1
II. Nucleophilic				
—Cl	C=O			109
—Br	C=O			274
— OR	C=O			85
—NH_2				215
—$OCOCH_3$				274
—Cl	PO			343

In the strict sense of tautomerism, only those cases should be considered where there is evidence for both ring and chain tautomers and for a rapid equilibrium between the two; but such examples are rare. Since the classification of ring and chain tautomers has commonly been made without strict regard for this requirement, examples will be drawn from those which conform to the general structures I–VI.

II. Enumeration of Types

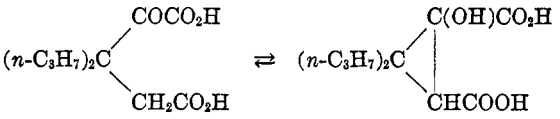
Types of ring-chain tautomers can be grouped according to the nature of X in the general formulas I–VI. Consider the formation of a ring tautomer from I or IV. In a formal way at least, the bond between X and its adjacent atom is broken while a new bond is formed between X and either Y or Z. If X tends to be electron-deficient, it will become attached to the more electronegative atom Z and thus form II or V. This type of interconversion might be called "electrophilic tautomerism." On the other hand, "nucleophilic tautomerism" would be exemplified by a case where X, being electron-rich, becomes attached to Y in the formation of III or VI. While this is a formal classification, which is not necessarily related to the mechanism of conversion, it is a helpful one for scrutinizing the structural possibilities of ring-chain tautomers.

In the table are listed some of the recorded examples of several structural types of ring and chain tautomers, arranged according to the suggested classification—electrophilic or nucleophilic. Both members of the isomeric pair have not been isolated in each case; in some instances the existence of one of the tautomers has merely been proposed on the basis of indirect evidence.

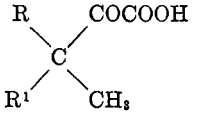
A. Electrophilic

By far the majority of examples of electrophilic ring-chain tautomers are those where the "electrophile" is hydrogen. In fact, only one example appears in the table where X is ethyl rather than hydrogen. This is a somewhat special case in the phthaleins, where the tautomeric change can be visualized as an addition—elimination to a quinoid–phenol system (1).

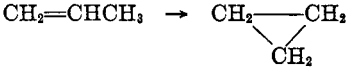
The mobile hydrogen in ring-chain tautomers is usually one of considerable acidity, according to expectation. In the chain tautomer, this hydrogen is most likely attached to oxygen, sulfur, or nitrogen, or is a carboxylic hydrogen. Only rarely are examples of ring-chain tautomers encountered in which the hydrogen is attached to carbon, although some of the earliest examples fall into this category. In these cases, the electrophilic hydrogen possesses some degree of mobility because of an adjacent activating group. For example, tautomerism as found in 3,3-dipropyl-2-ketoglutaric acid (15)



would not be anticipated with similarly substituted α-ketobutyric acids, in which there is no activating carboxyl function.

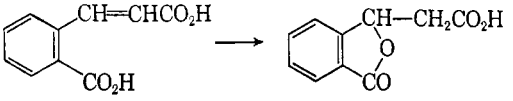


The case of propylene–cyclopropane (317) might appear as exceptional, but there is clearly no tautomeric equilibrium existent in this pair of ring-chain compounds.



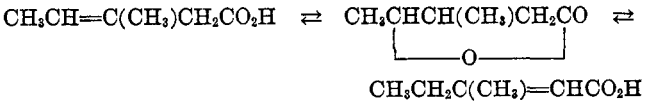
The nature of the unsaturated group YZ appears to be limited, and the polarity of the multiple bond is probably important. The majority of cases in which a nonpolar C=C bond participates in ring-chain tautomerism are those in which the hydrogen source is a carboxyl group; and thus the ring tautomer is a stable lactone.

As early as 1877 Gabriel observed the conversion of *o*-carboxylcinnamic acid (chain tautomer) to 3-phthalidylacetic acid (ring tautomer) (95).



Other reports of the interconversion of *o*-alkenylbenzoic acids and 3-substituted phthalides have appeared in several instances (37, 38, 102, 174, 344); the isomerism does not always proceed in both directions, however, and conditions necessary to effect the conversions are severe.

By contrast, 3-alkenoic acids (and, in some instances, 2- and 4-alkenoic acids) undergo rapid equilibration with ring-tautomeric γ-lactones at room temperature in the presence of mineral acid (45, 46, 172, 173, 195, 196, 197, 198, 199). The following equilibrium serves as an example (173).



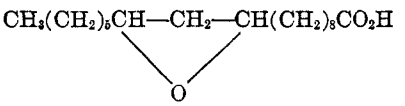
Structural relationships of this type were sufficiently prevalent, that Linstead coined the term "lacto-enoic tautomerism" to describe them (198). This equilibrium has been found to be important in the Stobbe condensation (147, 148, 149, 150, 151), from which the products after decarboxylation are likely to be a mixture of 3-alkenoic acid and γ-lactone. A similar

tautomeric pair has been encountered by way of the Grignard reaction with succinic anhydride (13).

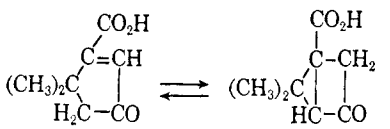
Only rarely have other examples of ring-chain tautomerism involving a C=C bond been reported. One such instance is the equilibrium shown below, where the electrophilic hydrogen originates from a hydroxyl group. Although the ring tautomer was not isolated and characterized, its existence was proposed to explain all of the degradation products of ricinoleic acid (24).

$CH_3(CH_2)_6CH(OH)CH_2CH{=}CH(CH_2)_7CO_2H \rightleftarrows$

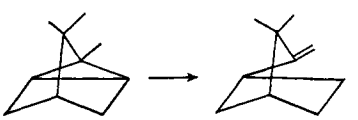
Ricinoleic acid



Striking examples of ring-chain tautomerism in which YZ is C=C and X is carbinyl hydrogen,  , are provided from the work of Ingold (67, 88, 89, 118, 144). On the basis of chemical properties, various cyclopentenones such as 3-carboxy-4,4-dimethyl-2-cyclopentenone were assumed to be in equilibrium with a bicyclic ring tautomer



Tautomeric rearrangements of this type are known in the terpene series. Thus, tricyclene, the "ring tautomer," isomerizes to camphene, the "chain tautomer," in the presence of a nickel catalyst at 180–200° in an atmosphere of nitrogen (234).



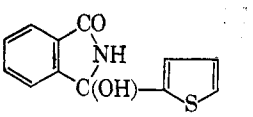
"ring" "chain"

The latter case is particularly interesting because there is no reason to expect a mobile hydrogen in tricyclene or camphene.

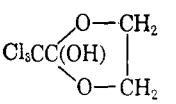
While the C=C bond is subject to tautomeric cyclizations, instances of the participation of other nonpolar multiple bonds in ring-chain tautomerism are lacking. No examples could be found in which either the C≡C or N=N function was involved.

By far the most susceptible unsaturated group with regard to ring-chain tautomerism is the carbonyl function. Appropriately constituted aldehydes may isomerize to their cyclic, hydroxy tautomers (4, 9, 44, 55, 57, 58, 71, 72, 87, 117, 130, 131, 135, 188, 192, 235, 282, 283, 297, 325, 332); one of the familiar examples is the formation of cyclic hemiacetals in the sugar series (9, 68, 202). Ketones may tautomerize to the corresponding cyclanol if X = C—H (15, 16, 19, 29, 77, 91, 180, 181, 260, 301); to the cyclic hemiacetal or "ketol" if X = OH (36, 74, 80, 81, 106, 114, 123, 169, 216, 218, 219, 220, 224, 228, 246, 294, 300, 319); or to the cyclic hydroxylactone ("lactol") if X = CO_2H (7, 12, 25, 51, 73, 107, 110, 111, 127, 170, 187, 209, 210, 211, 212, 213, 214, 217, 221, 227, 229, 248, 252, 268, 269, 270, 271, 272, 273, 284, 285, 291, 295, 325, 333).

If an aldehyde or ketone also contains an N—H function suitably distant from the unsaturated site, it could conceivably exist in the ring tautomeric form as a hydroxyamine or hydroxyamide. In a few instances such a ring structure has been suggested (63, 107, 139, 205, 242, 243, 275, 329) to rationalize the behavior of compounds of this type; for example, the amide of *o*-thienoylbenzoic acid has been assigned the "pseudo" structure (306).



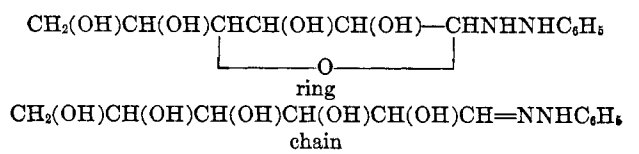
Although the carbonyl bond in acid chlorides and anhydrides is highly polar, no instances of their participation in electrophilic ring-chain tautomerism appear to have been recorded. This is not surprising, however, because of the marked instability of α-chloro- and α-acyloxyalcohols. On the other hand, there is some evidence for ring tautomers derived from esters (132, 133, 134, 232, 236, 237). The product from trichloroacetic acid and ethylene glycol, for example, was assigned the ring rather than the chain tautomeric structure (133, 236).



$Cl_3CCO_2CH_2CH_2OH$

The cyclization of an amide to the tautomeric α-hydroxyamine is an extremely interesting structural possibility—and might be useful to explain the behavior of certain compounds (186, 315, 316)—but evidence is lacking for the involvement of an amide carbonyl bond in ring-chain tautomerism.

In addition to the olefinic and carbonyl functions, both C=N and C≡N bonds are known to participate in ring-chain tautomerism. One such case is that of the phenylhydrazones of sugars, which has been the subject of extensive study and controversy (261). From recent evidence (240) there is strong indication that two of the three known phenylhydrazones of D-glucose possess ring tautomeric structures. The third is a chain tautomer.

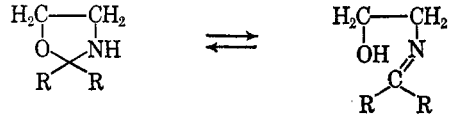


ring

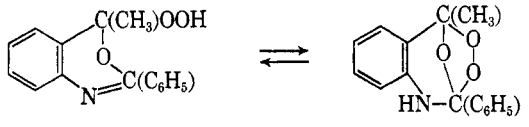
chain

On the other hand, the phenylosazone is probably acyclic (241).

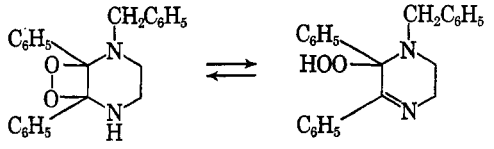
2,2-Disubstituted oxazolidines are mixtures of ring and chain tautomers, the latter being a hydroxyimine (32, 33).



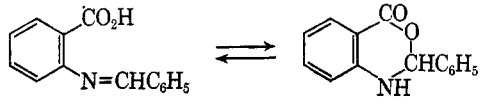
An —OH group is not the only source of a proton in ring-chain tautomers involving the —C=N group. The ozonides from various 2-aryl-3-methylindoles exhibit properties consistent with a mixture of a "true ozonide" (chain tautomer) and a cyclic imine hydroperoxide (ring tautomer) (337, 338, 339).



The peroxide from 1-benzyl-2,3-dihydro-5,6-diphenylpyrazine has been represented in an analogous way (205).

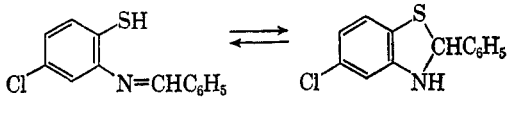


Likewise the benzal derivative of anthranilic acid is very probably a mixture of the two tautomers (302).

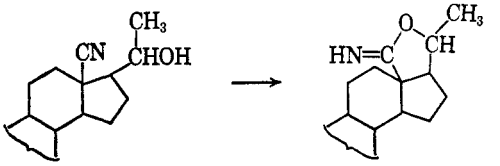


In this case the proton donor is a carboxyl function.

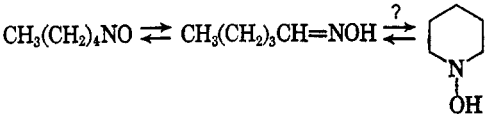
Although direct evidence is lacking, it is possible that the benzal derivative of 2-amino-4-chlorothiophenol is best represented as a ring-chain tautomeric mixture (182).



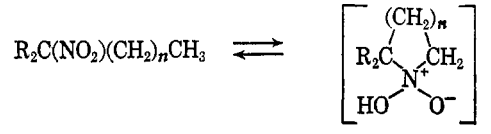
The generally observed low reactivity of nitriles is consistently verified by the dearth of examples in which the C≡N bond is involved in ring-chain tautomerism. Such participation might serve to explain certain transformations of *o*-cyanobenzoic acid and *o*-cyanobenzamide (4, 49, 78), but any direct proof is lacking. One concise example of this kind of cyclization appeared recently (26). An 18-cyanosteroid was converted by ethanolic hydrogen chloride into the isolable, cyclic imine—its ring tautomer.



Appropriately constituted nitroso compounds (YZ = NO) might conceivably exist in tautomeric equilibrium with the corresponding cyclic hydroxylamines. Thus 1-nitrosopentane (which is unstable and occurs almost exclusively as pentanal oxime) is, in a formal sense at least, the chain tautomer of the known N-hydroxypiperidine. There is no evidence, however, of any interconversion of these structures (341, 345). A rigorous test of the existence of ring-chain tautomerism

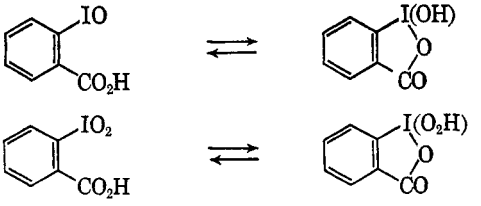


in which the NO group participated would require the examination of an α,α-disubstituted nitroso compound, in which isomerism to the oxime would be prohibited. By analogy, a fully substituted nitro compound might tautomerize to the interesting but as yet unknown hydroxylamine N-oxide.



Examples of ring-chain tautomerism in which YZ contains a sulfur atom are lacking, although the possibility of participation of such groups as CS and SO leads to the prediction of some novel classes of compounds: monothiohemiacetals, dithiohemiacetals, cyclic mercaptans, etc.

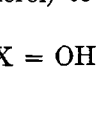
One recent suggestion that the IO and IO_2 functions might play a role in ring-chain tautomerism warrants attention. According to their spectral properties, *o*-iodosobenzoic acid and *o*-iodoxybenzoic acids are more accurately respresented as ring tautomers (30).

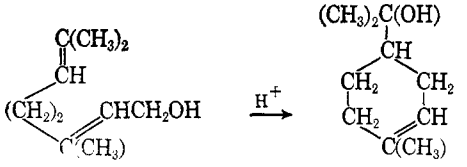


B. NUCLEOPHILIC

Ring-chain tautomerism in which a potential nucleophile or anion appears to exhibit mobility has received considerably less attention than its electrophilic counterpart. By a consideration of the possible nucleophiles (*e.g.*, OH, X, OR, OCOR, NH_2) and likely

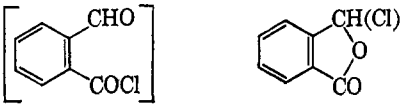
unsaturated centers (YZ) which could be involved in this kind of isomerism, it might be predicted that the number of types would be enormous. Only a few have been realized experimentally.

Any cyclizations accompanied by the rearrangement of an alcohol function may formally be classified as the formation of ring tautomers. The rearrangement of geraniol (or nerol) to α-terpineol (299) can be viewed in this way (X = OH; YZ = ).

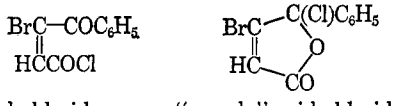


Unless such transformations, particularly prevalent in the terpene series, exhibit some degree of reversibility, however, they are customarily classified as molecular rearrangements. Indeed, there is often no unequivocal means of distinguishing tautomerism from a molecular rearrangement (334). The intent here is to exclude those cases conventionally considered to fall into the latter category.

By far the preponderance of examples of nucleophilic ring-chain tautomerism are those in which X = halogen (almost exclusively chlorine, occasionally bromine) and YZ = CO. The chlorine in the chain tautomer originates in most cases from an acid chloride, and the carbonyl function is part of an aldehyde, ketone, or acid chloride. Thus, 3-chlorophthalide is the ring tautomer whose acyclic counterpart would be *o*-formylbenzoyl chloride, a compound never yet isolated in pure form (12, 103). The analogous situation prevails for the bromo compound as well (274).



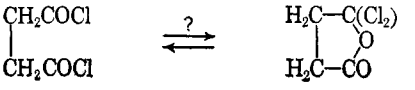
The ring tautomers (γ-chlorolactones) derived from several β-acylacrylic acids are markedly more stable than their chain tautomers, which would contain both ketone and "normal" acid chloride functions (51, 206, 207, 209, 210, 212, 213, 215, 227, 229, 247). One example is the "pseudo" acid chloride from β-bromo-β-benzoylacrylic acid; no evidence could be found for the "normal" chain tautomer (229).



"normal" acid chloride (chain) "pseudo" acid chloride (ring)

An acid chloride exhibiting ring-chain tautomerism (YZ = —COCl) is *o*-phthaloyl chloride. It is known in both the chain and ring tautomeric forms, and the latter isomerizes to the former when allowed to stand (258). There is ample evidence for the occurrence of both forms in various reaction mixtures (75, 109, 159 175, 287, 289).

By contrast, only one form of succinyl chloride has been isolated; the most recent evidence has led to the conclusion that this form is the chain tautomer (64). It had been previously assumed on other grounds that this acid chloride was an equilibrium mixture of ring and chain tautomers (256, 286). Glutaryl chloride,

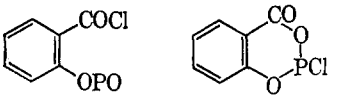


which would form a six-membered ring tautomer, has also been assigned the chain structure (65).

Tautomerism between *o*-trichloromethylbenzoyl chloride and 1,1,3,3-tetrachlorophthalan is probably one of the few instances where nucleophilic chlorine does not originate from an acid chloride function. Both tautomers are isolable and interconvertible (257).

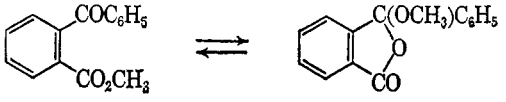
Participation of a —PO bond in nucleophilic ring-chain tautomerism may be involved in the reaction product of salicylic acid and phosphorus pentachloride (Couper's compound). Evidence seems to favor the ring tautomer, but no conclusive proof against the chain tautomer has been found (265).

A similar product from phosphorus trichloride seems clearly to possess the ring rather than the chain structure (61, 343).

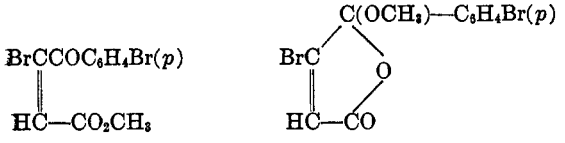


Instances of the participation of a mobile —OR, —NR_2, or —OCOR group in ring-chain tautomerism have been most carefully examined in families of keto-acids. In these cases equilibrium would exist, respectively, between ketoester and alkoxylactone; ketoamide and aminolactone; or ketoanhydride and acyloxylactone. The first type has been authenticated in several laboratories. Both the "normal" (chain tau-

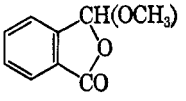
tomer) and "pseudo" (ring tautomer) methyl esters of *o*-benzoylbenzoic acid have been prepared (85, 107, 126, 168, 233, 249, 291) and are interconvertible under a variety of conditions (85, 107).



Several alkyl ester of other *o*-aroylbenzoic acids exhibit stability in both ring and chain forms (85, 90, 107, 168, 244, 250, 252). Esters of β-aroylacrylic acids are known in both forms (209, 210, 211, 212, 214, 217, 229, 247). Either the normal or pseudo methyl ester can be obtained from the acid chloride of β-bromo-β-*p*-bromobenzoylacrylic acid (229).

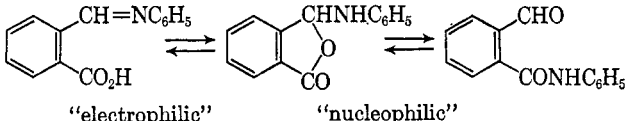


With *o*-phthalaldehydic acid only one methyl or ethyl ester is known (274). These esters, as well as a large number of other alkyl derivatives reported recently, are undoubtedly ring tautomers (332).



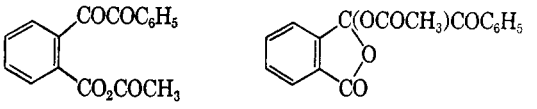
There are probably no unequivocal cases of the interconversion of a ketoamide and its ring tautomer, the aminolactone. Both types are known, and their stability is highly dependent on other structural features in the molecule. The "dimethylamide" derived from *o*-(*p*-chlorobenzoyl)-benzoic acid is the chain tautomer (107); that from *o*-phthalaldehydic acid is the ring tautomer (332). It is interesting to note

that, in almost every case where the amide originates from a primary amine, it possesses neither of the above structures but is a hydroxylactam, the "electrophilic" ring tautomer (215, 227, 229). 3-Anilinophthalide is an exception (332), but this cyclic amide can be considered either as the "electrophilic" ring tautomer of *o*-phthalaldehydic acid anil or the "nucleophilic" ring tautomer of *o*-phthalaldehydamide.

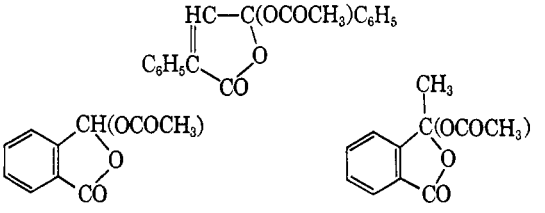


"electrophilic" tautomerism "nucleophilic" tautomerism

Nucleophilic ring-chain tautomerism where X = OCOR is known with certainty in only one instance. Both the mixed anhydride (chain tautomer) and the "pseudo acetate" (ring tautomer) of *o*-carboxybenzil have been prepared by different routes and characterized. They do not appear to be interconvertible, however (291).



Other acetyl derivatives of ketoacids are ring tautomers, which are evidently more stable than the mixed anhydride. Some examples are 2,4-diphenyl-4-acetoxy-2-butenolactone (51), 3-acetoxyphthalide (274), and 3-acetoxy-3-methylphthalide (96, 152).

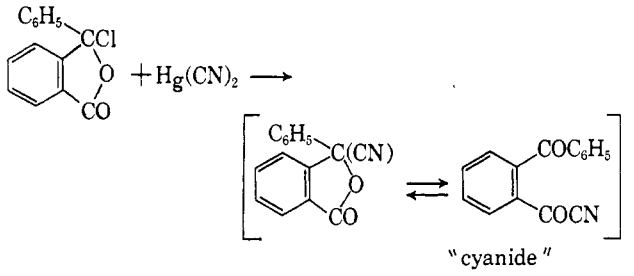


The latter two compounds were first considered to be normal anhydrides. Although not recognized at the time it was first reported, the last compound is probably the first recorded instance of the formation of a ring tautomer.

III. Effect of Structure on Stability of Ring and Chain Tautomers

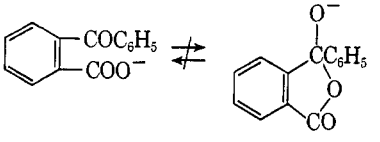
A. Nature of X, Y, and Z

As is evident from the table of representative examples of ring-chain tautomers, a great many conceivable structures either have not yet been realized or are incapable of existence for some reason. In the case of electrophilic ring-chain tautomerism, the electrophile X is almost invariably hydrogen. The one instance in which it is an alkyl group is a rather special one, where the participating unsaturated system is conjugated (1). There is a wider variation in X for nucleophilic ring-chain tautomerism, but examples in which many other likely nucleophiles participate are lacking. Only chloro and bromo halogens are known to participate in ring tautomer formation, although an iodo group would be expected to be more labile in a ring-chain tautomeric system. It is not surprising that the fluoro group shows no such mobility. There are no cases where a cyano group, often viewed as a pseudo-halogen, is clearly involved. A "cyanide" was reported as arising from the acid chloride of *o*-benzoylbenzoic acid and mercuric cyanide, but its structure has not been determined (231). On the basis of analogy, it may very likely be partially or wholly cyclic; if so, this would constitute a case where nucleophilic CN is participating in ring-chain tautomerism.

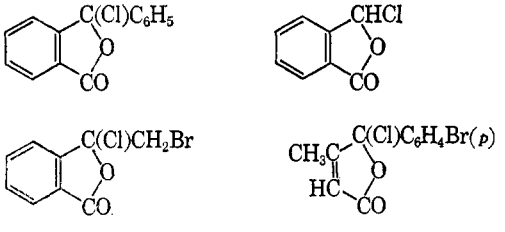


Few generalizations can be advanced concerning the relative stabilities of ring and chain tautomers as related to the nature of X, but two striking correlations are consistently observed.

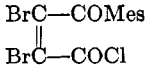
(1) In the case of acids and acid derivatives exhibiting ring-chain tautomerism, the acid salts are always acyclic. The carboxylate anion in such a salt is the analog of an enolate anion, but, unlike the latter, is not a resonance hybrid. This follows from the marked difference in location of atoms in the acyclic and cyclic structures. Apparently there is no ready interconversion of the two anionic valence tautomers.



(2) Acid chlorides, derived from keto- or aldehydo-acids appropriately substituted so as to form five- or six-membered rings, are, with one possible exception, always cyclic. Thus, for example, only one acid chloride is known from *o*-benzoylbenzoic acid (85, 107, 112, 231), and it is the cyclic tautomer (107, 291, 155). Among other ring-tautomeric acid chlorides which have been characterized are those from phthalaldehydic acid (40), phthalonic acid (73), *o*-bromoacetylbenzoic acid (79), and β-(*p*-bromobenzoyl)-crotonic acid (207).



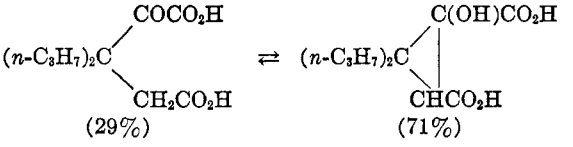
The one exception is the acid chloride of β-mesitoyl-α,β-dibromoacrylic acid, which was reported to be acyclic (247).



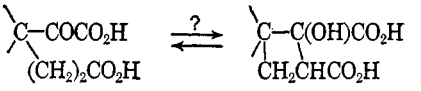
B. RING SIZE AND PROXIMITY EFFECTS

It is to be expected that the stability of ring tautomers will be strongly dependent on the number of atoms in the ring, and the tendency for a chain tautomer to cyclize will depend on the spatial proximity of the groups X and YZ.

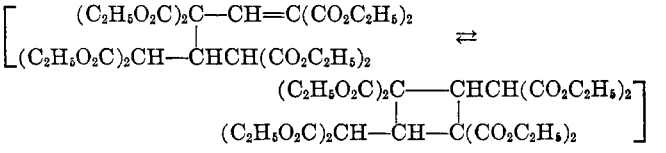
Some of the earliest reports of ring tautomers were those involving three-membered rings. It was presumed that various β,β-dialkyl-α-ketoglutaric acids were mixtures of ring and chain tautomers. One of them, β,β-di-*n*-propyl-α-ketoglutaric acid, was estimated to consist of 71% of the ring tautomer—a cyclopropanol (15).



It is conceivable that substituted α-ketoadipic acids would tautomerize to the corresponding cyclobutanols, but apparently this has not been observed.

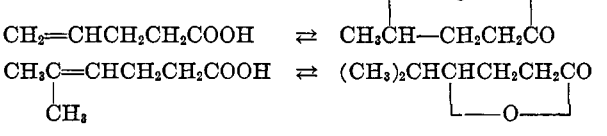


In fact, only rarely has a four-membered ring tautomer been encountered or proposed. One example is the reaction mixture from base-catalyzed dimerization of 1,1,3,3-tetracarbethoxypropene; two isomers were separated and assigned ring and chain tautomeric structures (144).



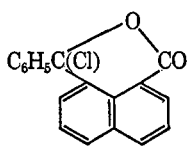
Four-membered ring tautomers derived from acids (where YZ = CO_2H) have not been encountered, probably because of the instability of β-lactones.

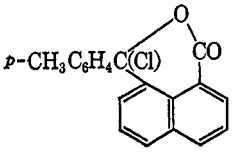
Five- or six-membered rings are formed preferentially, in accord with their high stability as generally observed. There is often likely to be a marked tendency for the formation of a five-membered ring in preference to a six-membered ring when either might arise from a chain structure. In the case of sugars, this is often observed, although the common hexoses (except fructose) tautomerize preferentially to the six-membered hemiacetals (68). Unsaturated acids in tautomeric equilibrium with lactones invariably lactonize to γ-lactones rather than to δ-lactones. 4-Pentenoic acid, for example, tautomerizes exclusively to the γ-lactone, as does 5-methyl-4-hexenoic acid (198).



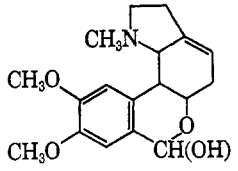
In many cases where a six-membered ring is the only structural possibility, the ring tautomer is perfectly stable. Indeed, the acid chlorides of 8-benzoyl-

1-naphthoic acid and 8-*p*-toluyl-1-naphthoic acid (254), as well as other similar naphthalene derivatives appear to be free of chain tautomer.

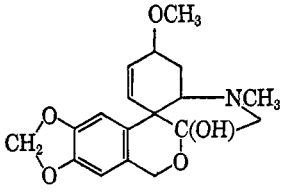




Alkaloids such as lycorenine (162) and tazettine (143) occur in nature as the cyclic, six-membered hemiacetal and hemiketal, rather than the open chain tautomeric hydroxyaldehyde and hydroxyketone.

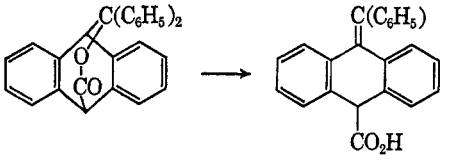


Lycorenine

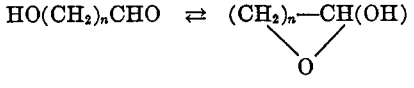


Tazettine

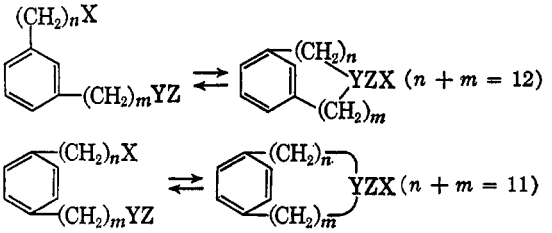
A seven-membered ring tautomer is exemplified by the "transannular lactone" of anthracene, which rearranges in acid to the chain tautomer, 9-diphenylmethylene-9,10-dihydroanthracene-10-carboxylic acid (281).



Ring tautomers with seven or more members are rare, however. This is shown clearly from an examination of the position of tautomeric equilibrium in dioxane of saturated ω-hydroxyaldehydes. When the tautomeric, cyclic hemiacetal contains five or six atoms (n = 3, 4), it is the predominant isomer (89–93%); for the next higher homolog, however, where the ring tautomer is seven-membered, this constitutes only about 15% of the mixture. The amount of cyclic tautomer falls off even further for larger rings up to those with eleven members (142).

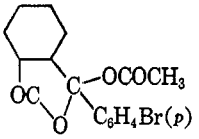


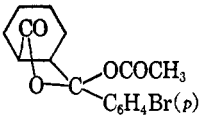
If aldehydes of this structure were to be examined where considerably larger rings could be formed ($n \geqq 14$), it might be found that the tendency for cyclization increases again. This is in accord with the enhanced formation of rings containing sixteen or more members, and it is interesting to contemplate structural possibilities for some macrocyclic ring tautomers, which would resemble known macrocycles already shown to be stable. They might contain a saturated chain, an unsaturated aliphatic chain, or a *m*- or *p*-bridged aromatic ring. The examples below are written for the case of electrophilic tautomerism.



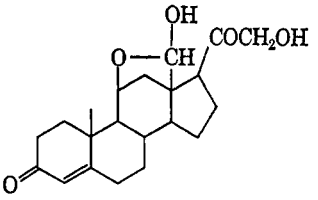
No ring-chain tautomerism involving large rings such as these has been reported.

Just as the success of cyclizations to large rings depends on the proximity in space of the two interacting functional groups, so the tendency of a molecule to exist as a ring tautomer will be influenced by the nearness of the groups —X and —YZ. For example, both *cis*- and *trans*-2-*p*-bromobenzoylcyclohexanecarboxylic acid form cyclic pseudo-acetates (167), these being, respectively, the axial-equatorial and diequatorial conformers.

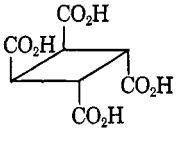




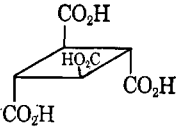
1,3-Diaxial substituents in cyclohexane derivatives are favorably situated for interaction. This is illustrated with aldosterone, which possesses the ring tautomeric structure in solution (300).



The size and flexibility of the ring are probably quite important factors in their effect on the proximity of groups and, therefore, on the ease of ring formation. Recently two isomeric cyclobutane-1,2,3,4-tetracarboxylic acids were investigated, as well as their corresponding acid chlorides and esters. In addition the isomeric 1,2,3,4-tetrabenzoylcyclobutanes were examined. In no case was there any chemical or spectroscopic evidence for ring tautomer formation (115, 116). This is surprising, since the acid chlorides were allowed to react in the presence of aluminum chloride, conditions which readily effect the cyclization of phthaloyl chloride to its ring tautomer (109).

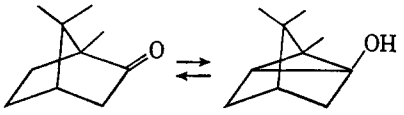


cis, trans, cis

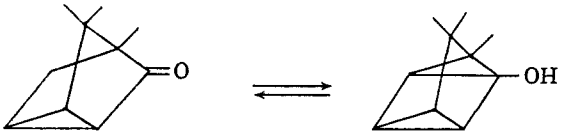


trans, trans, trans

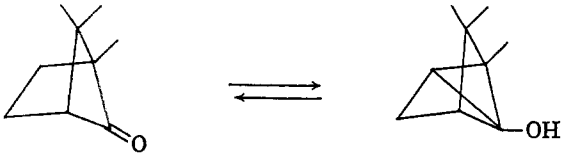
Because of the current extensive interest in the chemistry of small ring compounds, it is interesting to consider the formation of strained ring tautomers containing three or four members. Favorable structural features for this behavior would include a rigid ring system and two potential interacting functional groups in close proximity. These requirements would seem to be accommodated in bicycloheptane and fused bicycloheptane molecules. For example, it is conceivable that camphor might "enolize" to a ring tautomer rather than to the usual enol.



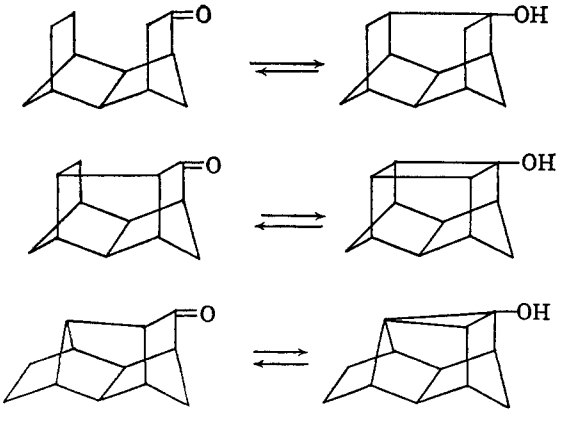
In the case of isocyclenone, normal enolization would constitute a violation of Bredt's rule, and ring tautomerism appears as an alternative path. No mention has been made of any experimental evidence for this kind of tautomeric ring formation in these ketones or in the more highly strained bicyclo[2.1.1]1,6,6-trimethyl-5-hexanone (238).



Isocyclenone

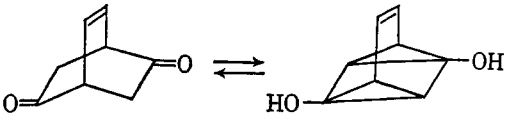


Since it has recently been shown that opposing hydrogens in fused bicycloheptanes are extremely close (163), it is attractive to predict the likelihood of ring tautomer formation in ketones with this structure. Some of them, together with their corresponding, hypothetical ring tautomers, are listed below.

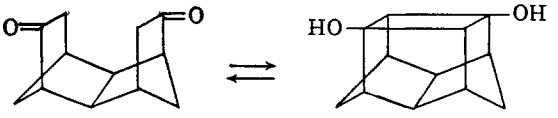


Although only partial information on the spectral properties of these ketones has been published, there was no suggestion that the carbonyl group is abnormal (163).

While the geometry of molecules in these bicyclo systems seems favorable to ring formation—more so, at least, than in flexible, open-chain structures—the tautomeric change is unlikely because of the lack of acidity of the mobile hydrogen (X) in each case. One structure in which this mobile hydrogen is rendered acidic is that of bicyclo[2.2.2]oct-7-ene-2,5-dione, a compound recently reported. In fact, it is possible to predict a "double" ring tautomer in this case, where each mobile hydrogen is adjacent to an activating carbonyl function. According to the report, however, this compound shows no tendency to enolize (119).



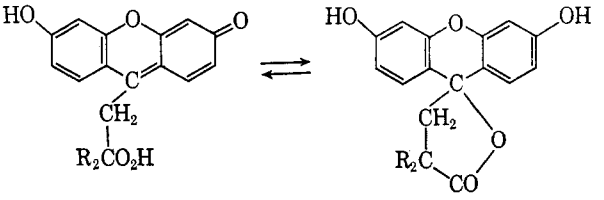
One fused bicycloheptane derivative with acidic hydrogens is the diketone shown below, which has not yet been synthesized. On the basis of ring rigidity, proximity effects, and hydrogen mobility, it is the cyclic compound perhaps most favorably constituted for ring tautomerism to a strained structure.



C. RING SUBSTITUTION AND RING UNSATURATION

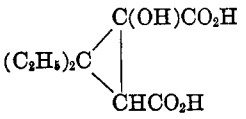
The general observation that ring stability increases with increasing substitution is borne out in an examination of the effect of alkyl substituents on the tendency of a compound to isomerize to its ring tautomer. It is concluded that, in a series of homologous compounds of the general structure I–V, the amount of ring tautomer at equilibrium will be augmented with increasing substitution.

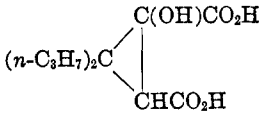
This is shown in the behavior of phenolsuccineins, where the amount of ring tautomer is greater with R = CH_3 than with R = H (83).

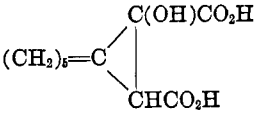


The same trend shows up in phenolglutareins. Moreover, ring tautomerism is further exalted by changing R to larger alkyl groups, an observation which suggests that the size of substituents is also important. That not only the number but the bulk of substituents affects the position of ring-chain tautomeric equilibrium is exemplified by the β,β-dialkyl-α-ketoglutaric acids.

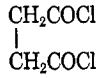
While the diethyl compound contains about 62% ring tautomer at equilibrium, the di-*n*-propyl analog is 71% ring tautomeric; the cyclohexylidene compound is entirely free of chain tautomer (141, 180).

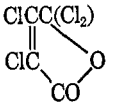

(62%)


(71%)

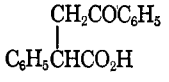

(100%)

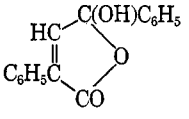
A second generalization arising from a survey of ring-chain tautomerism is that ring formation is much more likely if the ring is unsaturated. According to the most recent evidence, both succinyl chloride and glutaryl chloride are predominantly if not exclusively chain tautomers (63, 64, 65). By contrast, the acid chloride from dichloromaleic acid has been considered to be cyclic (256).



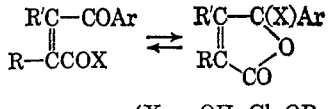


While β-benzoyl-α-phenylpropionic acid shows no tendency to cyclize, the unsaturated analog, β-benzoyl-α-phenylacrylic acid, is predominantly the ring tautomer in ethanol solution (51).


(100% chain tautomer)


(70% ring tautomer)

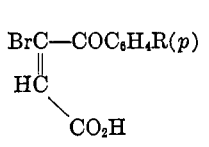
Acids of this latter type—*cis*-β-aroylacrylic acids—have been the subject of extensive examination by Lutz for several years, and they are probably the most thoroughly studied of any class of compounds exhibiting ring-chain tautomerism. The substituents R and R′ are found to have a significant effect on the tendency


(47, 51, 206, 207, 208, 209, 210, 211, 212, 214, 215, 217, 221, 227, 229, 247)

(X = OH, Cl, OR, OCOR, NR_2)

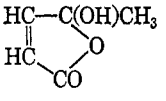
of these acids to exist partially or wholly as ring tautomers. In general, from the several cases studied, those acids or derivatives of this group with no substituents are acyclic; those with both R and R′ occupied by groups other than hydrogen are predominantly or exclusively cyclic. If only one substituent is present, they are likely to exist as a mixture of the two tautomers, but it does not appear possible to make a consistent prediction about the position of equilibrium for acids with only one substituent.

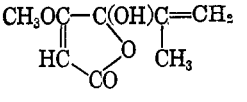
In the acid where both R and R′ are —H, all evidence points to the conclusion that it is wholly the chain tautomer (217, 279); the methyl ester is acyclic (X = OCH_3), and all attempts to prepare the acid chloride have been unsuccessful. On the other hand, the acids are exclusively ring tautomers when R, R′ = Br (except where the aroyl group is mesitoyl) (206, 247, 297) and when R, R′ = CH_3 (209, 214, 227). Mixtures of the two tautomeric acids are encountered when R = H, R′ = Br (229) and when R = C_6H_5, R = H (51, 166). Substitution in the aroyl group, from the limited number of cases examined, has a profound effect on the position of ring-chain equilibrium. Electron-withdrawing substituents facilitate cyclization, while electron-donating groups exert the opposite effect. Apparently the reactivity of the carbonyl ketone function toward addition is involved. In a series of β-bromo-β-aroylacrylic acids, the amount of ring tautomer in chloroform solution varies from 50% for *p*-chloro to 0% for *p*-methoxy (229).



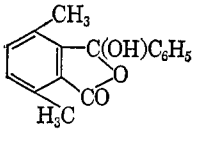
R	% ring tautomer
Cl	50
Br	30-40
H	30
OCH_3	0

In other families of γ-keto-α,β-unsaturated acids the effect of substitution at the olefinic bond may vary. For example, both 4-keto-2-pentenoic acid and penicillic acid are ring tautomers in water solution (295).




Penicillic acid

Unsaturation in a ring tautomer is often provided by an aromatic nucleus, such as that in phthaloyl chloride (109). *o*-Benzoylbenzoic acid, whose ring tautomer would contain this unsaturation is, nevertheless, acyclic in solutions of methanol and carbon disulfide (252). It has been concluded that substituents in positions *ortho* to either the acid function or the carbonyl group promote cyclization to the ring tautomer (249, 250, 252). A case in point is 3,6-dimethyl-2-benzoylbenzoic acid, which was estimated to consist of only 14% chain tautomer in solution (252).


(14% chain tautomer)

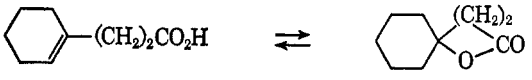
IV. METHODS OF DETERMINING STRUCTURES OF RING AND CHAIN TAUTOMERS

The assignment of a ring or chain structure to a compound capable of tautomerism has been based on a wide variety of chemical and physical methods. Because ring tautomers sometimes possess considerable stability, in contrast to enolic tautomers, it is possible to carry out structure determinations with less difficulty. Considerable care must be exercised, however, since often both tautomers are not available for direct comparison.

A. CHEMICAL METHODS

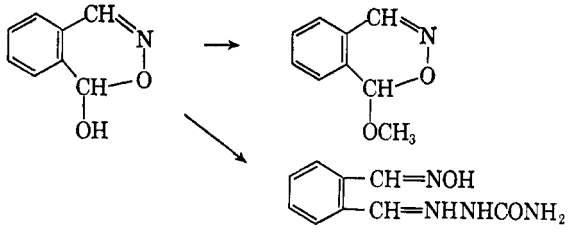
The chemical approach to determining ring and chain tautomeric structures is based on a consideration of the functional groups present in each. Ketoacids have been assigned the ring structure because of their low reactivity in base (285). This has been particularly useful in comparing *cis*-β-aroylacrylic acids of low solubility (therefore ring tautomers) with the *trans* isomers, incapable of ring-chain tautomerism and found to be much more readily soluble in base (209, 210, 213). On a quantitative basis, it has been found that, on potentiometric titration, normal acids of this type exhibit an inflection at pH 6–7, while that of ring tautomers is at pH 9–10 (73, 217, 227).

Olefinic acids, such as 3-cyclohexenylpropanoic acid, and their ring tautomers are analyzed with facility, since the latter is not acidic. The composition of such mixtures has been estimated by bromine titration (199), by ethereal extraction of the lactone from an alkaline mixture (196), or by determination of a neutralization equivalent (151).



Low reactivity may be a generally helpful criterion in assigning the ring structure, but it does not appear to be widely accepted or consistently valid. Thus, cyclic acid chlorides have been so assigned because of their stability toward water and alcohols (206, 207); but there are no acyclic tautomeric acid chlorides known for comparison. A similar situation holds for cyclic acetates, which are tautomeric with the open-chain, mixed anhydrides. While the failure of these acetates to dissolve in ammonia or alkali (96, 192, 235) is strongly suggestive of the ring structure, authentic examples of tautomers with the chain structure are lacking. No generalization holds for esters, since the early notion that pseudo-esters are more readily hydrolyzed by acid than normal esters was later invalidated (249).

It has quite generally been concluded that, if a tautomer reacts to form derivatives of the functional groups present in the chain tautomer, then it does, in fact, possess the chain structure. Formation of derivatives corresponding to the ring tautomer would lead to assignment of the ring structure. For example, a ketoacid capable of ring-chain tautomerism may form a semicarbazone or it may be converted to a cyclic, "pseudo" ester. On the simple basis of chemical behavior alone, it would be assigned the chain structure in the former case; the ring structure in the latter. An acid such as levulinic acid, which forms both derivatives (12, 50, 129), is considered to be a mixture of ring and chain tautomers, and it is often presumed that the relative amounts of the two derivatives serve as an indication of the amounts of ring and chain tautomers in the starting acid. This method of analysis may lead to erroneous results for at least two reasons. First, it is based on the assumption that the ring-chain equilibrium is the same in the pure compound and in the presence of reagents and that the formation of derivatives is considerably faster than equilibration of the tautomers. A second necessary assumption for this method is that chain tautomers react to form only acyclic compounds while ring tautomers from only cyclic derivatives. This is clearly incorrect, since it would require that no reactions of ring and chain tautomers could occur with rearrangement. A case in point is the monooxime of *o*-phthalaldehyde, a sharp-melting, apparently homogeneous substance, which was assigned the cyclic structure. Yet it is reportedly converted both to a cyclic methyl ether and to an acyclic semicarbazone (117).

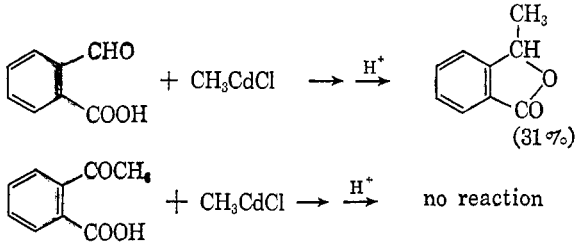


For a few compound types it has been generally observed that reaction does indeed take place without rearrangement, and the use of such reactions is valuable in assigning structure. Silver salts, for example, believed to be chain tautomers, react with alkyl halides (usually methyl iodide or ethyl iodide) to form, in every case, the acyclic, normal ester. On this basis the structures of methyl esters of 4,5-dimethoxyphthalaldehydic acid (87) and *cis*-β-benzoylacrylic acid (217) have been established, as has the ethyl ester of phthalaldehydic acid (274).

Acid chlorides of ketoacids are also useful starting materials for obtaining esters of known structure. Almost invariably ring tautomers, they react with alcohols to form cyclic, "pseudo" esters. This was the method of assignment in preparing the ring tautomeric methyl esters of substituted *o*-benzoylbenzoic acids (85, 233, 249, 250, 291) and many others (103,

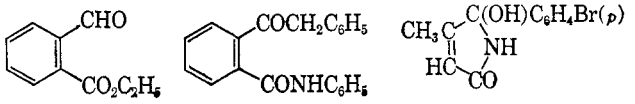
210). It is interesting that thionyl chloride in some instances will effect the isomerization of chain ester to ring ester (244). Diazomethane was used to prepare the acyclic methyl esters (249, 250); here the assumption is made that, regardless of the tautomeric structure of the acid, it will form the normal ester with diazomethane (90, 212, 217). This synthetic method is less reliable, however, for ring structures have been assigned to products from diazomethane in some instances (213, 236). The Fischer esterification procedure may lead to either tautomer or a mixture of the two (87, 103, 166, 212, 249, 250, 253, 297, 327) and thus is unsatisfactory for obtaining a pure tautomer or for estimating a tautomeric equilibrium.

A possible chemical method for estimating equilibria involves the abnormal behavior toward organocadmium reagents of certain aldehydoacids and ketoacids, which form lactones (152, 153). The methylcadmium reagent converts phthalaldehydic acid partially to 3-methylphthalide, while *o*-acetylbenzoic acid is unaffected under the same conditions.



Since carbonyl or acid functions do not ordinarily react with organocadmium compounds, it has been proposed that lactone formation involves only the ring tautomer. With this assumption, it would hold that the amount of lactone formed is a direct measure of the degree of ring tautomerism of the acid under the reaction conditions (provided equilibration of tautomers is slower than reaction with methylcadmium). Justification for this assumption comes from the observation that ring tautomers of known structure, such as "pseudo" esters, acid chlorides, and anhydrides, form lactones with organocadmium reagents (153). Recently it has been shown that mesitylmagnesium bromide effects a similar transformation of a "pseudo" ester (253).

The problem of structure determination is greatly simplified in dealing with one or both members of a tautomeric pair which are not readily interconvertible. Hence the structural assignment to stable derivatives of acids—esters and amides, for example—is often more straightforward than that to the parent acids. The method amounts to the qualitative identification of a second functional group present in the molecule. For example, the acyclic structure for the ethyl ester of phthalaldehydic acid was based on its positive reaction toward Tollens reagent, which was taken as evidence for the presence of an aldehyde group (274). Similarly, the formation of an oxime derivative was used to assign the chain structure to the anilide of *o*-phenylacetylbenzoic acid (97), and the ring structure for β-(*p*-bromobenzoyl)-β-methylacrylamide was assumed because it formed a methyl ether with methanolic hydrogen chloride (215).



(positive Tollens) (forms oxime) (forms methyl ether)

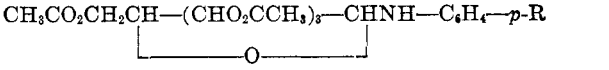
In some instances specific tests are available to identify a tautomer. The "formazan reaction"—coupling in pyridine with benzenediazonium salts to produce a red color—is diagnostic for a phenylhydrazone structure (—CH=NNHC$_6$H$_5$). It has been used to assign ring and chain structures to phenylhydrazones and phenylosazones of sugars (240, 241).

B. PHYSICAL METHODS

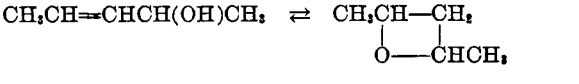
Since physical measurements can be performed on relatively undisturbed molecules, they would appear to be extremely valuable means of estimating ring-chain tautomer equilibria, particularly for those pairs which undergo rapid interconversion. Significant difficulties are often encountered in the use of physical methods and because of such problems and the recent innovation of some of the techniques, it has not been sufficiently exploited. There is little doubt, however, that physical measurements constitute a more reliable means of tautomeric structure determination than does the chemical approach.

1. Optical Activity

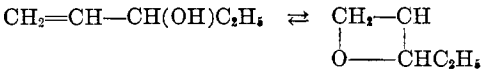
The classical investigations of ring-chain tautomerism in the sugars included as an important part the determination of optical rotation and, in particular, mutarotation. This is directly related to ring-chain tautomerism, of course, because the ring tautomer contains one more asymmetric carbon atom than does the chain tautomer; the former can always exist in two diastereomeric forms. A measure of the rate of mutarotation is thus dependent on the rate of tautomeric equilibration. This method has been extended to derivatives of sugars, notably tetraacetylglucosylanilines, which, because of similar behavior, are assumed to be ring tautomers (17, 20).



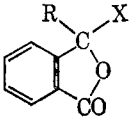
Mutarotation of simple, optically active compounds has been used as a diagnostic test for the presence of ring tautomer as, for example, in the case of 3-penten-2-ol (136). The fact that the (+) isomer



exhibited both mutarotation and an anomalous rotatory dispersion was attributed to equilibration with the ring tautomer, which contains a second asymmetric center. It is noteworthy that optically active 1-penten-3-ol, whose ring tautomer contains no additional asymmetric carbon, shows no such abnormalities. Considerable care must be exercised in the use of this method, since



a change in optical rotation might arise for other reasons: racemization, rearrangement, etc. It is interesting that ring tautomers of all derivatives of *o*-acylbenzoic acids contain an asymmetric carbon atom, but its presence has never been used for structure determination.



2. *Parachor*

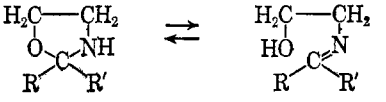
The parachor as a physical means of determining tautomeric structures has been employed in several instances, and this depends on the expected lowering of the value of the parachor with ring formation. Thus the experimental values for 3-penten-2-ol (228.9) and for 1-penten-3-ol (228.0) are considerably less than those calculated for the chain structure (238.2) and much nearer that (226.0) expected for the ring tautomer (136). Even cinnamyl alcohol has been assigned predominantly the ring structure on the basis of its parachor (136). The observed parachor for succinyl chloride is that calculated for the chain tautomer; in the case of phthaloyl chloride, the lower melting isomer has the higher parachor and is therefore assigned the chain structure while the higher melting dichloride is assumed to be the ring tautomer (105). This method was also reported as a means of assigning ring structures to early examples of valence tautomers in the phorones (145, 308). The recently introduced refrachor, related both to the parachor and refractive index, may be more useful in establishing ring-chain tautomerism, because the calculated difference between the two tautomers is much larger. It is a surprisingly accurate method for estimating keto–enol tautomerism in those cases already reported (157).

3. *Molar Volume*

A related measurement employed very early was the molar volume of a liquid. After a correction for the presence of a ring, it was found that the molar volume for succinyl chloride is intermediate between the calculated values for the chain and ring tautomers and, in fact, closer to the latter. Thus it was concluded that succinyl chloride is largely cyclic, contrary to the belief based on the parachor and more recent spectroscopic evidence (63). From the molar volumes of the acid chlorides of dichlorofumaric and dichloromaleic acids, it would be supposed that the latter is essentially, if not exclusively, the ring tautomer (256).

4. *Molecular Refractivity*

Because the molecular refractivity of a cyclic compound is expected to deviate from that of its chain tautomer, measurements of this property have been useful in establishing structures. An extensive list of observed exaltations for derivatives of *o*-acylbenzoic acids (both ring and chain tautomers) is available (12), but, unfortunately, values for the parent acids are lacking. In a more recent example, the equilibrium position for ring (oxazolidine) and chain (Schiff base) tautomers derived from ketones and ethanolamine was based on a comparison of the observed and calculated molecular refractivities (33).



5. *Polarography*

Polarographic determinations have been used to assign ring and chain structures as well as to calculate the rate of tautomerism. In an examination of amides of *o*-benzoylbenzoic acid in buffered and unbuffered tetrabutylammonium iodide at the dropping mercury electrode, ring and chain species were identified by characteristic half-wave potentials, and their relative concentrations estimated from the diffusion currents. The authors conclude that *o*-benzoylbenzamide is about 66% cyclic, the N-ethylamide is 100% cyclic, and the anilide is acyclic (329). There was no rigorous proof for the structure of the cyclic amides, however, and there is still considerable confusion over their constitutions. A similar study of esters in alkaline medium led to an assignment of a characteristic pH-independent half-wave potential to pseudo-esters (328).

Both glucose and 2-ketogulonic acid have been examined polarographically. Kinetics of the stepwise process of mutarotation of glucose was calculated on the assumption that only the chain tautomer undergoes reduction (201, 202).

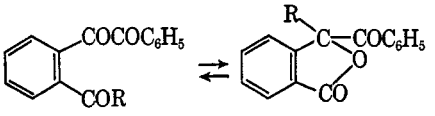
6. *Spectroscopy*

By far the most promising physical method for structure determination of ring-chain tautomers is the use of absorption spectra. It is invariably an un-

equivocal method of assigning constitution to an isolated, stable tautomer and will often be the method of measuring the equilibrium position of a pair of labile tautomers. To date structural studies have been based on visible, ultraviolet, and infrared spectra; use of the near-infrared region has not been worthwhile thus far. There is no doubt that these spectral regions will be increasingly valuable, and the method will certainly be extended to include nuclear magnetic resonance spectroscopy.

a. Visible and Ultraviolet

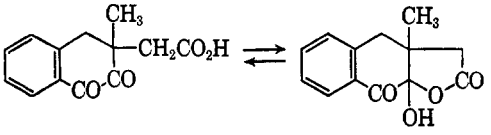
A very simple application of the use of visible spectra is to observe color changes in highly conjugated compounds. For example, benzil-*o*-carboxylic acid exists in two forms: one yellow and one colorless (111, 125, 291). Its derivatives are likewise either yellow or colorless. It is assumed that the yellow compounds possess the benzil chromophore and are, therefore, chain tautomers. On the basis of color, structures have been assigned to salts (125), acid chlorides (125), esters (111, 125, 291), and acetates (291), as well as to the acids themselves (125, 291).



(yellow) (colorless)

(R = OH, OCH_3, OC_2H_5, $OCOCH_3$, ONa, OAg, Cl)

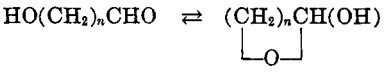
The appropriate structures were ascribed to the bicyclic ketoacid and tricyclic lactol—one yellow, the



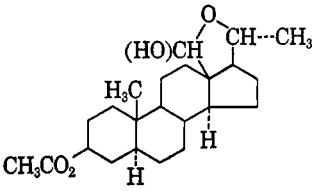
other colorless—by the same reasoning; and the appearance and disappearance of color with heating was taken as evidence for the reversibility of the rearrangement (170).

This dependence of color on structure is most striking with indicators such as fluorescein, rhodamine (83), phenolphthalein, phenolsuccinein, and phenolglutarein (84), where the chain tautomer is a quinoid and thus highly colored.

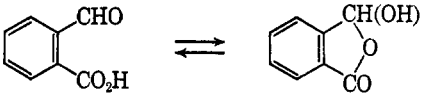
Although simple, unconjugated chromophores give rise to only weak absorption in the ultraviolet region, they can often be analyzed quantitatively. The position of the equilibrium between ω-hydroxyaldehydes and their ring tautomers was obtained by observing the absorption at 286–289 mμ (72, 142), the methyl ether, $CH_3O(CH_2)_nCHO$, being used as standard.



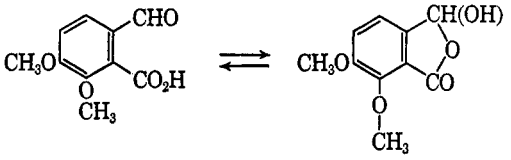
The fact that certain "aldehydo" steroids show no ultraviolet absorption above 200 mμ was taken as evidence that they possess the hemiacetal structure. An example is 3-β-acetoxy-20-β-hydroxy-5-α-pregnan-18-al hemiacetal (26).



Compounds with more highly conjugated systems are even more readily adaptable to ultraviolet analysis. The spectra of ring and chain forms of phthalaldehydic acid should be distinguishable, for example. Model



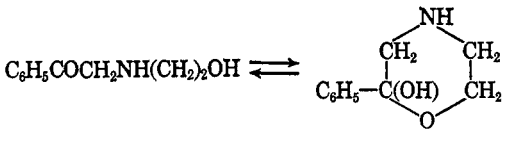
compounds used have been phthalaldehyde (62), phthalic acid (8), phthalide (333), and others. Difficulty in interpretation of the results stems from the complexity of the spectrum and the uncertainty of the effect on absorption of the hydroxyl function in the ring tautomer. Nevertheless, the equilibrium position has been estimated in several solvents from the ultraviolet spectrum (55). Numerous substituted phthalaldehydic acids, notably opianic acid, have been investigated as well.



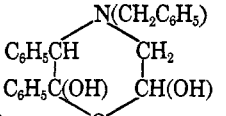
Opianic acid

Here a useful model compound has been 3-methoxymeconin, the pseudo methyl ester. It is concluded that the equilibrium mixture, although sensitive to the medium, usually consists predominantly of the ring isomer (57, 58). Phthalonic acids have been studied this way (54, 59), as has *o*-acetylbenzoic acid, which, it is suggested, is chiefly lactol in solution (333).

No such ambiguity interferes with analysis of various phenacylethanolamines, which are in equilibrium with the surprisingly stable, heterocyclic ring tautomers. A model for the chain tautomer, such as phenacyldibenzylamine, shows strong absorption; 240–250 mμ (ε 9000–13,000) (74, 114). The cyclic methyl ether



(ketal), on the other hand, as would be predicted for the ring tautomer, exhibits weak absorption at about the same wave length (ε 300–500) (74). The compositions of a large number of aminoketones of this family, examined by comparison with model compounds, were shown to vary considerably. The stability of tautomers is highly dependent on substituents on the nitrogen, the aromatic ring, and on the carbon atoms adjacent to the nitrogen (74, 114, 219, 224, 228). An interesting case arose with the ethylacetal and hydrate shown below. Acyclic and cyclic structures, respectively,



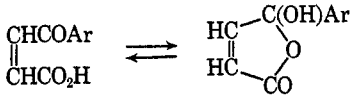
$C_6H_5COCH(C_6H_5)N(CH_2C_6H_5)CH_2CH(OC_2H_5)_2$

were ascribed to these two on the basis of their ultraviolet absorption. The acetal showed a maximum at 240–250 mμ (ε 12,500), while the hydrate had no significant absorption in the ultraviolet region (222). Similarly, strong absorption at 250 mμ was the reason for assigning the chain structure to the chloro compound (205).

$$C_6H_5COCH_2NH(CH_2)_2Cl$$

Some other compounds whose structural assignments depend on ultraviolet spectroscopy are lycorenine, a ring tautomer (162), tetraphenylpyrilium pseudo bases (36), various anils (340), indole ozonides (337, 338), 2-pyridones (275), penicillic acid (295), and phthalyl chloride (289).

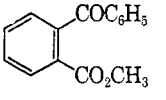
In every case the spectral interpretation is based on comparison with model compounds. Model compounds are not so easily available when one is examining more highly conjugated systems, as for example, the β-aroylacrylic acids. If the *trans*-(aroyl, carboxyl) acid is known, it is a most useful model for the



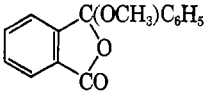
chain tautomer. Because acid salts are generally acyclic, a determination of the ultraviolet spectrum in alkaline solution is also an approximate measure of absorption by the chain tautomer. Cyclic derivatives, if attainable and of unquestioned structure, can serve as models for the ring tautomer. A case in point is α-methyl-α-benzoylacrylic acid (221). The *trans*-(benzoyl, carboxyl) isomer absorbs at 258–262 mμ (ε 13,500) in both ethanol and alkali. The *cis* isomer shows very low absorption in ethanol (267 mμ, ε 2000), but in alkali its spectrum is comparable to that of the *trans* acid. Thus, it was concluded that the *cis* acid is largely cyclic in ethanol. A large number of similarly substituted acrylic acids have been examined, and in cases where both tautomers contribute significantly to the equilibrium mixture, comparisons are made both in strong acid and strong alkali (51, 227, 229).

b. Infrared

Identification of tautomers is more generally accomplished from infrared spectra than from ultraviolet spectra, since the former does not depend on a conjugated chromophore. Invaluable for assigning a structure to a pure tautomer, the use of infrared spectroscopy involves identification of functional groups from their characteristic absorption bands, and it is undoubtedly the most reliable method for ascertaining the structure of a pure tautomer which does not rearrange during measurement of the spectrum. Thus, the normal methyl ester of *o*-benzoylbenzoic acid in carbon disulfide exhibits two carbonyl bands at 1724 cm.$^{-1}$ and 1667 cm.$^{-1}$ (ester and ketone, respectively), while the spectrum of the pseudo ester contains only one lactone carbonyl band at 1754 cm.$^{-1}$ (252). In a similar way, a large number of derivatives of ketoacids



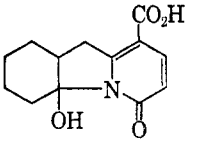
(1724, 1667 cm.$^{-1}$)



(1754 cm.$^{-1}$)

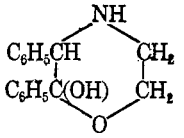
and aldehydoacids have been assigned structures, which, for the most part, are ring tautomers (107, 120, 122, 139, 152, 153, 227, 229, 252, 332).

Aldosterone was assigned the hemiacetal structure because of the absence of an aldehyde carbonyl band; the two carbonyl bands present, at 1706 and 1672 cm.$^{-1}$, were assigned to ester and ketone functions, respectively (300). Similarly, the lack of carbonyl absorption in the infrared spectrum of tazettine was used to identify this alkaloid as a ring tautomer (143). The ring structure below—like that in the strychnine alkaloids—is preferred over the chain isomer (a ketopyridone) because of absorption typical of hydroxyl

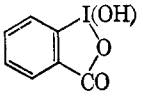


and pyridone groups (275). The interpretation is subject to question, however, because of broad absorption at 3125–2500 cm.$^{-1}$, which is most probably ascribed to an N—H group.

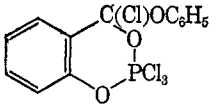
Often the absence of absorption is taken as evidence for a structure. Certain N-phenylacylethanolamines, such as the one from desoxybenzoin, are considered cyclic because there is no absorption around 1670



cm.$^{-1}$, typical of a conjugated ketone (228). Likewise the reason for suggesting a cyclic structure (among others) for *o*-iodosobenzoic acid is the lack of bands attributable to the carboxyl function (30). Since no

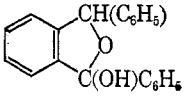


ester carbonyl absorption appears in the spectrum of the product from phenyl salicylate and phosphorus pentachloride, it was assigned the ring structure (263). Structures of other similar phosphorus compounds are based on infrared spectra (265).



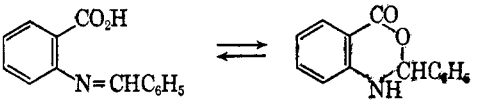
The spectrum of succinyl chloride in carbon tetrachloride contains one carbonyl band at 1786 cm.$^{-1}$, consistent with the chain structure; while γ-lactone carbonyl absorption would be expected at a somewhat lower frequency, the difference is not large enough so as to exclude the possibility of ring tautomer. The apparent intensity of the carbonyl band, based on two functions per molecule, is closely comparable to the apparent carbonyl intensity of a simple acid chloride. Although not an unequivocal proof, this information is strongly suggestive of the chain tautomer (63). Glutaryl chloride, with a similar carbonyl infrared absorption, is assumed to be acyclic (65). Levulinyl chloride, on the contrary, is cyclic (63).

Doubtless a large number of compounds reported before the advent of modern spectroscopy could be identified by their infrared spectra. 1-Hydroxy-1,3-diphenylphthalan and other similar compounds (123,

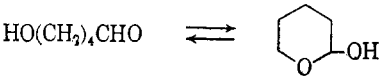


169) were formulated as the products from a Grignard reaction but with little or no supporting evidence. Their spectra would likely serve effectively to affirm or reject the structures.

On a qualitative or, at best, semiquantitative basis, infrared spectroscopy can be used to detect one or both members of a mobile tautomeric pair. In the infrared spectrum of benzalanthranilic acid in carbon tetrachloride, for instance, there is absorption attributable both to the carboxyl and to NH. For this



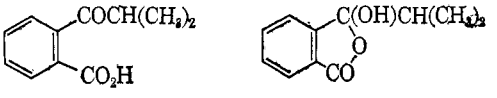
reason it was considered to be a mixture of tautomers (302). Oxazolidine–Schiff base mixtures have been estimated qualitatively by the relative intensities of infrared bands due to —NH, C=N, and OH functions (32). It was concluded that 5-hydroxypentanal contains appreciable amounts of the ring tautomer, 2-hydroxytetrahydropyran, because of the appearance of absorption bands characteristic of hydroxyl and aldehyde groups and also of the pyran ring (72).



Analysis from infrared spectra has been carried out in a semiquantitative manner with β-aroylacrylic acids. This was effected by observing the ratio of transmittances at 1695 cm.$^{-1}$ (ketone in the chain tautomer) and at 1754 cm.$^{-1}$ (lactone carbonyl in the ring tautomer) in the chloroform spectrum of β-(*p*-bromobenzoyl)-β-bromoacrylic acid, for example (229). Results are highly sensitive to the solvent.

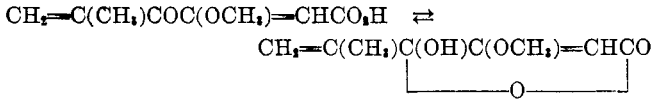
Acids and their derivatives capable of ring-chain tautomerism often exhibit complex infrared spectra, which may be interpreted in more than one way. This is the case with the spectrum (in Nujol) of phthalaldehydic acid, which contains bands at 3322, 1755, and 1745 cm.$^{-1}$ (332). It was concluded that the acid is primarily cyclic (lactol), because of the presence of the hydroxyl band, but no adequate explanation was offered for an extraneous carbonyl band. Different values for the Nujol spectrum were reported from another laboratory (120) but interpreted in the same way. Here the single carbonyl band at 1738 cm.$^{-1}$ was assigned to lactone, although this is a low value for a typical unsaturated γ-lactone (82, 121, 137). *o*-Acetylbenzoic acid, on the other hand, whose spectrum in Nujol (122) (and in solution, as well (152)) resembles that of phthalaldehydic acid, has been assigned the chain (152) and ring (266) structure by varying the interpretation of the spectrum.

That the infrared spectra of ketoacids are sensitive to medium and difficult to interpret is shown with *o*-isobutyrylbenzoic acid (or 3-hydroxy-3-isopropylphthalide) (187). As a solid in potassium bromide, it exhibits infrared bands at 3333 cm.$^{-1}$ (OH) and 1739



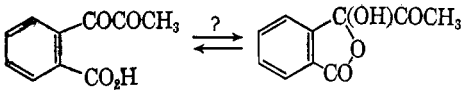
cm.$^{-1}$ (lactone carbonyl?), and so it was assigned the ring structure. In chloroform solution, however, there is no typical hydroxyl absorption, and the lone car-

bonyl band appears at about 1770 cm.$^{-1}$. The lack of an hydroxyl band would suggest the chain tautomer, but an explanation, not readily apparent, would be required for the presence of only one carbonyl band at an abnormally high frequency for either a ketone or acid function. The spectra of the two isolable forms of penicillic acid are unusual; the chain isomer shows no ketone carbonyl absorption, and the lactone carbonyl band in the lactol is unusually low at 1738 cm.$^{-1}$. No values were given for the hydroxyl region (248).



Penicillic acid

Because of the difficulty in interpreting infrared spectra of tautomeric acids, it is necessary to exercise caution in assigning structures. The report, for example, that the acid below exists as the cyclic tautomer is open to question, since no experimental results are



included to support the assignment (35). With the accumulation of a much larger number of spectra, it is possible that a consistent correlation of structure and absorption will evolve.

c. Other

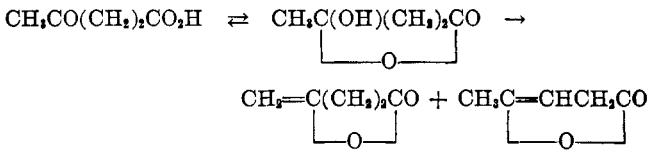
The reported use of Raman measurements is very sparse, but it is equally as effective as infrared absorption, for example, in determining the structures of *o*-benzoylbenzoic acid derivatives (168). Raman displacements at 1715 cm.$^{-1}$ have been employed to obtain thermodynamic data on the acetoacetic ester equilibrium (318). There is no reason to believe it might not be adaptable to the study of ring-chain tautomeric equilibria as well.

Nuclear magnetic reasonance spectroscopy appears as a most effective method for ring-chain structure determination, although its use for this purpose has apparently not been reported to date. The n.m.r. spectra of 3-methoxyphthalide, 3-phenoxyphthalide, and 3-acetoxyphthalide, as determined in deuteriochloroform, are consistent with the ring structure (154); interpretation of the spectra of phthalaldehydic acid and *o*-acetylbenzoic acid (in perdeuterioacetone) are less straightforward, but it is clear that each is partially if not wholly cyclic (154). Classical keto–enol tautomerism has been investigated quantitatively from n.m.r. spectra. The equilibrium values for acetylacetone (146, 277) and, more recently, for oxaloacetic acid, diethyl oxaloacetate, and diethylfluorooxaloacetate (177) are undoubtedly the most reliable obtained by any method. Tautomeric equilibria in pyridones have been examined by comparing n.m.r. spectra with those of model compounds (156). It is hoped that the method will be utilized much more extensively in the future for ring-chain tautomerism.

V. USE OF RING-CHAIN TAUTOMERISM TO EXPLAIN CHEMICAL BEHAVIOR

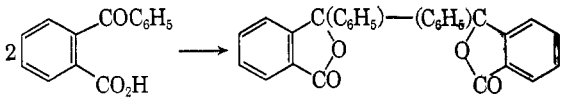
The identification of ring and chain tautomers and an understanding of their properties are of value for rationalizing chemical behavior in many cases which might otherwise remain unexplained. Notably any reaction which proceeds with ring opening or cyclization is one potentially involving ring-chain tautomerism, providing the starting materials and products are appropriately constituted. It is, of course, not the only tenable explanation for the course of all such transformations, and the use of this phenomenon should be considered only in the absence of compelling evidence in favor of an alternative rationale.

Few instances of appropriate ring opening reactions are at hand, but there are a number of examples of ring closures, in which the mechanism is open to discussion. In the dehydration of levulinic acid to a mixture of α- and β-angelicalactone, it was suggested as early as 1886 that only the ring tautomer undergoes elimination (50). The preferential reactivity of

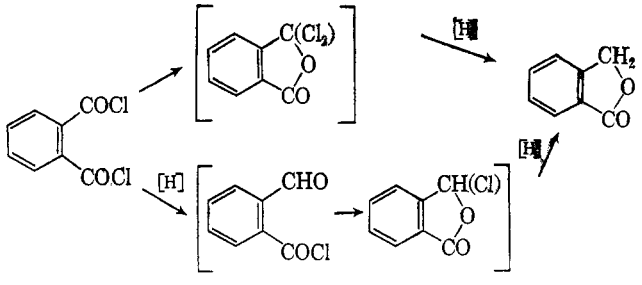


enolic tautomers is now well known in reactions such as the acid-catalyzed halogenation of ketones.

The reductive coupling of *o*-benzoylbenzoic acid with phosphorus and hydriodic acid might involve inital formation of the lactol or some other ring tautomer, for example the pseudo acyl iodide (321).

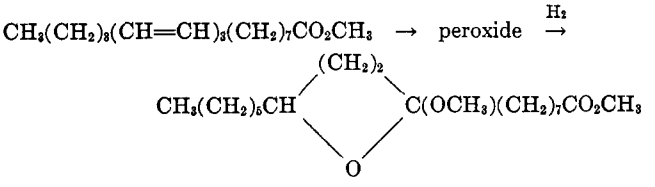


A reduction recently reported involving ring formation is that of *sym*-phthaloyl chloride to phthalide with dibutyltin hydride (176). Phthalide could conceiv-

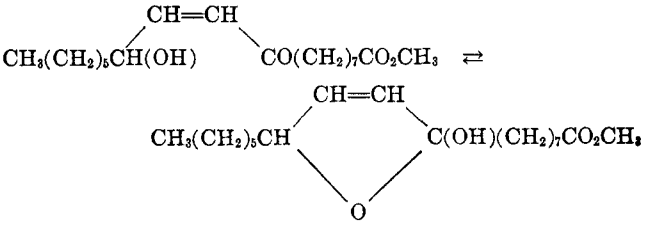


ably arise by tautomerism of the acid chloride to 3,3-dichlorophthalide, which would undergo reduction, or the initial reduction product, 2-formylbenzoyl chloride, might rearrange to its ring tautomer before the second reductive step.

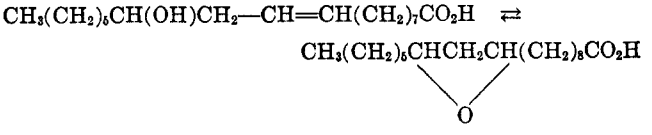
The peroxide from methyl eleostearate, after hydrogenation, gives rise to a mixture of products, including a pseudo methyl ester. To rationalize its formation from an acyclic precursor, it was suggested



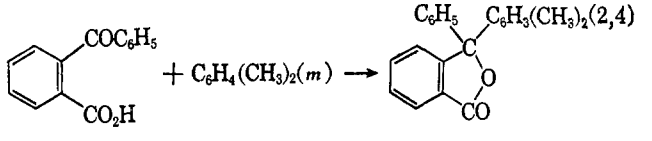
that, during the reduction, the following ring-chain tautomerism occurs (319).



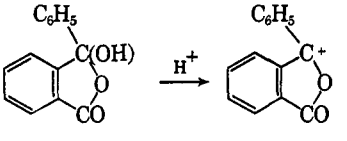
The related compound, ricinoleic acid, was designated as a tautomeric mixture because some of its degradation products were much more readily explained from the ring tautomer (24).



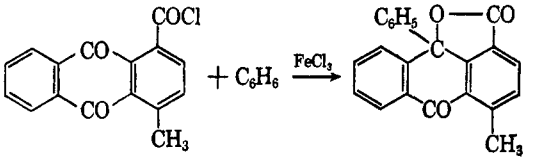
Certain acylations may involve cyclization through a ring tautomer. The formation of 3-phenyl-3-*m*-xylylphthalide from *o*-benzoylbenzoic acid and *m*-xylene, which is catalyzed by perchloric acid (52, 53, 66), is an example. Since 3-phenylphthalyl carbonium ion



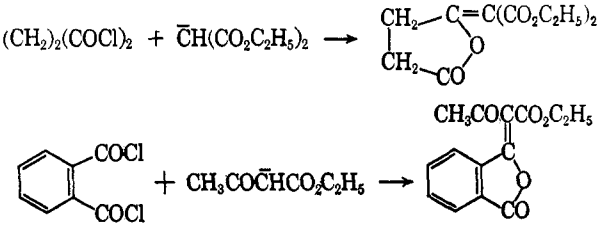
has been proposed as an intermediate, its immediate precursor would most likely be the lactol acid.



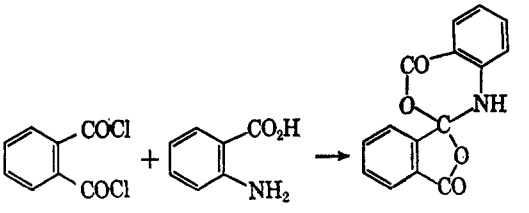
Similarly, participation of cyclic acid chloride is strongly implied in the Friedel–Crafts acylation of benzene with 4-methylanthraquinone-1-carbonyl chloride; in addition to the expected product, 1-benzoyl-4-methylanthraquinone, the major product is a lactone (293).



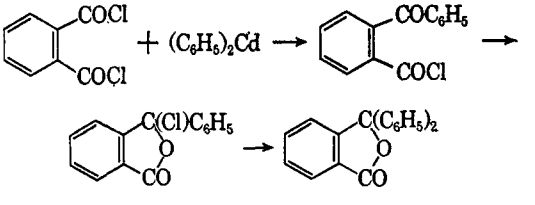
Both succinyl chloride (286) and liquid phthaloyl chloride (287) react with active methylene compounds to form lactones instead of the expected ketones. It is highly likely that tautomerism to cyclic intermediates is occurring, because, from all evidence, the starting materials are acyclic in each case. The same explanation holds for the formation of a spiro compound from



phthaloyl chloride and anthranilic acid (159).



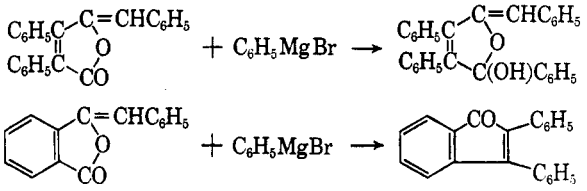
Acyclic phthaloyl chloride also forms a lactone with diphenylcadmium (93). The initial product is most likely *o*-benzoylbenzoyl chloride, which is known only in the ring tautomeric form. That this cyclic acid chloride is an intermediate in formation of the lactone is supported by the observation that it, too, is converted to 3,3-diphenylphthalide under similar conditions (155).



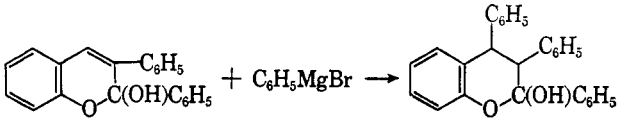
The acid chloride from 8-benzoyl-1-naphthoic acid, undoubtedly the ring tautomer, also leads to lactones with organocadmium reagents (254). Cason and Reist have reported products from succinyl chloride and glutaryl chloride and the ethylcadmium reagent, which are rationalized on the basis of intermediate ring-chain tautomeric equilibria (64, 65).

Grignard reagents lead to ring tautomers directly

in some cases; one is the formation of hemiketal from phenylmagnesium bromide and the lactone derived from diphenylmaleic anhydride (203). Its analog, 3-benzalphthalide, suffers rearrangement to 2,3-di-

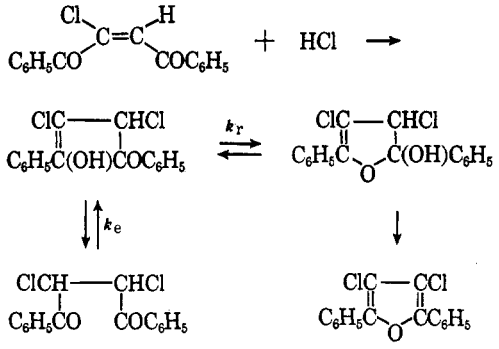


phenylindenone with the same Grignard reagent, but the corresponding hemiketal might very likely be isolable under properly chosen conditions. A Grignard reaction of particular interest is that where one ring tautomer is converted to another: transformation of a chromenol to a chromanol (106). The addition of



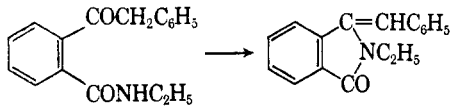
phenylmagnesium bromide probably takes place with a magnesium complex of the chromenol chain tautomer (a phenyl styryl ketone). The two methyl esters of 2-benzoyl-1-naphthoic acid—ring and chain tautomers—were found to behave differently toward methylmagnesium iodide. One formed lactone; the other was apparently unreactive and so was assigned the ring structure. Since it has been shown more recently, however, that pseudo esters of this type are reactive both toward Grignard (253) and cadmium (153) reagents, an alternative explanation may be correct.

Cyclization of 1,2-dibenzoylethylenes to furans is another example where ring-chain tautomerism has been used to explain the products (220). This has been suggested by Lutz in the formation of 1,4-diphenyl-2,3-dichlorofuran and 1,2-dichloro-1,2-dibenzoylethane from 1,2-dibenzoyl-1-chloroethylene and hydrogen chloride.



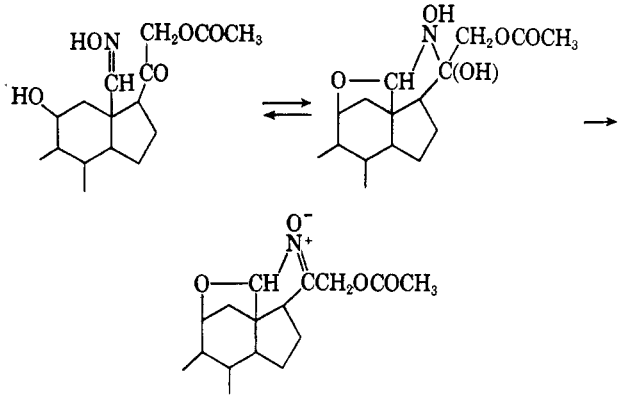
The equilibria k_r and k_e constitute ring-chain tautomerism and the usual keto–enol tautomerism in competition with one another, since the "chain" tautomer and "enol" are one and the same structure. On the basis of product ratios under different conditions, it was concluded that the former equilibrium is favored at room temperature while the latter is predominant at 0° (225).

Ring closure to nitrogen heterocycles may involve a similar mechanism. An example is cyclization of *o*-phenylacetyl-N-ethylbenzamide to the lactam by dehydration (99), and other similar amides behave in



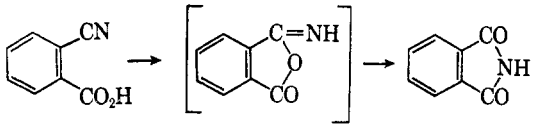
the same way (70, 100). Support for the importance of the ring tautomers here comes from observations on the difference in properties of amides and anhydrides of succinic and phthalic acids. In reactions with amines (315, 316) or anils (204), the succinic acid derivatives invariably form acyclic products, while those from phthalic acid lead to cyclic compounds. Saturated ring tautomers, such as those from succinic acid, are generally much less stable than unsaturated tautomers (part III).

The recent explanation (27) for formation of a nitrone from aldosterone-21-acetate oxime was participation of the ring tautomer shown, which can be visualized as arising from two consecutive ring-chain

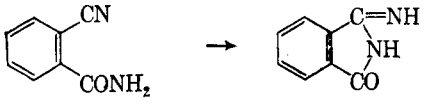


tautomeric equilibria.

Because of the close relationship between tautomerism and rearrangements, which are sometimes indistinguishable, it is apparent that certain molecular rearrangements may be explained by ring-chain tautomeric equilibria. An instance of considerable interest is the well known rearrangement with heat of *o*-cyanobenzoic acid to phthalimide (4, 78); the two are isomers but not tautomers. The "electrophilic"

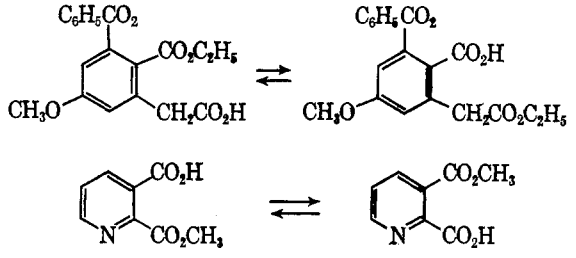


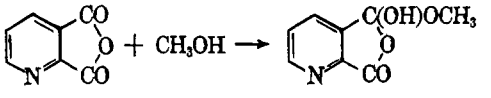
ring tautomer, an iminophthalide, may well be the structure undergoing rearrangement, however. This is suggested because *o*-cyanobenzamide is pyrolized to the iminolactam (49); a similar rearrangement takes



place with the phthalan shown below (307).

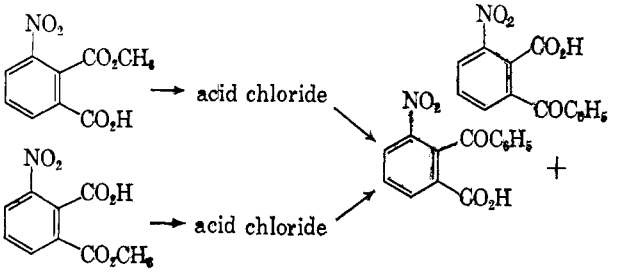
Reversible functional exchange in acid esters is a striking example of a rearrangement very likely occurring with tautomerism. It has been observed with a homophthalic acid (5) and a pyridine-2,3-dicarboxylic acid (160) pair. A cyclization mechanism is particularly attractive because it has been shown in the latter case that the rearrangement of esters of optically active alcohols proceeds with retention of configuration. A ring tautomer has been suggested as the initial product from methanol and pyridine-2,3-dicarboxylic anhydride; it then isomerizes to the two acid esters (160).



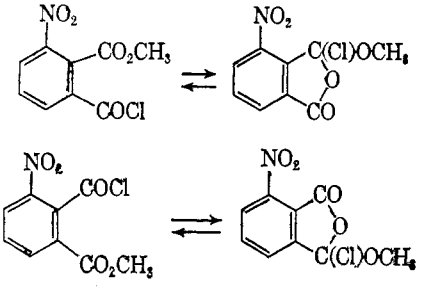


Some closely allied rearrangements are an ester exchange (148) and the acyl migration of glyceryl esters (133, 134) and of acyl derivatives of salicylamides (232). In each case ring-chain tautomerism seems to play an important role, as, indeed, it may in certain nucleophilic reactions of carboxylic acid derivatives leading to anhydrides (31).

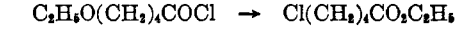
Considerable attention has been given to the rearrangement of acid chlorides of half-esters of dibasic acids (69, 128, 288, 303), where the positions of the two functional groups are interchanged. The ring tautomer has been suggested as an intermediate in these interchanges (128, 288). An example of synthetic importance involves the two monomethyl esters of 3-nitrophthalic acid (69). Friedel–Crafts acylation of benzene with the acid chloride from either half-ester leads to the same mixture of ketoacids. This mixture of



products is readily explicable if it is assumed that the acid chlorides are tautomeric mixtures. The ring tautomers might rearrange to the isomeric acyclic acid chlorides, or they might react directly with benzene to form pseudo esters, which would subsequently be hydrolyzed.



In the rearrangement of 5-ethoxypentanoyl chloride by heat to the isomeric chloroester, an oxonium intermediate was suggested (267); a ring tautomer similar to those above seems highly likely.

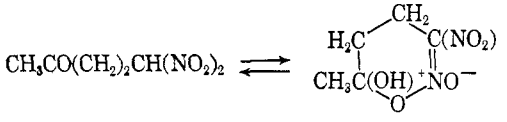


The equilibrium mixture of dibenzoylstilbene in base is unusually rich in the *cis* isomer, and this has been explained by a stabilization of the *cis*-hydrate through formation of a ring tautomer, the cyclic hemiketal (230). On the other hand, it has been concluded from kinetic measurements that in the base-catalyzed rearrangement of benzil-*o*-carboxylic acid, only the chain tautomer is participating (331).

Beside being used to explain unusual reaction products or rearrangements, ring-chain tautomerism can be a convenient rationalization for the unexpected stability or reactivity of various compounds. *o*-Acetylbenzoyl chloride, for example, is peculiarly unreactive. Attempts to convert it to *o*-diacetylbenzene by a malonic ester condensation or to *o*-acetylbenzaldehyde by a Rosenmund reduction have failed (280). Its reaction with amines to form amides has resulted in failure or very low conversions (124, 158, 276). This behavior is actually to be expected if one considers that the acid chloride, prepared in each case with thionyl chloride, is undoubtedly cyclic, and ring tautomeric acid chlorides invariably lead to cyclic products rather than those intended in the pre-

parative attempts. It is interesting that, in none of the reports was the acid chloride or product considered to be cyclic. An amide of *o*-acetylbenzoic acid has been obtained in some attempts, but its structure is highly questionable (124, 158, 276, 280). It decomposes spontaneously (276), a fact suggesting the chain structure is incorrect. Its spectral properties have not been reported.

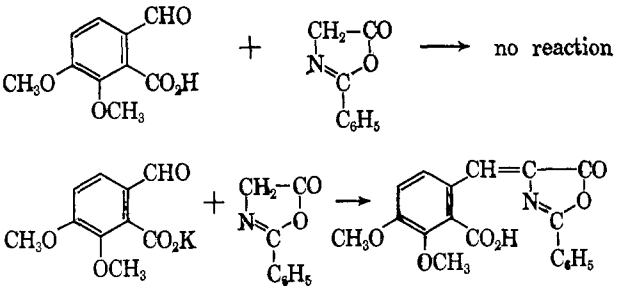
trans-Dibenzoylstilbene is stable toward lithium aluminum hydride, sodium borohydride, and aluminum isopropoxide, while the *cis* isomer undergoes reductive cyclization with all three reagents. It was proposed that a ring-chain tautomeric equilibrium, possible only with the *cis* compound, is responsible for the difference in reactivity (223). The surprising resistance of 5,5-dinitro-2-pentanone to reduction with sodium borohydride was ascribed to its ability to exist as a ring tautomer (296). This is supported by the contrasting behavior of 5,5-dinitro-2-hexanone and 4,4-dinitropentanal, which are readily reducible and



structurally incapable of forming an analogous ring tautomer. An alternative ring structure, involving addition of enolic hydrogen to the nitro group, could be written for all three. The presence of a ring tautomer may explain a difference in reactivity toward lithium N-dihydropyridylaluminum hydride, a selective reducing reagent. Conversion of *o*-benzoylbenzoic acid to 3-phenylphthalide is considerably more extensive than that of the methyl ester (183). Although alternative rationalizations are at hand, the possibility exists that the ester is, in fact, a tautomeric mixture and that the ring tautomer is less easily reduced.

This is the case with N-phenacylethanolamines and aluminum isopropoxide. The cyclic tautomers are unreactive, while the chain tautomers are readily reduced to aminodiols (216, 218). It is interesting that the ring isomers are reducible with sodium isopropoxide, however; this can be explained by the greater reducing power of the sodium reagent or by its effect on the ring-chain equilibrium (228).

The failure of opianic acid to undergo the Erlenmeyer azlactone synthesis may be attributed to its lactol structure. With hippuric acid and acetic anhydride it is converted to lactol acetate, and attempts to condense it with 2-phenyl-5-oxazolone have failed. The potassium salt, however, which undoubtedly exists as the chain tautomer, reacts readily with 2-phenyl-5-oxazolone to form the azlactone.



Potassium phthalaldehydate similarly forms the azlactone (278).

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