(3) 3.312, 3.156, 2.586, (1) 5.273, 3.682, 3.367, 2.952; N,N'-dinitropiperazine (10) 5.467, (8) 3.790, (7) 3.235, (3) 3.097, (2) 2.650, 2.712, 3.040, (1) 1.922, 5.352; N,N'-dinitro-2-methylpiperazine (10) 5.196, (9) 4.951, (8) 4.019, 3.470, (4) 3.201, 2.824, (2) 3.904, 3.066, (1) 2.928; N,N'-dinitro-2,5-↑↑-dimethylpiperazine (10) 6.702, (9) 3.195, (8) 5.078, 4.870, (7) 8.185, 3.076, (6) 3.652, (5) 4.010, (4) 5.941, 5.552, 3.524, (1) 7.338, 4.583, 2.523.

ONTARIO, CANADA

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Detection and Structural Analysis of Furans by Proton Magnetic Resonance

BY E. J. COREY, GEORGE SLOMP, SUKH DEV,[1] S. TOBINAGA[1] AND E. R. GLAZIER[2]

RECEIVED OCTOBER 7, 1957

Measurements are reported herein which show that proton magnetic resonance spectroscopy is a powerful tool for the detection of furan rings and for the location of substituents attached thereto.

The detection of the furan ring system as a constituent of complex organic structures has previously been a difficult matter because of the lack of a generally informative diagnostic method. Chemical and color tests are, at best, only suggestive in this regard because of their lack of specificity and also due to wide variation in the chemical properties of the furan ring system.[3] Ultraviolet spectroscopy is of very limited usefulness because of the rather non-characteristic absorption by furans in that region.[4] Although correlations of certain bands in the infrared spectra of several furans have been made,[5] the nature of the absorption and the necessary assumption that no interfering bands are present render the infrared data of little use when more than corroborative evidence is desired. Another important problem in the case of simple as well as complex structures containing the furan system is the location of substituents on the nucleus. This problem also has resisted solution by physical methods.

In connection with investigations of the structures of certain natural products which are being pursued in these laboratories and also because of the widespread occurrence of furan systems in nature,[5] we have been concerned with these problems and have sought to apply other methods to their solution. In this paper we describe the structural analysis of furans by proton magnetic resonance, a technique which has been conspicuously successful in the cases studied thus far.

Our nuclear magnetic resonance measurements with furan derivatives show that in general the protons attached to the furan nucleus are less shielded than protons attached to double bonds and in this respect are similar to protons attached to benzenoid nuclei.[6] Comparison of furans with vinyl ethers, their non-aromatic structural analogs, indicates that proton resonance occurs at lower fields for the former than for the latter, as would be anticipated from the occurrence of diamagnetic π-electron currents around the furan ring (*cf.* recent discussions of benzenoid annular currents).[7,8] This difference between furanoid and ethylenic and paraffinic proton resonance, although not unexpected, is a useful and desirable one for purposes of structural analysis. At least of equal significance and utility is the fact that furan α-hydrogens are usually less shielded than furan β-hydrogens, *i.e.*, resonance occurs at lower fields for the former.

Experimental

All proton magnetic resonance spectra were determined at 40 mc. rf. with a Varian model V-4300B high-resolution spectrometer fitted with a field-sensing stabilizer ("Super Stabilizer"). The compounds were measured as *ca.* 10% solutions in methylene chloride and in some cases also in deuterio-chloroform, tetrachloroethane or carbon tetrachloride. The chemical shifts expressed herein in c.p.s. relative to water were actually determined relative to methylene chloride, using a concentric-tube cell[9] with methylene chloride in the outer compartment when it was not used as solvent. Subtraction of 26 c.p.s. from shifts relative to methylene chloride was used in figuring shifts in c.p.s. relative to water. Chemical shifts were essentially the same in methylene chloride, tetrachloroethane and deuteriochloroform solutions and generally were *ca.* −15 c.p.s. from those in carbon tetrachloride (*i.e.*, resonance occurred at higher fields in the case of carbon tetrachloride).

The furan compounds studied were in many cases generously supplied by other laboratories: cafestol (Dr. Carl Djerassi), columbin (Dr. Michael Cava), 3-furoic acid and derivatives (Dr. Henry Gilman), menthofuran (A. M. Todd Co.) and 2,5-dimethylfuran (Quaker Oats Co.). Otherwise, purified samples obtained in our laboratories were used.

Results and Discussion

Part A.—The proton magnetic resonance spectrum of furan itself (I) in methylene chloride solution (Table I) is composed of two sharp triplets centered at −113 and −71 c.p.s. with a signal ratio of 1:1. We assign the triplet at −113 c.p.s. to the two α-hydrogens and that at −71 to the two β-hydrogens. This assignment is that dictated from the inductive unshielding effect of oxygen, expected to be greater for α- than for β-protons, and is clearly supported by the data on substituted furans. The triplets, anticipated to result from spin–spin coupling between α- and β-hydrogen

(1) U. S. Public Health Fellow.

(2) Alfred P. Sloan Foundation Fellow.

(3) See W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward and T. F. Holley, *J. Chem. Soc.*, 2540 (1953).

(4) For example, furan itself shows shoulder-like absorption with no sharp or characteristic maxima; L. W. Pickett, *J. Chem. Phys.*, **8**, 293 (1940); W. C. Price and A. D. Walsh, *Proc. Roy. Soc. (London)*, **A179**, 201 (1941).

(5) (a) See for example, R. C. Elderfield and T. N. Dodd, Jr., in Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 189; (b) *Ann. Rep. Chem. Soc.*, **53**, 208 (1956).

(6) L. H. Meyer, A. Saika and H. S. Gutowsky, THIS JOURNAL, **75**, 4567 (1953).

(7) J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956).

(8) J. S. Waugh and R. W. Fessenden, THIS JOURNAL, **79**, 846 (1957).

(9) J. R. Zimmerman and M. R. Foster, *J. Phys. Chem.*, **61**, 282 (1957).

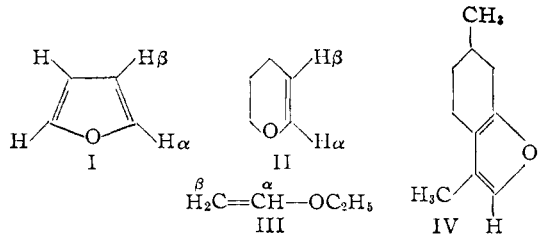
TABLE I

PROTON RESONANCE (40 Mc.)

Compound	Rel. to H_2O (c.p.s.) α[a]	β[a]	Signal ratio $\alpha:\beta$	Solvent
Furan	− 98(t)	− 55(t)	1:1	CCl_4
Furan	−112(t)	− 70(t)	1:1	$Cl_2CHCHCl_2$
Furan	−113(t)	− 71(t)	1:1	CH_2Cl_2
2-Methylfuran	−104(m)	− 65, −54(m)	1:2	CH_2Cl_2
2,5-Dimethylfuran	...	− 35(s)	..	CCl_4
2,5-Dimethylfuran	...	− 48.5(s)	..	CH_2Cl_2
Menthofuran (IV)	− 85	...	..	CCl_4
Menthofuran	− 96	...	..	CH_2Cl_2
Furfurol	−101	− 56.5	1:2	CCl_4
Furfurol	−111	− 65	1:2	CH_2Cl_2
Furfural	−116(s)	− 96(d), −71(q)	1:2	CCl_4
Furfural	−122(s)	−104(d), −77(q)	1:2	CH_2Cl_2
2-Furoic acid	−116(q)	−106(q), −75(q)	1:2	CH_2Cl_2
3-Furoic acid	−136, −109	− 83	2:1	$CDCl_3$
2-Methyl-3-furoic acid	−101	− 79	1:1	$CDCl_3$
4-Methyl-3-furoic acid	−136, −103	...	..	$CDCl_3$
Cafestol (V)	−104(d)	− 63(d)	1:1	CH_2Cl_2
Columbin (VI)	−113	− 69	2:1	CH_2Cl_2
Limonin	−113	− 70	2:1	$CDCl_3$ or CH_2Cl_2

[a] Resonance bands marked s, d, t, q, m, appeared as singlets, doublets, triplets, quadruplets and higher multiplets, respectively. Bands not marked appeared as a single unresolved (but possibly multiplet) band.

pairs, show coupling ($J\alpha\beta$) constants[10-12] of *ca.* 1.5 c.p.s. It is instructive to compare the ethylenic protons of dihydropyran (II) with the data on



furan. The α-ethylenic hydrogen of the former shows a resonance doublet at −69 and −63 c.p.s., whereas the β-ethylenic hydrogen appears at −1 c.p.s. as a complex J multiplet. Similarly, the ethylenic protons in vinyl ethyl ether (III) appear as an α-quadruplet at −71.5, −64.9, −57.9 and −51.4 c.p.s. and two β-doublets at +24.7 and +35 c.p.s. (signal ratio $\alpha,\beta_1\beta_2$ of 1:1:1). Clearly ethylenic hydrogens alpha to oxygen in a vinyl ether are less shielded than those beta to oxygen. Furthermore, the α- and β-hydrogens of furan are less shielded than α- and β-hydrogens of a vinyl ether, a point which has been alluded to in the introductory section. These data provide much of the basis for the utility of proton magnetic resonance in structural analysis of furans and suggests that when benzenoid and other aromatic rings[13] are absent the method will be particularly effective.

α-Methylfuran shows furan proton resonances at −104, −65 and −54 c.p.s. (signal ratio 1:1:1) due to the α-hydrogen and the two β-hydrogens, respectively. 2,5-Dimethylfuran shows only β-hydrogen absorption at −48.5 c.p.s., as expected. Menthofuran (IV), an α,β,β-trisubstituted furan, shows only α-hydrogen absorption at −96 c.p.s. The greater shielding of protons on alkylated furan nuclei may be due to electron release by the alkyl substituents. On this basis one can interpret the β-hydrogen resonances in 2-methylfuran at −65 and −54 c.p.s. as attributable to C_4–H and C_3–H, respectively, a conclusion which is in accord with the data on 2,5-dimethylfuran. It is important to note that the paraffinic protons in the above mentioned substances are so far separated from the furan protons that there is no interference whatsoever from them (*e.g.*, the methyl protons of 2-methylfuran appear at +91 c.p.s.).

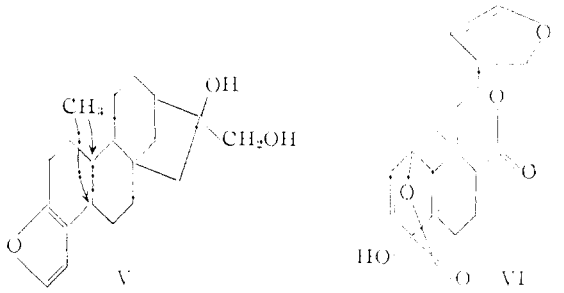
Whereas furfuryl alcohol (Table I) corresponds closely to 2-methylfuran, furfural proton resonances occur at much lower fields: aldehyde proton −194 c.p.s.; furan protons −116, −96 and −71 c.p.s. This fact is understandable in view of the electron-withdrawing influence of the α-carbonyl substituent at C_2 which unshields C_3–H and C_5–H considerably and C_4–H hardly at all, as would be expected from consideration of contributing canonical ("resonance") forms. The formyl proton characteristically shows resonance at relatively low fields. The case of 2-furoic acid is analogous to that of furfural. 3-Furoic acid, in agreement with the above considerations, shows one further unshielded α-hydrogen (C_2–H) at −136 c.p.s. and "normal" α- and β-hydrogens at −109 and −83 c.p.s., respectively, for C_5–H and C_4–H. 2-Methyl-3-furoic acid and 4-methyl-3-furoic acid show proton magnetic resonance spectra in excellent accord with this assignment.

Thus the data in Table I provide a strong case for the effectiveness of proton magnetic resonance in dealing with structural problems in the furan series.

It seems apparent from preliminary studies that proton magnetic resonance may be a valuable tool in other heterocyclic series also. The nuclear protons

(10) J. E. Wertz, *Chem. Revs.*, **55**, 829 (1955).
(11) H. S. Gutowsky, *Ann. Rev. Phys. Chem.*, **5**, 333 (1954).
(12) J. N. Shoolery and H. E. Weaver, *ibid.*, **6**, 433 (1955).
(13) These structural types commonly show proton resonance in the neighborhood of −100 c.p.s. in dilute solution in chlorinated solvents (see ref. 8).

on the carbons of pyrrole are separated into two multiplets with centers at −70 and −54 c.p.s. (in carbon tetrachloride) indicating a distinction between α- and β-hydrogens. The α- and β-protons of thiophene, however, are not spread apart and only one complex multiplet (center at −96 c.p.s. in carbon tetrachloride) appears.



Part B. Application to Certain Natural Products.—Using proton magnetic resonance it took just a few minutes to confirm the nature of furan substitution in cafestol (V)[5b] from the appearance of α- and β-hydrogen resonances at −104 and −63 c.p.s. as doublets of equal intensity and each one-third as intense as the methyl group. The β-monosubstituted furan ring in columbin (VI)[14] was immediately apparent from proton resonances at −113 and −69 c.p.s. (signal ratio of 2:1) for two α- and one β-hydrogen, respectively. The chief bitter principle of citrus, limonin, $C_{26}H_{30}O_8$, whose structure has not yet been described in the literature, is also a β-monosubstituted furan as evidenced by proton resonance at −113 and −74 c.p.s. (signal ratio of 2:1). Such an assignment accounts for the unsaturation in limonin and one of the "ether" oxygens. The −113 and −74 c.p.s. bands are absent in the spectrum of tetrahydrolimonin, the saturated derivative, and those of several other derivatives in which the furan ring has been removed.[15] These data provide the most compelling evidence for the presence of a furan ring in limonin and, in addition, show clearly the type of nuclear substitution.[16]

In conclusion, it should be mentioned that although structural analysis of furans by n.m.r. is remarkably straightforward, caution must always be exercised with regard to: (1) the effect of ring substituents, (2) possible interference from other protons attached to sp^2 hybridized carbon, especially in aromatic systems, and (3) applying corrections for solvent and bulk diamagnetic effects on observed shifts.[17]

(14) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2085, 2090 (1956).

(15) We hope to publish complete details on these spectra together with an account of extensive structural studies on limonin in the near future.

(16) For a very recent publication on limonin chemistry see A. Malera, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **40**, 1420 (1957).

(17) A. A. Bothner-By and R. E. Glick, *J. Chem. Phys.*, **26**, 1647, 1651 (1957).

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

The Steric Inhibition of Periodate Oxidation of Glycosides[1,2]

BY E. F. GARNER,[3] IRWIN J. GOLDSTEIN, R. MONTGOMERY AND F. SMITH

RECEIVED OCTOBER 19, 1957

Large groups have been shown to have a steric effect on the periodate oxidation of glycosides.

Although periodate oxidation is regularly used as a tool in analytical[4] and synthetic organic[5-7] chemistry, there seems to have been little work which demonstrates the primary site of attack of this reagent on an α,β,γ-triol grouping in a hexopyranoside. Reported herein are two instances in which the primary site of oxidation has been determined and which depends upon the directive influence of a bulky group.

The mechanism of periodate oxidation has been elucidated[8-10] and it appears to proceed through the formation of a five-membered heterocyclic ring involving the iodine atom and the glycol grouping. It is known that a *cis*-glycol group is attacked more readily than the *trans* modification[11-14] and that the rigidity imposed upon a system by bicyclic ring formation renders the *trans*-glycol group inert to attack by periodate.[15-17]

This paper is concerned with two compounds,

(1) Part of this paper is taken from a thesis submitted by E. F. Garner to the Graduate School of the University of Minnesota, in partial fulfillment of the requirements for the degree of Ph.D., 1956.

(2) Paper No. 3816 Scientific Journal Series, Minnesota Agricultural Experiment Station.

(3) Joseph Schlitz Brewing Co., Milwaukee, Wisc.

(4) E. L. Jackson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 341; J. R. Dryer, "Methods of Biochemical Analysis," Vol. III, ed. by D. Glick, Interscience Pub., Inc., New York, N. Y., 1956, p. 111.

(5) J. C. Sowden, THIS JOURNAL, **72**, 808 (1950).

(6) J. C. Sowden, *ibid.*, **73**, 5496 (1951).

(7) I. J. Goldstein, J. K. Hamilton and F. Smith, *ibid.*, **79**, 1190 (1957).

(8) R. Criegee, *Sitzber. Ges. Beförder. ges. Naturw. Marburg*, **69**, 25 (1934); *C. A.*, **29**, 6820 (1935).

(9) R. Criegee, L. Kraft and B. Rank, *Ann.*, **507**, 159 (1933).

(10) C. C. Price and M. Knell, THIS JOURNAL, **64**, 552 (1942).

(11) C. C. Price and H. Kroll, *ibid.*, **60**, 2726 (1938).

(12) H. Klosterman and F. Smith, *ibid.*, **74**, 5336 (1952).

(13) P. F. Fleury, J. E. Courtois and A. Bieder, *Compt. rend.*, **233**, 1042 (1951).

(14) P. F. Fleury, J. E. Courtois and A. Bieder, *Bull. soc. chim. France*, 118 (1952).

(15) B. H. Alexander, R. J. Dimler and C. L. Mehltretter, THIS JOURNAL, **73**, 4658 (1951).

(16) R. J. Dimler, H. A. Davis and G. E. Hilbert, *ibid.*, **68**, 1377 (1946).

(17) F. Smith, *J. Chem. Soc.*, 633 (1944).