

Advances in Heterocyclic Chemistry

By A. R. KATRITZKY

Volume 2

Advances in
HETEROCYCLIC
CHEMISTRY

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Preface

The continuing rapid advance of knowledge in the heterocyclic field explains the publication of the present book so rapidly after the first volume of the series. The reviews in these volumes fall into two categories—those dealing with a particular ring system or group of ring systems (isoxazoles, selenazoles, oxazines, quinoxalines, three-membered rings with two hetero atoms) and those covering a type of reaction or a chemical or physical property. Previous publications on heterocyclic chemistry have been mainly concerned with the first type, i.e., all the topics mentioned (except the novel three-membered rings). It is our policy to make reference to previous reviews and then to concentrate on the subsequent literature, giving older references only for special reasons.

Reviews dealing with a specific reaction or property from the heterocyclic point of view have been rarer—tautomerism (continued from Volume 1), free radical substitution, metal catalysts and pyridines, acid-catalyzed polymerization of pyrroles, and diazomethane reactions have been covered in this volume.

It is planned to publish Volumes 3 and 4 of this series early and late in 1964, respectively. Suggestions for contributions to further volumes will be welcomed; they should be in the form of a short synopsis.

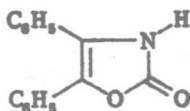
I would like to thank the authors of the reviews for their cooperation, the members of the Editorial Board, the publishers, and, especially, the assistant editors Dr. A. J. Boulton and Dr. J. M. Lagowski.

A. R. KATRITZKY

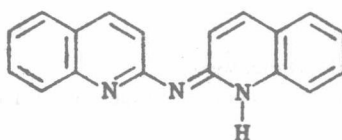
Norwich, England
June 1963

ERRATA

In Volume 1, in the chapters on Prototropic Tautomerism by
A. R. Katritzky and J. M. Lagowski,
p. 333, formula (53) should be



p. 342, line 1 of Section A, α,γ -Dihydroxy- should read α - and
 γ -Hydroxy-
p. 410, formula (239) should be



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Prototropic Tautomerism of Heteroaromatic Compounds: III. Five-Membered Rings and One Hetero Atom*

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J. M. LAGOWSKI

Genetics Foundation, The University of Texas, Austin, Texas

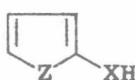
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The most important potentially tautomeric thiophenes and furans are those carrying hydroxyl, mercapto, and amino groups. In these compounds a prototropic shift can occur between the functional group

*The first two chapters in this volume conclude the series of four articles on prototropic tautomerism; the first two articles appeared in Volume 1. Cross references to these articles include, for easy identification, the roman numeral given in the title.

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and a ring carbon atom, cf. type *ii* described in Volume 1, Section I,A, of article I by Katritzky and Lagowski. A single functional group in the α -position gives rise to three possible tautomeric structures, 1-3, whereas two structures, 4 and 5, are possible with one functional group in the β -position. Similar structures are possible for the analogous pyrroles, but pyrroles which do not carry a substituent on the hetero nitrogen atom can undergo additional types of tautomerism (see later). The proportion of the various forms present at equilibrium is dependent upon their relative stability. Forms 1 and 4 are "aromatic," and, since the aromatic stabilization decreases in the order thiophene > pyrrole > furan, forms of this type would be expected to be the most favored for thiophenes. The nonaromatic forms are, however, also mesomeric as indicated by curly arrows in 2, 3, and 5.



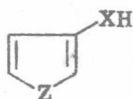
[1]



[2]



[3]



[4]



[5]

Systems 2 and 3 are cross-conjugated, but 5 is not, and it might have been expected that α -substituted compounds would be more prone to exist in the aromatic form 1 than the β -compounds to exist as 4. From the limited evidence available, the reverse appears to be the case. When the hetero atom is not a very strong electron donor, i.e., $Z = S$ or O , structure 3 would be expected to be relatively more stable than 2, and this is supported by the evidence available. When $Z = NR$, the difference in the stabilities of 2 and 3 could be smaller.

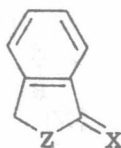
The nature of the substituent group X plays an important role in determining the relative stability of the various tautomeric forms. In aliphatic systems the tendency of $:C=\dot{C}-XH$ to become $:CH-\dot{C}=X$ increases markedly in the order $X = CH_2 < NH < O$, and certainly hydroxy compounds show less inclination to exist as such than do amino compounds. The position of S in this series is not completely

clear (see discussion in Section III of article II, Volume 1); however, the thione-thiol equilibrium $6 \rightleftharpoons 7$ appears to be more in favor of 7 than in the case of the corresponding keto-enol equilibrium.¹ In agreement with this contention, mercaptothiophenes are more stable than the hydroxythiophenes (discussed later).

Electron-withdrawing substituents stabilize the aromatic forms 1 and 4, as would be expected, by acting as an "electron sink" and by forming intramolecular hydrogen bonds with the XH group when this is sterically possible. On the other hand, a benzene ring fused in the 3,4-position greatly stabilizes 8 as compared to 9. The effect of a benzene ring fused in the 4,5-position is smaller, but probably also causes some preferential stabilization of the nonaromatic forms corresponding to 2 and 5.

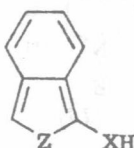


[6]



[8]

[7]



[9]

I. Tautomerism of Pyrroles Not Involving the Functional Group

The tautomeric forms 11 and 12, called pyrrolenines, have often been postulated for pyrrole (10), but there is no conclusive evidence for their existence.² The report³ that two isomers exist as the pyrrolenine forms 13 and 14 (Ar = 3,4-dimethoxyphenyl) must be regarded with considerable doubt.

Chemical evidence led to the conclusion that the conjugate acids of pyrrole probably exist predominantly as 16 or 17 rather than as 15.^{2,4,5} Although infrared spectra were initially interpreted on the

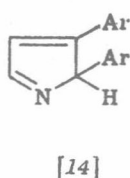
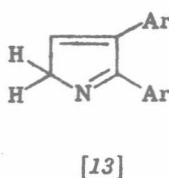
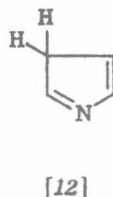
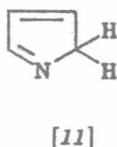
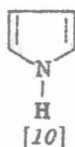
¹ Z. Reyes and R. M. Silverstein, *J. Am. Chem. Soc.* **80**, 6367 (1958).

² A. Treibs and G. Fritz, *Ann. Chem. Liebigs* **611**, 162 (1958).

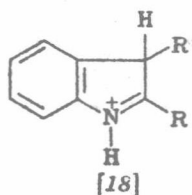
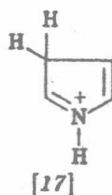
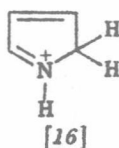
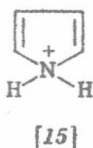
³ D. A. Guthrie, A. W. Frank, and C. B. Purves, *Can. J. Chem.* **33**, 729 (1955).

⁴ A. Treibs and K. H. Michl, *Ann. Chem. Liebigs* **577**, 129 (1952).

⁵ A. Treibs and A. Ohorodnik, *Ann. Chem. Liebigs* **611**, 139 (1958).

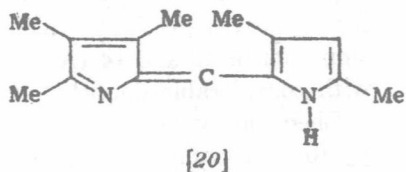
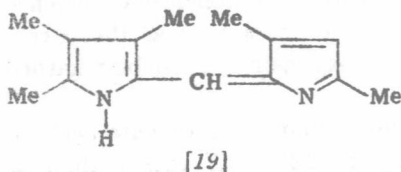


basis of structure 15,⁶ nuclear magnetic resonance spectra later proved that structures of type 16 were favored in solution.⁷ Similarly, ultraviolet⁸ and nuclear magnetic resonance spectra⁹ and basicity measurements^{9a} show that indole cations are formed by protonation at the



β -position to give 18, substantiating the postulation which had been offered earlier on theoretical grounds.⁵

Dipyrromethenes rapidly exchange the hydrogen atom attached to nitrogen, and the two isomers of unsymmetrical compounds (e.g., 19 and 20) cannot be separately isolated.¹⁰ Dipyrromethenes form meso-



⁶ E. Bullock, *Can. J. Chem.* **36**, 1686 (1958).

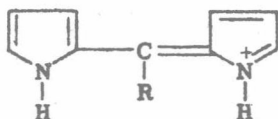
⁷ R. J. Abraham, E. Bullock, and S. S. Mitra, *Can. J. Chem.* **37**, 1859 (1959).

⁸ M. J. Kamlet and J. C. Dacons, *J. Org. Chem.* **26**, 220 (1961).

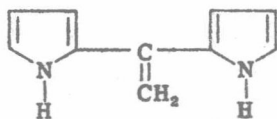
⁹ R. L. Hinnar and J. Lang, *Tetrahedron Letters* No. 21, 12 (1960).

^{9a} G. Berti, A. Da Settimo, and D. Segnini, *Gazz. chim. ital.* **91**, 571 (1961).

¹⁰ H. Fischer and B. Walach, *Ann. Chem. Liebigs* **450**, 109 (1926).



[21]



[22]

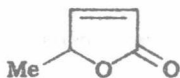
meric cations (cf. 21) by proton addition at nitrogen,⁵ whereas olefinic derivatives such as 22 undergo proton addition on carbon.

II. Compounds with a Potential Hydroxyl Group

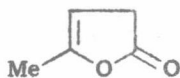
Heterocyclic compounds carrying hydroxyl groups may be compared with phenols. Thomson¹¹ has reviewed the tautomeric behavior of phenols; often both tautomeric forms of polycyclic compounds such as naphthols can be isolated. Early work on hydroxythiophenes and -furans was also reviewed by Thomson,¹¹ but until recently their chemistry has been in a somewhat confused state. A pattern is now beginning to emerge, at least for the α -substituted compounds, which appear to exist as Δ^3 -oxo derivatives and to attain equilibrium slowly with the corresponding Δ^4 -oxo forms. For the α -hydroxy compounds, the equilibrium generally favors the Δ^3 -oxo form.

A. HYDROXYFURANS

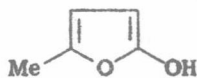
Unsaturated γ -lactones, e.g., α - (23) and β -angelica lactone (24), are well known. Compounds 23 and 24 are both converted by alkaline catalysts into an equilibrium mixture in which 23 predominates, the amount of the hydroxy form (25) present at equilibrium being exceedingly small. True α -hydroxyfurans are unknown, and, although the preparation of both α - and β -hydroxyfurans has been reported,^{12,13} these claims have often been refuted (see, e.g., reference 14).



[23]



[24]



[25]

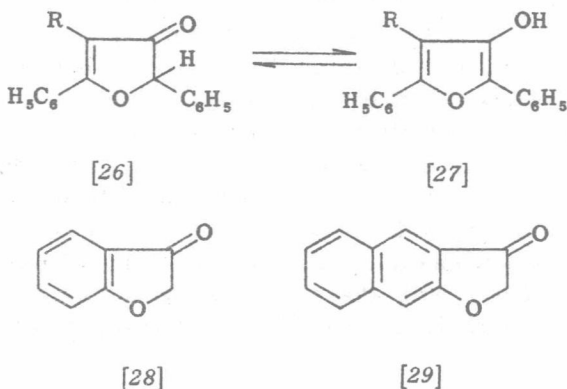
¹¹ R. H. Thomson, *Quart. Revs. (London)* 10, 27 (1956).

¹² H. H. Hodgson and R. R. Davies, *J. Chem. Soc.* p. 806 (1939).

¹³ H. H. Hodgson and R. R. Davies, *J. Chem. Soc.* p. 1013 (1939).

¹⁴ M. P. Cava, C. L. Wilson, and C. J. Williams, *J. Am. Chem. Soc.* 78, 2303 (1956).

Very little is known concerning the simple, monocyclic 3-hydroxyfurans (cf. reference 15). Both the oxo and hydroxy forms of the substituted 3-hydroxyfurans **26** and **27** ($R = H, C_6H_5$) have been isolated,^{16,17} but the individual tautomers slowly undergo interconversion. The enol forms give a positive reaction with ferric chloride, react rapidly with bromine, and form a peroxide with oxygen. From chemical evidence, the benzo derivatives of 3-hydroxyfuran, **28**¹⁸ and **29**,¹⁹ appear to exist predominantly in the oxo form, and this is further supported by ultraviolet spectral data.²⁰ Stefanye and Howard²¹



concluded from infrared spectroscopic data that 5,7-dichloro-3-hydroxybenzofuran exists in the oxo form, but that the hydroxy form of its 2-(5',7'-dichlorobenzofuryl) derivative, i.e., 3-hydroxy-5,5',7,7'-tetrachloro-2,3'-bibenzofuran, apparently predominates.

B. POTENTIAL DIHYDROXYFURANS

α -Keto- γ -lactones appear to exist in the dioxo form **30**,²² but enolization can occur when this leads to extended conjugation. The

¹⁵ E. Votoček and S. Malachta, *Collection Czechoslov. Chem. Commun.* **4**, 87 (1932).

¹⁶ E. P. Kohler, F. H. Westheimer, and M. Tishler, *J. Am. Chem. Soc.* **58**, 264 (1936).

¹⁷ E. P. Kohler and D. W. Woodward, *J. Am. Chem. Soc.* **58**, 1933 (1936).

¹⁸ K. v. Auwers and E. Auffenberg, *Ber. deut. chem. Ges.* **52**, 92 (1919).

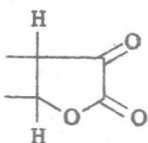
¹⁹ P. Emmott and R. Livingstone, *J. Chem. Soc.* p. 4629 (1958).

²⁰ Mme. Ramart-Lucas and M. van Cowenbergh, *Bull. soc. chim. France* p. 1381 (1935).

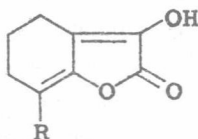
²¹ D. Stefanye and W. L. Howard, *J. Org. Chem.* **20**, 813 (1955).

²² Pl. A. Plattner and L. M. Jampolsky, *Helv. Chim. Acta* **26**, 687 (1943).

enol forms of **31** ($R = C_6H_5$) and **31** ($R = H$) have been shown to be predominant by chemical evidence²³ and by infrared spectral data,²⁴



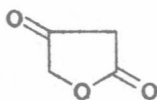
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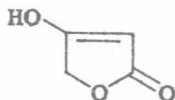
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respectively.

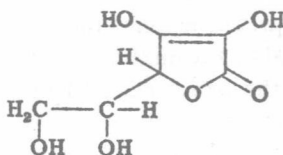
Tetronic acids exist predominantly in the dioxo form (**32**) in solvents of low polarity, while the existence of the mono-enol form (**33**) has been established in other solvents by infrared²⁵ and ultraviolet spectral comparisons²⁶ and from dipole moment data.²⁷ Haynes and Plimmer^{27a} have recently reviewed the structure of these compounds [see also reference 28(a)], and the tautomerism of vitamin A (**34**), which has a related structure, has also been surveyed.^{28(b)} Analogous compounds carrying an amino group in the 3-position are also known.^{28(c)}



[32]



[33]



[34]

Succinic anhydride (**35**, $Z = O$) can theoretically tautomerize to **36**, but all the evidence indicates that it exists overwhelmingly as **35**; for example, the infrared spectrum shows $\nu C=O$ bands.²⁹

²³ W. E. Bachmann, G. I. Fujimoto, and L. B. Wick, *J. Am. Chem. Soc.* **72**, 1995 (1950).

²⁴ L. Mangoni and M. Belardini, *Ann. chim. (Rome)* **50**, 322 (1960).

²⁵ L. A. Duncanson, *J. Chem. Soc.* p. 1207 (1953).

²⁶ E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.* p. 1419 (1949).

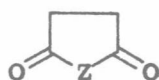
²⁷ W. D. Kumler, *J. Am. Chem. Soc.* **62**, 3292 (1940).

^{27a} L. J. Haynes and J. R. Plimmer, *Quart. Revs. (London)* **14**, 292 (1960).

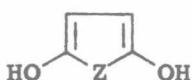
²⁸ H. von Euler and B. Eistert, "Chemie und Biochemie der Reduktone und Reduktonate," (a) p. 159, (b) p. 185, (c) p. 261. F. Enke, Stuttgart, Germany, 1957.

²⁹ H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangel, "Infrared Determination of Organic Structures." D. Van Nostrand, New York, 1949.

Infrared and nuclear magnetic resonance spectral evidence led Kendall and Hajos³⁰ to conclude that furan-3,4-dione (37) exists as such, which is surprising since cyclic α -diketones with five-membered rings are usually mono-enolized. The 2,5-dicarbethoxy derivative 38 was earlier stated to exist in the dihydroxy form.³¹



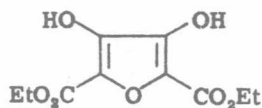
[35]



[36]



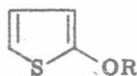
[37]



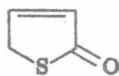
[38]

C. α -HYDROXYTHIOPHENES

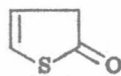
The infrared spectrum of 2-hydroxythiophene was originally interpreted as showing both ν OH and ν C=O peaks indicating that it exists as a mixture of the hydroxy form 39 ($R = H$) and at least one of the oxo forms, 40 and/or 41.³² The ultraviolet spectrum of 2-hydroxythiophene is different from that of the corresponding methyl ether (39, $R = Me$) suggesting the presence of the chromophore contained in structure 40. The facts that this compound gives a positive



[39]



[40]



[41]

color test with ferric chloride, is a weak acid, and undergoes reactions characteristic of a phenolic hydroxyl group have been advanced as further evidence for the presence of the hydroxy form.³² The infrared

³⁰ E. C. Kendall and Z. G. Hajos, *J. Am. Chem. Soc.* **82**, 3219 (1960).

³¹ W. H. Hoehn, *Iowa State Coll. J. Sci.* **11**, 66 (1936); *Chem. Abstr.* **31**, 1800 (1937).

³² C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.* **72**, 5543 (1950).