Steric Effects in Ketal Hydrolysis

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The rates of acid-catalyzed hydrolysis of diethyl ketal and 2,2-disubstituted 1,3-dioxolane derivatives of both aromatic and aliphatic ketones have been measured in 50% dioxane–water (v/v) at 30°. The 1,3-dioxolane derivatives of acetophenone and propiophenone hydrolyze considerably slower than 2-phenyl-1,3-dioxolane, whereas the diethyl ketal derivatives of these ketones hydrolyze much faster than does benzaldehyde diethyl acetal, indicating the presence of a large steric retardation of the rate of hydrolysis of the 2-phenyl-2-alkyl-1,3-dioxolanes. The rates of hydrolysis of 2,2-dialkyl-1,3-dioxolanes appear to be subject to smaller steric effects. The observed retardations in rate are associated with less favorable ΔH^* values. Values of ΔS^* are nearly constant for all of the 2-phenyl-1,3-dioxolanes. A constant ΔS^* difference of 8–10 eu appears to exist between 1,3-dioxolanes and the corresponding diethyl acetal or ketal regardless of substitution at the 2 position.

The accepted mechanism for the acid-catalyzed hydrolysis of acetals and ketals involves a fast preequilibrium protonation of the substrate followed by a unimolecular rate-determining decomposition to an alcohol and a resonance-stabilized carbonium ion.[1] In a previous study[1] it was found that substituted benzaldehyde diethyl acetals and the corresponding 2-(substituted phenyl)-1,3-dioxolanes hydrolyze by such an A1 mechanism and give plots of the logarithms of the rate constants *vs.* σ, the Hammett substituent constant,[2] with curvature for *para*-substituted compounds. Correlation was also poor with σ^+ constants,[3] these constants overcompensating greatly for interaction of *para* substituents with a carbonium ion. Thus, it is evident that the transition state for the hydrolysis of these compounds does not resemble a carbonium ion to an extent sufficient to give a good correlation between the logarithms of the rate constants and the σ^+ constants. It was also found that the value of ΔS^* was in each case 8–10 eu more negative for hydrolysis of a 1,3-dioxolane derivative than for the corresponding diethyl acetal. To obtain further information concerning the hydrolysis of compounds of this general type, a series of diethyl ketal and 2,2-disubstituted 1,3-dioxolane derivatives have been studied.

Experimental Section

Materials.—Diethyl ketals were synthesized by treating the commercially obtained ketones with a mixture of equimolar quantities of triethyl orthoformate and absolute ethanol; 1 drop of ethanolic HCl was added as a catalyst. After allowing the mixture to stand 24 hr at room temperature, anhydrous potassium carbonate was added to neutralize the excess acid. The excess ethanol was removed by flash evaporation, and the residual liquid was distilled. The properties of the products are given in Table I.

TABLE I

PROPERTIES OF DIETHYL KETALS

Compd	Ketone	Bp, °C (mm)	$n^{24}D$	Ref
I	Acetophenone	93–95 (12)	1.4778	*a*
II	Propiophenone	92–93 (8)	1.4860	*b*
III	Acetone	112–113 (760)	1.3865	*c*

[a] R. C. Fuson and D. M. Burness, *J. Am. Chem. Soc.*, **68,** 1270 (1946). [b] E. L. Beals and F. A. Gilfillan, *J. Am. Pharm. Assoc.*, **25,** 426 (1936). [c] C. D. Hurd and M. A. Pollack, *J. Am. Chem. Soc.*, **60,** 1905 (1938).

The 2,2-disubstituted 1,3-dioxolanes were prepared by treating the appropriate ketone with ethylene glycol in refluxing benzene. A trace of *p*-toluenesulfonic acid was added as a catalyst. Water was continuously removed from the reaction by azeotropic distillation with the benzene. At the conclusion of the reaction the mixture was washed with 1 *M* sodium hydroxide solution. The benzene extract was dried over anhydrous sodium sulfate. The benzene was removed by flash evaporation, and the residual material was purified either by distillation or by recrystallization from an ether–hexane mixture. The properties of the products are given in Table II.

TABLE II

PROPERTIES OF 2,2-DISUBSTITUTED 1,3-DIOXOLANES

Compd	2 substituents	Mp or bp (mm), °C	$n^{24}D$	Ref
IV	C_6H_5, CH_3	57–58		*a*
V	C_6H_5, C_2H_5	101.5–103 (11)	1.5070	*a*
VI	$(C_6H_5)_2$	125–128 (0.9)	1.5965	*b*
VII	$(CH_3)_2$	89.5 (760)	1.4044	*c*
VIII	CH_3, C_2H_5	112–113 (760)	1.4119	*d*
IX	CH_3, $CH(CH_3)_2$	127 (760)	1.4151	*e*
X	CH_3, $C(CH_3)_3$	144–145 (760)	1.4229	*f*
XI	$[CH(CH_3)_2]_2$	170 (760)	1.4318	*g*

[a] E. J. Salmi, U. Tamminen, and P. Louhenkuru, *Suomen Kemistilehti*, **20B,** 1 (1947). [b] M. Sulzbacher, E. Bergmann, and E. R. Pariser, *J. Am. Chem. Soc.*, **70,** 2827 (1948). [c] R. Leutner, *Monatsh.*, **60,** 317 (1932); H. Dauben, Jr., B. Loken, and H. Ringold, *J. Am. Chem. Soc.*, **76,** 1359 (1954). [d] R. Dworzak and K. Herrmann, *Monatsh.*, **52,** 83 (1929). [e] M. J. Astle, J. A. Zaslowsky, and P. G. Lafyatis, *Ind. Eng. Chem.*, **46,** 787 (1954). [f] E. J. Salmi and V. Rannikko, *Ber.*, **72B,** 600 (1939). [g] *Anal.* Calcd for $C_9H_{18}O_2$: C, 68.35; H, 11.39. Found: C, 68.20; H, 11.40.

Kinetic Measurements.—The rates of hydrolysis were measured in 50% dioxane–water[4] (v/v) at a constant ionic strength of 0.1 *M* made up with KCl. The rates were measured spectrophotometrically with a Zeiss PMQ 11 spectrophotometer by following the increase in optical density due to the ketone product. The rates were generally followed to 75–90% completion. The kinetic procedure and treatment and the equipment employed were the same as previously described.[1]

In work utilizing 99.8% D_2O as solvent, the glass electrode correction formula of Fife and Bruice[5] was employed in the determination of a_D.[6] In the determination of activation energies from slopes of plots of log k_{obsd} *vs.* $1/T$, points were obtained at four temperatures (20, 30, 40, and 50°). The rates were measured in triplicate with an average deviation of less than 2% in the rate constants in all cases. The kinetic results are presented in Tables III–V.

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(1) For the evidence which has lead to this mechanism and the pertinent references, see T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30,** 1492 (1965).

(2) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffe, *Chem. Rev.*, **53,** 191 (1953).

(3) Y. Okamoto and H. C. Brown, *J. Org. Chem.*, **22,** 485 (1957).

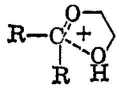
(4) Dioxane was purified according to the procedure of L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 284.

(5) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65,** 1079 (1961).

(6) The relationship pD = pH meter reading +0.40 has been found in D_2O at 25°: P. K. Glasoe and F. A. Long, *ibid.*, **64,** 188 (1960). That the same relationship holds in 50% dioxane–D_2O is an assumption.

Results and Discussion

Salomaa and Kankaanpera[7] have found the relative rate ratios given in Table VI for hydrolysis of methyl-substituted 1,3-dioxolanes. The fact that replacement of a hydrogen at the 2 position by one methyl group produced an increase in rate of over 5000 times, quite similar to the difference in rates of hydrolysis of formaldehyde and acetaldehyde diethyl acetals,[8] while substitution of the second methyl further increased the rate of hydrolysis by only a factor of 10 was interpreted as indicating that the presence of two substituents results in steric retardation of the rate so that the normal rate enhancement due to the inductive and hyperconjugative effects of the methyl groups is reduced. Since the rate increase due to substitution of the first methyl group was found to be so large, it was thought that steric effects were probably absent in the case of monosubstitution. In explaining these effects,[7] it was assumed that the transition state has a great deal of oxo carbonium ion character so that the bond between oxygen and the carbon at the 2 position has partial double-bond character. The groups bonded by these atoms would,



therefore, approach coplanarity, resulting in steric interaction between one of the substituent groups and the ring. Presumably only the smaller of the two substituent groups would be turned toward the ring so that steric retardation of the rate would only become apparent in the case of disubstitution. It has recently been found[9] that variation of the alkyl substituent from methyl to *t*-butyl in a series of 2-alkyl-1,3-dioxolanes gives no evidence for any steric effects on the rates of hydrolysis of these compounds, the logarithms of the rate constants less a hyperconjugation term giving good correlation with Taft's[10] σ^* constants. A similar correlation has been found in the present work for the hydrolysis of ethylene ketal derivatives of a series of methyl ketones, as seen in Figure 1. The logarithms of the rate constants less the hyperconjugation term $0.54\Delta n$,[8] where n is the number of α-hydrogen atoms, the standard being 2,2-dimethyl-1,3-dioxolane ($n = 6$), give a good linear correlation with the σ^* constants with a ρ^* of $-4.0°$.[11] The point for 2,2-diisopropyl-1,3-dioxolane falls below this line, however, by a factor of 0.37 log unit. This deviation is likely due to a steric effect, but it can be concluded that even when both of the alkyl substituents at the 2 position are large bulky groups the observed rate-retarding effect is fairly small. If arbitrary lines of lower slope are drawn through these points, then the negative deviation of the point for 2,2-diisopropyl-1,3-dioxolane is even much less.

TABLE III

RATES OF HYDROLYSIS OF DIETHYL KETAL AND 1,3-DIOXOLANE DERIVATIVES IN 50% DIOXANE–WATER OR 50% DIOXANE–DEUTERIUM OXIDE[a]

Compd	λ, mμ[b]	pH	k_{obsd}, min^{-1}	k_H,[c] l. mole^{-1} min^{-1}	k_D,[d] l. mole^{-1} min^{-1}
e				723.3[e]	
I	280	4.76[f]	0.421	24,200	
II	279	4.76[f]	0.117	6,724	
III	280	6.42[g]	0.0313	82,370	
h				25.4[h]	70.1
IV	280	1.31	0.245	5.00	14.76
V	279	1.31	0.0511	1.04	3.13
VI	265	0.31[i]	0.106	0.216	
VII	280	1.31	0.222	4.53	
VIII	280	1.31	0.192	3.92	
IX	277	1.31	0.142	2.90	
X	280	1.31	0.150	3.06	
XI	280	1.31	0.0375	0.765	

[a] At 30 ± 0.1°. [b] Wavelength at which appearance of product was followed. [c] $k_H = k_{obsd}/a_H$. [d] $k_D = k_{obsd}/a_D$. [e] Benzaldehyde diethyl acetal.[1] [f] Formate buffer. [g] Acetate buffer. [h] 2-Phenyl-1,3-dioxolane.[1] [i] 0.5 *M* HCl.

TABLE IV

TEMPERATURE DEPENDENCE OF k_{obsd} FOR HYDROLYSIS OF DIETHYL KETAL AND 1,3-DIOXOLANE DERIVATIVES IN 50% DIOXANE–WATER[a]

Compd	pH	k_{obsd}, min^{-1}			
		20°	30°	40°	50°
I	4.76[b]	0.182	0.421	0.930	1.78
II	4.76[b]	0.0437	0.117	0.259	0.546
III	6.42[c]		0.0313	0.0743	0.159
IV	1.31	0.0989	0.245	0.633	1.49
V	1.31	0.0192	0.0511	0.141	0.336
VII	1.31	0.0759	0.222	0.595	1.52
XI	1.31	0.0125	0.0375	0.103	0.244

[a] $\mu = 0.1$ *M*. Temperature was controlled to ±0.1°. [b] Formate buffer. [c] Acetate buffer.

TABLE V

ACTIVATION PARAMETERS FOR HYDROLYSIS OF DIETHYL ACETALS AND KETALS AND 1,3-DIOXOLANE DERIVATIVES IN 50% DIOXANE–WATER

Compd	ΔH^*, kcal/mole	ΔS^*, eu[a]
Benzaldehyde diethyl acetal[b]	16.5	+1.0
Acetophenone diethyl ketal	14.0	−0.4
Propiophenone diethyl ketal	15.4	+1.7
Acetone diethyl ketal	15.2	+6.0
2-Phenyl-1,3-dioxolane[b]	15.5	−8.9
2-Phenyl-2-methyl-1,3-dioxolane	16.6	−8.6
2-Phenyl-2-ethyl-1,3-dioxolane	17.4	−8.9
2,2-Dimethyl-1,3-dioxolane	18.2	−3.3
2,2-Diisopropyl-1,3-dioxolane	18.5	−5.9

[a] Calculated at 30°. The rate constants have the units liters per mole per second. [b] Data from ref 1.

TABLE VI

RELATIVE RATES OF HYDROLYSIS OF 1,3-DIOXOLANES IN WATER AT 25°

Compd	Relative hydrolysis rate[a]
1,3-Dioxolane	1.0[b]
2-Methyl-1,3-dioxolane	5,132
2,2-Dimethyl-1,3-dioxolane	54,339

[a] See ref 7. [b] 2.65×10^{-6} l. mole^{-1} sec^{-1}.

From the data presented in Table III, it can be seen that replacement of the hydrogen atom at position 2 in 2-phenyl-1,3-dioxolane by an alkyl group results in a large rate decrease.[12] This effect can be contrasted with that obtained when one compares the rates of hydrolysis of benzaldehyde diethyl acetal and diethyl ketals of

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[7] P. Salomaa and A. Kankaanpera, *Acta Chem. Scand.*, **15**, 871 (1961).

[8] M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **77**, 5590 (1955).

[9] F. Aftalion, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. France*, 1497 (1965).

[10] R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 556.

[11] This ρ^* value is considerably more negative than that found by Kreevoy and Taft[8] for hydrolysis of diethyl ketals (−3.60) and Aftalion, *et al.*,[9] for hydrolysis of 2-alkyl-1,3-dioxolanes (−3.92 ± 0.49).

[12] See also O. Ceder, *Arkiv Kemi*, **6**, 523 (1954).

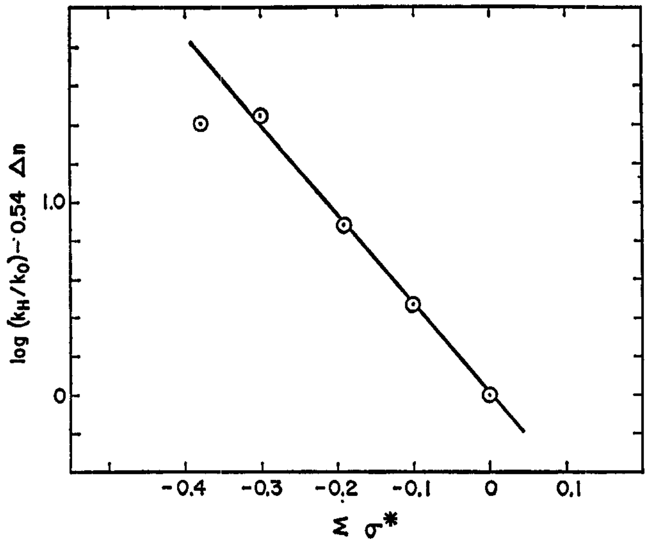


Figure 1.—Plot of log $(k_H/k_0) - 0.54\Delta n$ *vs.* $\Sigma\sigma^*$ for hydrolysis of 2,2-dialkyl-1,3-dioxolanes at 30 ± 0.1° and $\mu = 0.1\ M$. The standard of comparison is 2,2-dimethyl-1,3-dioxolane with k_0 being the second-order rate constant for hydrolysis of this compound.

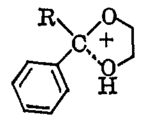
phenyl alkyl ketones, the ketals hydrolyzing much faster, as would be expected from the greater electron-releasing ability of an alkyl group than hydrogen.[8] Thus, 2-phenyl-2-methyl-1,3-dioxolane hydrolyzes only one-fifth as fast as 2-phenyl-1,3-dioxolane, while acetophenone diethyl ketal hydrolyzes approximately 33 times faster than benzaldehyde diethyl acetal. It is apparent that the observed order of reactivities indicates the presence of a larger rate-retarding effect in the hydrolysis of the 2-phenyl-2-alkyl-1,3-dioxolanes than in the 2,2-dialkyl-1,3-dioxolane series. Of special interest is the very slow rate of hydrolysis of 2,2-diphenyl-1,3-dioxolane.[12] It might have been expected that this compound would hydrolyze more rapidly owing to ability of the second phenyl group to stabilize a carbonium ion through a resonance effect. Kreevoy and Taft[13] have similarly found that the diethyl ketal of benzophenone hydrolyzes much more slowly than propiophenone diethyl ketal. Also, it was found that propiophenone diethyl ketal, although hydrolyzing faster than benzaldehyde diethyl acetal, did not hydrolyze as fast as would be expected from the assumption of additivity of effects of the two substituent groups.[13] These results were explained[13] as being due to either steric inhibition of resonance in the transition state or to the transition state resembling the protonated substrate so that conjugation effects would be unimportant.

Since the reported rate constants are composite constants, including the rate constant for the rate-determining step and the dissociation constant for the protonated acetal or ketal

$$k_{\text{obsd}} = (k_r/K_{\text{SH}^+})a_{\text{H}}$$

with k_{H} being equal to (k_r/K_{SH^+}), the observed relative rate ratios could be due to effects on one or both of these constants. For alkyl-group substitution at the reaction center to affect K_{SH^+} in the case of the cyclic derivatives so as to alter the order of reactivity found for the open-chain compounds, a relative acid-strengthening effect would have to be produced. This might result from greater strain in the conjugate acids,[14] or from steric hindrance to solvation.[15]

The alternative explanation that the observed rate retardations are primarily reflecting changes in k_r, the rate constant for the decomposition of the protonated substrate, would lead to the inference that the transition states probably do not closely resemble protonated acetals or ketals since steric retardation of rate in the 1,3-dioxolane series would not be expected in such a case, the transition states differing from their respective ground states primarily by the presence of one proton. There is no reason to suspect a change in mechanism in the hydrolysis of the 1,3-dioxolanes since the D_2O solvent isotope effects (Table III) are consistent with an A1 mechanism[16] ($k_{\text{D}}^{\text{D}_2\text{O}}/k_{\text{H}}^{\text{H}_2\text{O}} > 2.75$). Consequently, a reasonable general explanation for the large observed steric effects in the hydrolysis of the phenyl-substituted compounds would be steric inhibition of resonance with the incipient carbonium ion in the transition state. Steric interactions of the type postulated by Salomaa and Kankaanpera[7] might also, of course, be greatly increased by alkyl-group substitution. For either of these factors to be effective the transition states must have a significant amount of oxo carbonium ion character.



Activation parameters for hydrolysis of several of the 1,3-dioxolane and diethyl ketal derivatives are recorded in Table V. The rate difference between a 1,3-dioxolane and the corresponding diethyl acetal or ketal has increased from a factor of approximately 30 for the benzaldehyde derivatives to a factor of 4840 for the acetophenone derivatives; however, entropies of activation for the 2-phenyl-1,3-dioxolanes are constant at approximately −9 eu regardless of other substitution at the 2 position. The ΔS^* values for the diethyl acetals and ketals of phenyl ketones are also constant at approximately +1 eu. Thus, (a) the sterically caused rate retardation found for 1,3-dioxolane derivatives of phenyl ketones is due to an unfavorable effect on ΔH^* by the substituents at position 2,[17] and (b) the ΔS^* difference of 8–10 eu found for hydrolysis of corresponding cyclic and noncyclic acetals[1] and ketals is very likely a function of the five-membered ring and is independent of the substitution at the 2 position. It should be noted that the ΔS^* value for 2,2-dimethyl-

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(13) M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4016 (1957).

(14) Increased strain in the conjugate acids would also, of course, facilitate their decomposition to oxo carbonium ions.

(15) Steric hindrance to solvation may be a factor in the protonation of aliphatic ethers: E. M. Arnett and C. Y. Wu, *J. Am. Chem. Soc.*, **84**, 1680 (1962). The possibility of this factor being of major importance in determining the relative rate ratios is made less likely by the finding of nearly constant values of ΔS^* for each of the two series of phenyl substituted compounds (Table V).

(16) F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).

(17) An unfavorable effect on ΔH^* might be expected if steric inhibition of resonance was the cause of the rate retardations. Since resonance interaction of a substituent group with the incipient carbonium ion exerts its effect in acetal hydrolysis by lowering ΔH^*,[1] it is probable that inhibition of resonance would make ΔH^* more positive.

1,3-dioxolane is approximately 5 eu more positive than those for the phenyl-substituted compounds but is still 9 eu more negative than that for acetone diethyl ketal.

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The Structure of Paraldol

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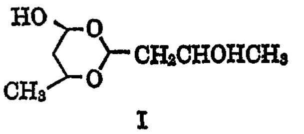
The structure and stereochemistry of paraldol are deduced by means of infrared and nmr spectroscopy. Equilibria which exist in solutions of paraldol are observed and discussed. Paraldol diacetate is shown to be a mixture of epimers.

It is only recently that the complexity of the relatively simple system acetaldehyde–water–base has begun to be understood. Experimental study of the mechanism of the aldol reaction has been hindered by the existence of several complicating conditions. For example, acetaldehyde exists in aqueous solution equilibrium with its hydrate,[2] the kinetic order of the aldol reaction is a function of the concentration of acetaldehyde,[3] and there is consumption of base during the reaction, perhaps because of a Cannizzaro reaction of acetaldehyde.[4] The facile conversion of the aldol product to crotonaldehyde and other compounds also interferes with easy study of the reaction;[4] if careful control of reaction conditions is not maintained, formation of brown resins occurs. Indeed, the discrete existence of aldol in aqueous solution has been questioned by Gruen and McTigue[4] who postulate the initial product formed in their study of the aldol reaction to be the cyclic hemiacetal from aldol and acetaldehyde. Various spectral examinations of commercial "aldol," a viscous liquid, have shown it to contain no carbonyl function.

It has long been known that commercial "aldol" may be carefully distilled under vacuum to give a mobile liquid which is the true aldol (3-hydroxybutanal); under normal conditions, the distillate rapidly and exothermically converts itself to a viscous, water-soluble fluid. Upon standing for several days, the viscous liquid begins to deposit white crystals of paraldol. These transformations were studied by Späth who deduced their nature and the gross structures of the products.[5] Paraldol was shown to be the cyclic hemiacetal I, a dimer of aldol. Crystalline paraldol was shown to be in equilibrium with a liquid isomer and it was suggested that the isomers differed in their stereochemistry at the hemiacetal carbon atom, analogous to the α and β forms of the pyranoses.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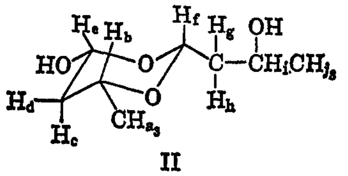
In connection with other work on the chemistry of acetaldehyde, we have investigated the structure of paraldol by infrared and nmr spectroscopy, determined its stereochemistry, and made observations of equilibria which exist in solutions of paraldol.

Results and Discussion

The infrared spectrum of crystalline paraldol in a potassium bromide pellet (Figure 1) is notable for the complete absence of any carbonyl absorption and the presence of strong hydroxyl absorption at 3.0 μ, in agreement with the Späth structure (I). The proton nmr spectrum of paraldol was investigated next, and not only was structure I confirmed but also the stereochemistry of the dioxane ring could be deduced readily.

The Späth formula for paraldol (I) contains four asymmetric carbon atoms and, consequently, there are eight possible racemic pairs of diastereomers. Ignoring the asymmetric center in the side chain, there are four possible pairs of isomers involving geometrical isomerism of the dioxane ring, II–V (only one mirror image is depicted in each case). The conformations illustrated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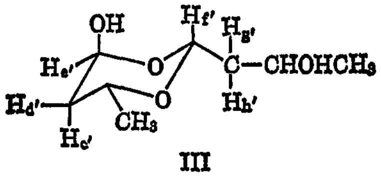
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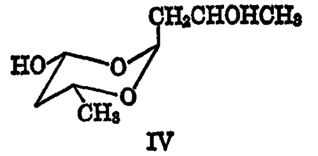
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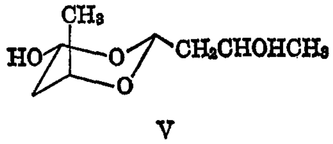
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[2] L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5217 (1963).

[3] A. Broche and R. Gilbert, *Bull. Soc. Chim. France*, **131** (1955); R. P. Bell and M. J. Smith, *J. Chem. Soc.*, 2983 (1960).

[4] L. C. Gruen and P. T. McTigue, *Australian J. Chem.*, **17**, 953 (1964).

[5] (a) E. Späth and H. Schmid, *Ber.*, **74**, 859 (1941); (b) E. Späth, R. Lorenz, and E. Fruend, *ibid.*, **75**, 1029 (1942); (c) E. Späth, R. Lorenz, and E. Fruend, *ibid.*, **76**, 62, 1196 (1943); (d) E. Späth and J. Meinhard, *ibid.*, **76**, 504 (1943).