Studies of 2-Thiohydantoins and Related Compounds

By

Ivan Lantos

In Memory of My Mother

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Department of Chemistry,
McGill University,
Montreal, Canada.

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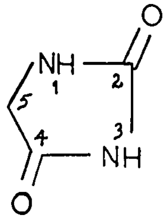
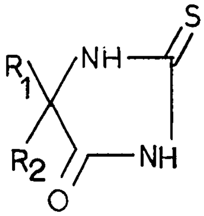
INTRODUCTION

2-Thiohydantoin (II; $R_1 = R_2 = H$), the simplest member of a class of compounds much investigated in connection with the structural studies of peptides (1,2) and of penicillin (3), was discovered by Klason in 1890 (4). It is derived from hydantoin (I) by replacement of the oxygen at the 2-position by sulphur.



I



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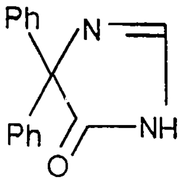
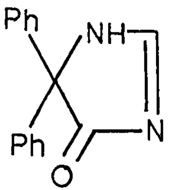
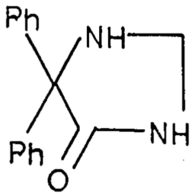


IIIa



IIIb

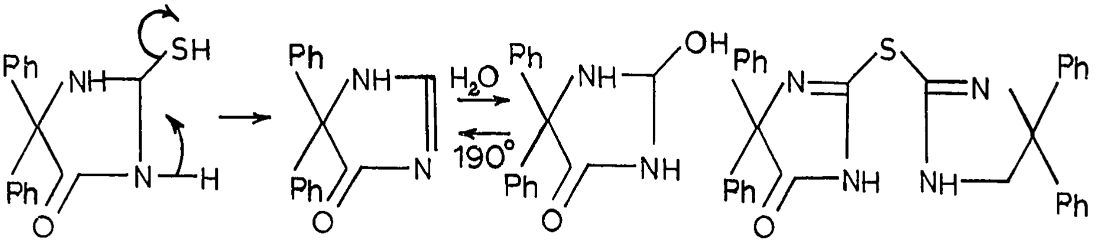


IV

The synthesis of 2-thiohydantoins and related compounds has been much investigated and has been reviewed in a number of articles (5-7). Considerably less attention has been paid to some compounds derived from 2-thiohydantoin (7). Among these are the reduction products (IIIa or IIIb, IV) of 5,5-diphenyl-2-thiohydantoin (II; $R_1 = R_2 = Ph$). The position of the double bond of the tautomeric compound (IIIa or IIIb) has been much debated but without definite conclusions being reached, and some of the reaction products of 5,5-diphenylimidazolid-4-one (IV) have been assigned unusual structures which merit confirmation by modern physico-chemical methods. At a more fundamental level only a beginning has been made in studying the mechanisms of the reactions of 2-thiohydantoins.

In the present thesis we consider first the problem of the structures of some compounds derived from 5,5-diphenyl-imidazolid-4-one (IV) (Part I); next that of the constitution of IIIa or IIIb and similar tautomeric compounds (Part II); and last, that of the ionization of 2-thiohydantoins in strong mineral acids (Part III).

5,5-Diphenylimidazolid-4-one (IV)* was first obtained by Biltz and co-workers (8) from treatment of 5,5-diphenyl-2-thiohydantoin (II; R_1=R_2=Ph) with sodium metal in refluxing amyl alcohol. The reduction can be more conveniently effected by Raney nickel in boiling ethanol (9-12), although under other conditions (i.e., using a small quantity of nickel, or carrying out the reduction in presence of sodium ethoxide (9)), the less completely reduced compounds (IIIa and/or IIIb) are obtained. The mechanism of formation of this latter reduction product most probably involves the thiol V as intermediate which can undergo β-elimination of hydrogen sulphide as shown.



V IIIb VII VI

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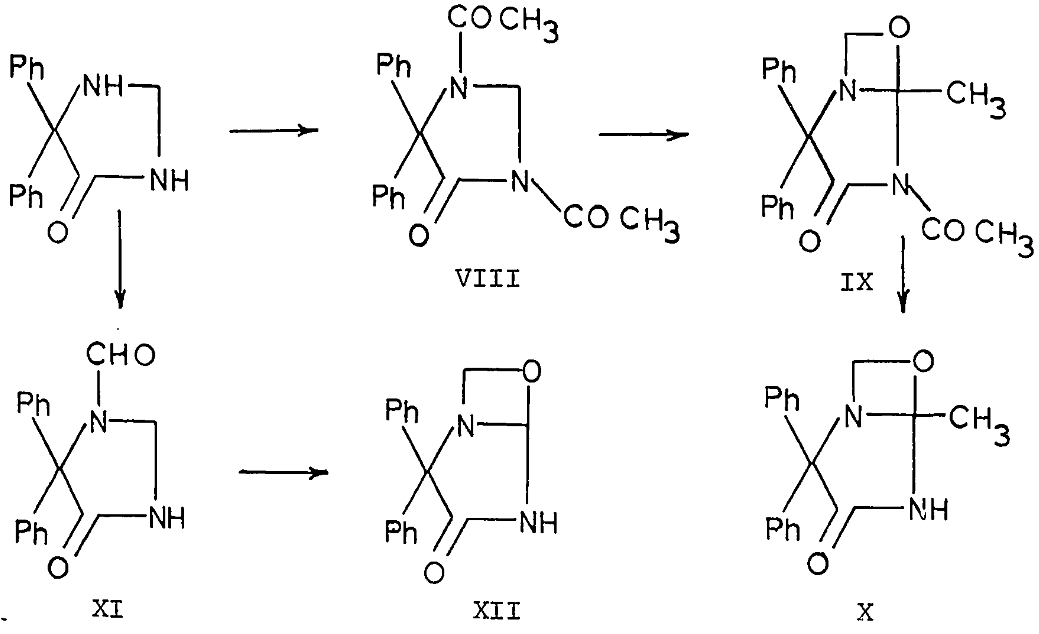
* The name accepted for this compound by Chemical Abstracts (42) is 5,5-diphenyl-4-imidazolidone. In this thesis we named all compounds according to the nomenclature favoured by the British literature for most of our references are found therein.

The sulphide VI, a by-product of these reactions under certain conditions (11), may be formed by the reaction of 5,5-diphenyl-2-thiohydantoin with IIIb with loss of two hydrogen atoms. Whalley <u>et al</u> (11) obtained in addition the hydroxyimidazolidone VII, which may also be prepared from 5,5-diphenylimidazolid-4-one (IV) by oxidation with alkaline potassium permanganate, or from the imidazolone III by addition of a molecule of water. When heated above 190° it loses water and regenerates the imidazolone (8).

From the reaction of 5,5-diphenylimidazolid-4-one (IV) with acetic anhydride Biltz, Seydel and Hamburger-Glaser (13) obtained a compound $C_{19}H_{18}O_3N_2$, m.p. 203-4°, formulated as 2-acetyl-4,4-diphenyl-1-methyl-2,5-diaza-7-oxabicyclo[3.2.0]-heptan-3-one (IX), rather than the expected 1,3-diacetyl-5,5-diphenylimidazolid-4-one (VIII) because only one acetyl group could be removed by drastic alkaline hydrolysis. The deacety-

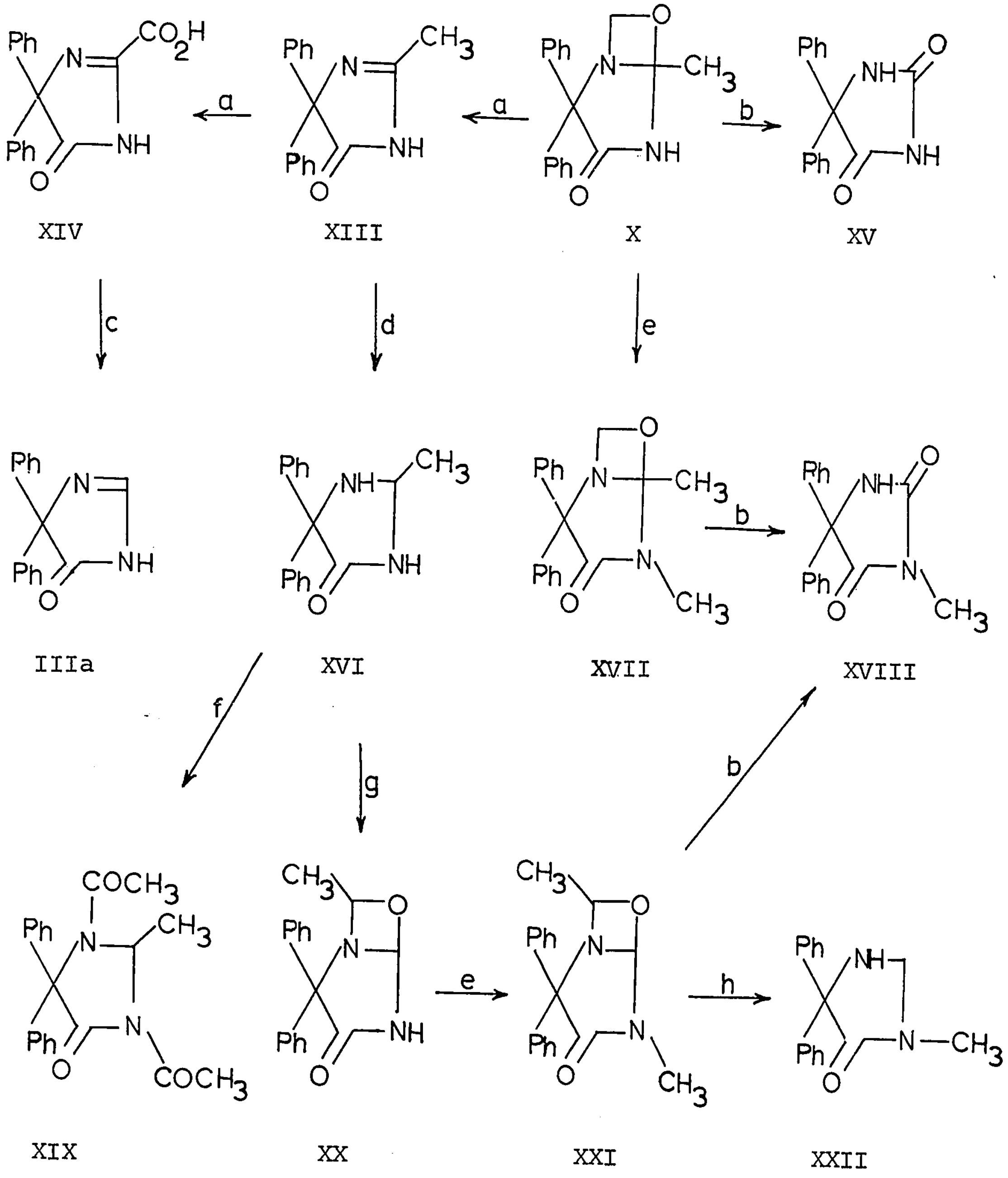


lated compound ($C_{17}H_{16}O_2N_2$, m.p. 204-5^o) was assigned the structure X. Similarly, the compound $C_{16}H_{14}N_2O_2$ obtained by treatment of IV with formic acid was formulated as XII, rather than the N-formyl derivative XI, because no formyl group could be removed by prolonged alkaline hydrolysis.

Further evidence for the structure X for $C_{17}H_{16}O_2N_2$ was obtained by its alkaline permanganate and chromic acid oxidations. The various reactions are outlined in reaction scheme I, which summarizes some of the experimental work of Biltz and his co-workers in terms of their structures.

The identification of the reaction products IIIa, XV, XVIII, previously known compounds, seems reasonably secure. Their formation was construed as evidence for the presence of an imidazolidone moiety in $C_{17}H_{16}O_2N_2$. The reaction sequence X→XIII→XIV→IIIa was interpreted as proof for the presence of an angular methyl group in $C_{17}H_{16}O_2N_2$.

The reduction of 2-methyl-4,4-diphenyl- 4H -imidazol-5-one (XIII) yielded 2-methyl-5,5-diphenylimidazolid-4-one (XVI). The latter compound, because of its structural similarity to IV, would be expected to react with formic acid and acetic anhydride to form compounds analogous to XII and IX respectively. Indeed, with formic acid it gave a compound which appeared to lack a N-formyl group (no alkaline hydrolysis) and which was accordingly formulated as XX. With acetic anhydride, however,



Reaction Scheme I

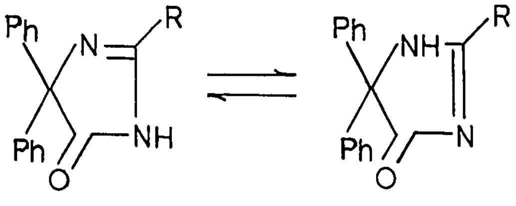
Reagents: a. $KMnO_4/OH^-$; b. $CrO_3/AcOH$; c. heat; d. Na/EtOH;
e. $(CH_3)_2SO_4/OH^-$; f. $(CH_3CO)_2O$; g. HCO_2H
h. HBr (conc.).

it gave a compound which lost two acetyl groups on treatment with 1 N potassium hydroxide and hence was formulated as XIX.

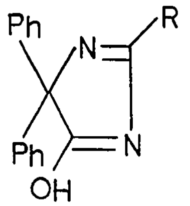
The structures advanced by Biltz et al are sufficiently remarkable to warrant their reinvestigation. In Part I of this thesis we show that the structures IX, X, XII, XVII, XX, XXI, and probably XXII are in error.

In part II the problem of the structures of IIIa or IIIb, and of related structures XXIIIa or XXIIIb, is discussed. (The latter class of compounds became available as a result of investigations discussed in Part I).

Early workers had attempted to choose between one of the two structures IIIa and IIIb by determining the structure of the methylation product. Biltz and Seydel (8) assigned structure IIIb(=XXIIIb,R=H) to the imidazolone obtained by the dehydration of hydroxyimidazolidone VII, because a product which was apparently the methyl derivative XXV, was obtained by methylation of the imidazolone with methyl iodide in alkaline solution.

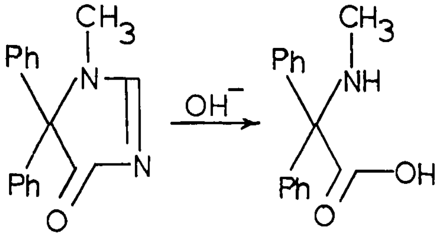


XXIIIa XXIIIb

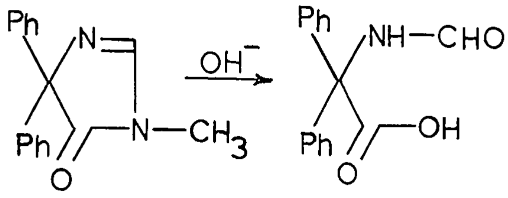


XXIV

This product was assigned the structure XXV because it was hydrolyzed to a compound formulated as α,α-diphenyl-α-methylaminoacetic acid(XXVI).

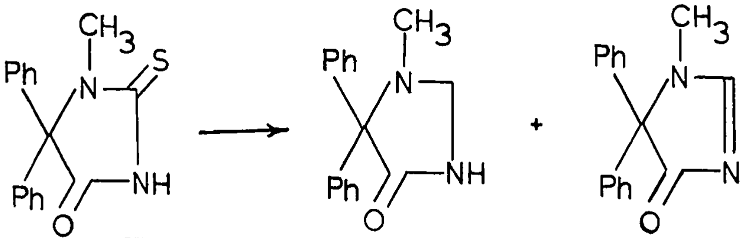


XXV XXVI



XXVII XXVIII

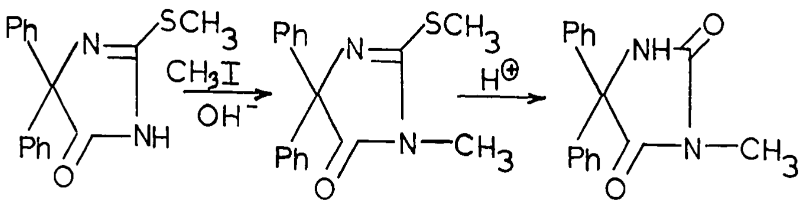
By Raney nickel desulphurization of various substituted 5,5-diphenyl-2-thiohydantoins, Carrington *et al* (10) were able to obtain both compounds XXV and XXVII in an unambiguous manner. Desulphurization of 5,5-diphenyl-1-methyl-2-thiohydantoin (XXIX) with Raney nickel in ethanol gave a mixture of the imidazolidone XXX and the imidazolone XXV.



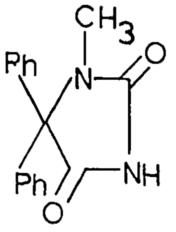
XXIX XXX XXV

The separate compounds XXX and XXV were best obtained pure by catalytic reduction or potassium permanganate oxidation, respectively, of the mixture. Similarly, the desulphurization of 5,5-diphenyl-3-methyl-2-thiohydantoin gave authentic XXVII. Carrington could then show that the methylation product of Biltz possessed in fact structure XXVII, its hydrolysis product being α,α-diphenyl-α——formylaminoacetic acid (XXVIII). These workers therefore proposed structure IIIa (XXIIIa;R=H) for the imidazolone.

These chemical methods designed to elucidate the tautomeric structure must be viewed with reserve because of the possibility of a tautomeric shift preceding methylation (14). The same considerations apply to early studies of the structure of the methylation product of 5,5-diphenyl-2-thiohydantoin. Biltz (15) had previously assigned structure XXXIa (=XXIIIa:R=MeS) to this compound because the dimethyl derivative obtained by further methylation was hydrolyzed to 5,5-diphenyl-3-methylhydantoin (XVIII). This finding was



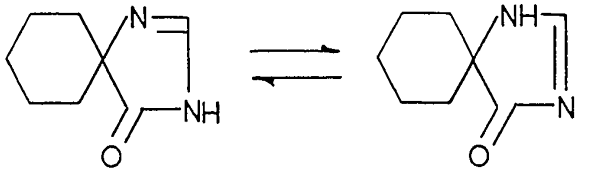
XXXIa XXXII XVIII



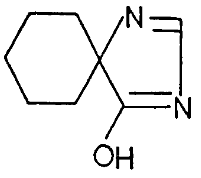
XXXIII

first disputed by Cattelaine and Chabrier (16), who claimed that the hydrolysis product was the 1-methylhydantoin (XXXIII) derivative, but was later substantiated by Carrington and Waring (17) in their exhaustive study of the methylation products of 2-thiohydantoins.

Physical methods were first applied to determine the position of the tautomeric equilibrium of imidazolones by Schipper and Chinnery (18). In their investigations of the spiroimidazolones XXXIVa and XXXIVb, they found evidence for the presence of both tautomeric forms in solution and none of the tautomer XXXV was discernible. These workers also



XXXIVa XXXIVb



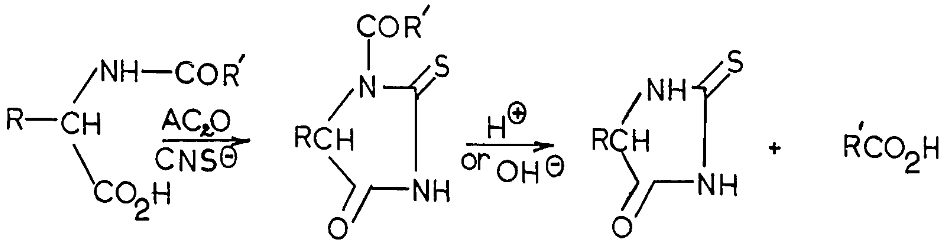
XXXV

found that the diphenyl compound exists in the form IIIa (XXIIIa; R = H) and the spiro compound in the form of XXXIVb in the crystalline state.

Lempert and coworkers (19) were able to isolate the two distinct tautomeric methylmercapto-imidazolones (XXIIIa and XXIIIb; R = MeS) by crystallizing the compound from solvents of different polarity. The crystalline solid obtained from the polar crystallizing solvent (pyridine/water) showed in its infrared spectrum (potassium bromide disc) C=O and C=N frequencies characteristic of the conjugated XXIIIb form, while the compound obtained from petroleum ether-chloroform showed in its spectrum the unconjugated form XXIIIa.

In Part II of the thesis we have used physical methods (infrared, ultraviolet, and n.m.r. spectroscopy, and basicity measurements) to investigate the tautomeric equilibria XXIIIa$\rightleftharpoons$XXIIIb (where R = H, Me, Et, Ph, and MeS) and XXXIVa$\rightleftharpoons$ XXXIVb.

In Part III a more fundamental study of one aspect of 2-thiohydantoin chemistry has been undertaken. The stepwise degradation of peptides (1) into the constituent amino acids is accomplished by converting the C-terminal amino acid residue (XXXVI) into a 1-acyl-2-thiohydantoin derivative (XXXVII) by treatment with acetic anhydride and ammonium thiocyanate, The 1-acyl-2-thiohydantoin is subsequently hydrolyzed by acid (20) or by alkali:



XXXVI XXXVII XXXVIII XXXIX

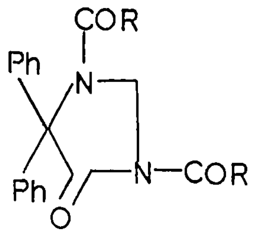
The group R' in XXXIX represents the remainder of the peptide chain which can be separated from the reaction mixture and then submitted to the same reaction sequence for a second time. The amino acid can be recovered from the 2-thiohydantoin XXXVIII by hydrolysis in strong mineral acid (21). The kinetics of such a degradation process, not yet understood must depend on the ionization behaviour of the 2-thiohydantoin (XXXVIII) in strong mineral acid.

We accordingly studied the protonation equilibria of 2-thiohydantoins in sulphuric acid, by Hammett's spectroscopic method (22). Similar studies of the ionization of thioureas (23) and thiolactams (24) had indicated that the behaviour of these weak organic bases does not follow Hammett's $\underline{H}_0$ function. In Part III we show that 2-thiohydantoins also deviate from the behaviour of Hammett bases, and that the deviation is largely caused by the different behaviour of the unionized thiohydantoin and of unionized Hammett bases with increase of acid concentration.

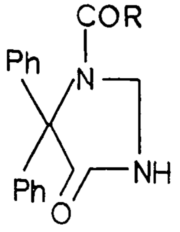
PART I

ACYLATION PRODUCTS OF 5,5-DIPHENYLIMIDAZOLID-4-ONE

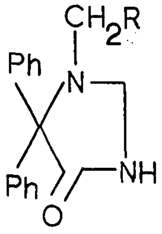
By treating 5,5-diphenylimidazolid-4-one (IV) with formic acid according to the procedure of Biltz, Seydel, and Hamburger-Glaser (13), we obtained a compound $C_{16}H_{14}O_2N_2$, m.p. 256-8°, agreeing in its properties with the compound obtained by Biltz and his colleagues and formulated as XII. However, the infrared spectrum of the compound showed strong peaks at 1720 and 1650 cm^{-1}, whereas XII would be expected (25), like IV (ν_{max}^{KBr} 1705 cm^{-1}), to show only one peak in this region. The second peak is due to a $N_{(1)}$- formyl group, and the structure XI (= XLI; R = H) for this compound was proved by reducing it with lithium aluminum hydride to 5,5-diphenyl-1-methylimidazolid-4-one (XLII; R = H) (10). This was converted by treatment with dimethyl sulphate to 1,3-dimethyl-5,5-diphenylimidazolid-4-one (XLIII; R = H), a compound also obtained by treatment of 5,5-diphenylimidazolid-4-one (IV) with dimethyl sulphate. Attempts to monomethylate IV with methyl iodide or dimethyl sulphate and obtain XLII (R = H) were fruitless, presumably



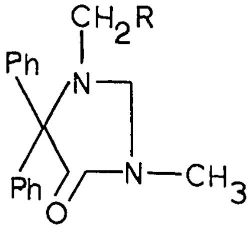
XL



XLI



XLII



XLIII

because the steric crowding about the amino group reduces its reactivity to that of an amide.

The reaction of 5,5-diphenylimidazolid-4-one with acetic anhydride gave a compound $C_{19}H_{18}O_3N_2$, m.p. 199-200^o, agreeing in its properties with those reported by Biltz et al for IX. However, its infrared spectrum showed strong peaks at 1760, 1720, and 1660 cm^{-1}, indicative of the structure VIII (= XL; R = CH_3) rather than IX. When treated with hot 1N sodium hydroxide it was converted into a compound $C_{17}H_{16}O_2N_2$, having infrared peaks at 1720 and 1650 cm^{-1}, and hence the structure XLI (R = CH_3) rather than X. Reduction with lithium aluminum hydride converted the latter compound into 5,5-diphenyl-1-ethylimidazolid-4-one (XLII; R = CH_3), which showed the characteristic signals for a N-ethyl group in its n.m.r. spectrum (Table I). In fact, the route IV→XL→XLI→XLII represents the most convenient method for alkylating the amino nitrogen of 5,5-diphenylimidazolid-4-one. Its generality was shown by using it to obtain the 1-propyl (XLII; R = C_2H_5) and 1-benzyl (XLII; R = Ph) derivatives.

Further support for our revised structures for Biltz's compounds came from their n.m.r. spectra. In all compounds the ten protons of the 5,5-diphenyl groups gave rise to broad singlets at 7.42 ± 0.06 p.p.m. downfield from the signals of tetramethylsilane. The peaks due to other protons, recognizable by their integrated areas or, in the case of

Table I

N.M.R. Spectra of Some 1- and 3-substituted 5,5-diphenyl-imidazolid-4-ones in deuterochloroform

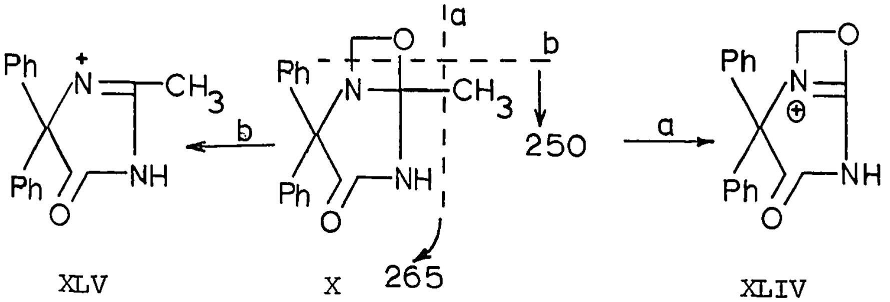
Substituent		N.M.R. Peaks*		
1-	3-	1 - Substit	$C_{(2)}$-H	3-Substit
H	H	2.76	4.40	7.96
Me	H	2.07	4.12	8.46
Et	H	2.20 (*q*), 1.10(*t*)[a]	4.20	8.50
Pr	H	2.00(*t*), 1.32(*m*), 0.88(*t*)[b]	4.12	8.85
$PhCH_2$	H	3.32, 7.40	3.97	8.30
CHO	H	8.00	5.05	7.93
$COCH_3$	H	1.52	5.15	8.25
COC_2H_5	H	1.70(*q*), 0.70(*t*)[c]	5.20	8.20
COPh	H	7.35	4.95	8.32
$COCH_3$	Me	1.53	5.10	3.02
COC_2H_5	Me	1.72(*q*), 0.73(*t*)[c]	5.13	3.05
COPh	Me	7.40	5.14	3.03
$COCH_3$	$COCH_3$	1.48	5.47	2.52
COC_2H_5	COC_2H_5	1.70(*q*), 0.75(*t*)[c]	5.48	2.90(*q*), 1.15(*t*)[d]
COPh	COPh	7.25	5.60	7.45

* In p.p.m. from tetramethylsilane as an internal standard; peaks singlets unless otherwise indicated (*t* = triplet, *q* = quartet, *m* = multiplet).

a, J = 7.4 c.p.s.; b, J = 7.0 c.p.s.; c, J = 7.5 c.p.s.; d, J = 7.2 c.p.s.

signals from $N_{(1)}$-H or $N_{(3)}$-H, by their disappearance on addition of D_2O to the solution, are listed in Table I. It is noticeable that the removal of the $N_{(3)}$-acyl group has a large effect on the chemical shift of the methylene protons. This would be expected (26) if $N_{(3)}$ were neighbouring the methylene group, as in XL, but not if it were remote, as in IX.

The mass spectrum of the compound $C_{17}H_{16}O_2N_2$ formulated as X would be expected to undergo fragmentations



XLV X XLIV

involving the loss of a methyl group (cleavage a) and of a formaldehyde molecule (cleavage b) to give XLIV and XLV, at 265 and 250 mass units respectively, of high intensity (27). In fact, only very weak peaks of these masses could be detected in the spectrum of the compound (Fig. 2).

On the other hand the alternative structure XLVI (R = H; = XLI; R = Me) allows a satisfactory interpretation to be given for all the prominent peaks in the mass spectrum of the compound (recorded in Table II). For comparison, compounds IV and XLVI (R = Me) were investigated at the same time. All three compounds showed only very weak parent

Table II

Partial Mass Spectra of 5,5-diphenylimidazolid-4-ones

	Relative Intensity*			Probable Composition of Ion
Mass	IV	XLVI; R = H	XLVI; R = Me	
294	-	-	0.01	$C_{18}H_{18}N_2O_2$ (XLVI; R = Me)
280	-	0.64	-	$C_{17}H_{16}N_2O_2$ (XLVI; R = H)
265	-	0.03	-	
251	-	1.05	0.10	
250	-	0.52	-	
238	2.0	14.9	2.0	$C_{15}H_{14}N_2O$ (IV); $C_{16}H_{16}NO$ (XLIX + H)
237	1.5	83.4	15.0	$C_{16}H_{15}NO$ (XLIX)
236	7.4	52.7	5.0	$C_{15}H_{12}N_2O$ (IV-2H); $C_{16}H_{14}NO$ (XLIX-H)
210	6.3	-	6.3	
209	18.5	-	18.5	
195	90.0	24.6	15.0	$C_{14}H_{13}N$ (XLVII)
194	100.0	100.0	45.0	$C_{14}H_{12}N$ (XLVIII)
193	12.1	-	-	$C_{14}H_{11}N$ (XLVIII^{-H})
182	34.4	13.0	7.5	$C_{13}H_{12}N$ (La or Lb)
180	32.6	14.4	5.0	$C_{13}H_{10}N$ (LI)
166	--	-	30.0	$C_{13}H_{10}$ (LIII)
165	-	27.9	21.5	$C_{13}H_9$ (LIV)
104	51.2	21.1	9.2	C_7H_6N (LII)
91	-	38.8	100.0	C_7H_7 (LV)

* The scale of relative intensities was defined by assigning a value of 100.0 to the most intense peak of mass greater than 90 in each spectrum.

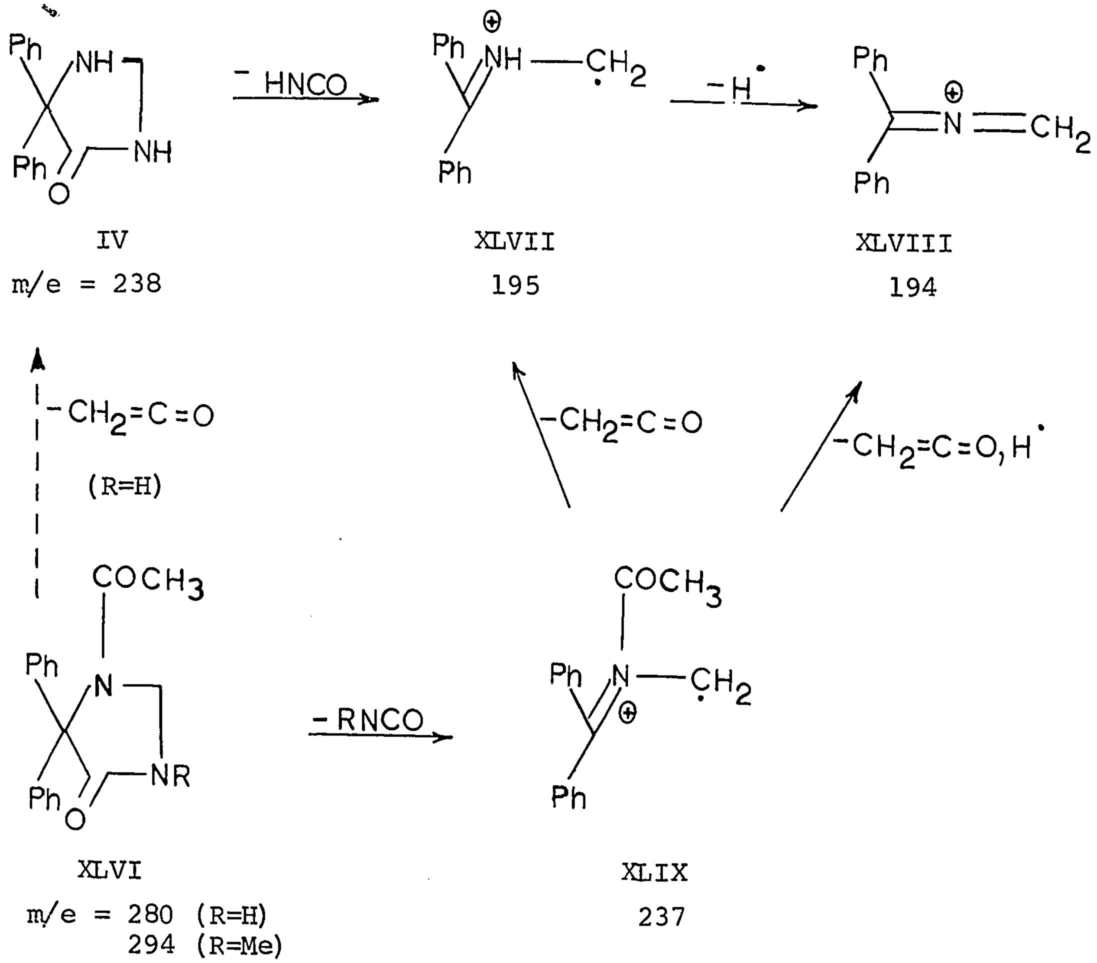
peaks (Figs. 1,2 and 3). The chief fission processes undergone by the parent ions are represented in Reaction Scheme II and receive support from the metastable peaks recorded in Table III.

Table III

Metastable Peaks for Fragmentation Processes Shown in Reaction Scheme II

Process	Metastable Peak	
	Calc.	Found
IV→ XLVII	159.5	159.9
XLVI (R = H) → XLIX	191.0	191.5
XLVI (R = Me)→ XLIX	200.8	200.6
XLIX → XLVII	160.3	160.4
XLIX → XLVIII	159.0	158.8

The processes all find abundant analogy in the literature. Thus lactams (28) and barbituric acids (29) readily lose HN=C=O on electron impact, analogous to IV → XLVII and XLVI (R = H) → XLIX, and amides readily lose ketenes (30) (cf. XLVI (R = H) → IV and XLIX → XLVII) or ketenes and a hydrogen atom (cf. XLIX → XLVIII). The peak at mass 238 in the spectrum of XLVI (R = H) probably results in part from loss of ketene to give the parent ion of IV, but the process is not strongly favoured because no peak at

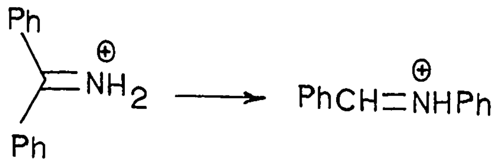


Reaction Scheme II

(Processes shown by solid arrows accord with observed metastable peaks).

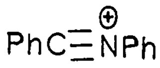
252, resulting from the loss of ketene from XLVI (R = Me), is discernible in the spectrum of the latter compound (Fig. 3).

The formation of the highly-stabilized ion-radical XLVII and ion XLVIII result in two of the strongest peaks in the spectra of all three compounds. It seems likely that many of the smaller ions are derived by further fragmentation of XLVIII; this would account for the large measure of similarity in the spectra of all three compounds at masses below 194. The peaks in Figures 1, 2 and 3 corresponding to these



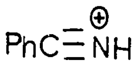
La
m/e = 182

Lb
182



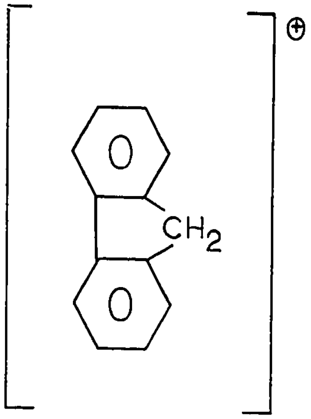
$PhC\equiv\overset{\oplus}{N}Ph$

LI
180

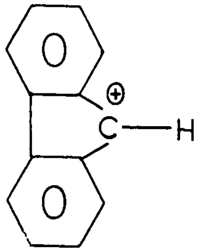


$PhC\equiv\overset{\oplus}{N}H$

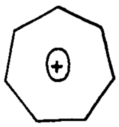
LII
104



LIII
m/e = 166



LIV
165



LV
91

smaller ions may reasonably be assigned, on the basis of analogies in the literature cited, to the ions La or Lb, LI, LII, LIII, LIV (31), LII (32), and LV (33), although in the absence of evidence from metastable peaks or deuterium-labelling experiments these assignments must be regarded as tentative. Hydrogen transfers of the type required to obtain La from XLVII or XLVIII have been observed in the fragmentation of aromatic amides by Bose (31), who has also observed phenyl shifts similar to that involved in La→Lb.

It is apparent that Biltz _et al_ were misled by the unusual resistance to hydrolysis of the $N_{(1)}$-acyl groups in several compounds into assuming that these groups were not present, and hence that a rearrangement had taken place. In fact, although the acyl groups resist hydrochloric and several other acids, they can be removed by concentrated hydrobromic acid - an experimental finding to which Biltz and his co-workers gave no weight in deducing their structures. We considered that perhaps the resistance of the $N_{(1)}$-acyl group to alkaline hydrolysis arose from the acidity of the $N_{(3)}$-H group (pK_{HA} 12)*, which causes 1-acyl-5,5-diphenylimidazolid-4-ones (XLI) to exist as the ions LVI in strongly alkaline solution. These ions will be protected from attack by hydroxide ions by coulombic repulsions. However, this effect is likely to be of minor importance, since when ionization is impossible, as in LVII (R = Me),

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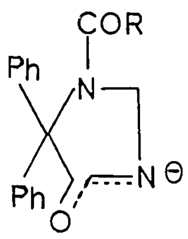
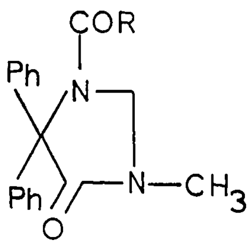
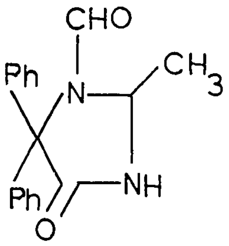
* Estimated on the basis of the solubility of 1-acetyl-5,5-diphenylimidazolid-4-one in buffers of varying pH.


LVI

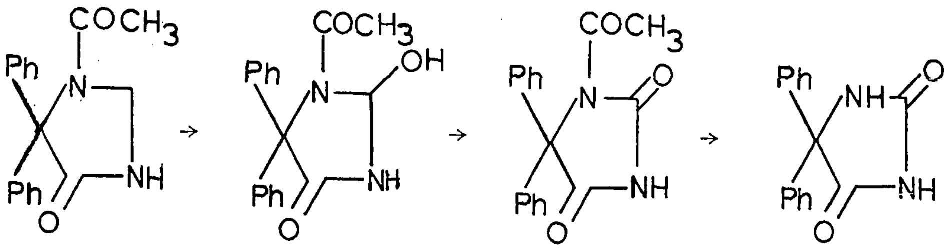

LVII


LVIII

hydrolysis is still negligible after 5 days in refluxing 2N potassium hydroxide. It seems likely that the major factor retarding the hydrolysis of N$_{(1)}$-acyl groups of XLI is the steric crowding of the adjacent geminal diphenyl group. However, on these grounds it becomes difficult to explain the lability of the N(1)-acetyl group of XIX to alkaline hydrolysis, especially when the N(1)-formyl group of XI (our reformulation of XX) resists hydrolysis. Further study of these reactions is desirable.

The reformulation of compound X as XLI (R = Me) makes it possible to explain its oxidation by alkaline potassium permanganate to XIII and by chromic acid to XV. The detailed steps in these oxidations are outlined in Reaction Schemes III and IV.

Oxidation by either reagent would be expected to take place, as in the permanganate oxidation of IV (8), at the methylene carbon atom, to give the carbinolamide, LIX. Chromic acid is known to oxidize alcohols rapidly to carbonyl compounds (34), and so subsequent oxidation of LIX with this reagent to 1-acetyl-5,5-diphenylhydantoin LX (Reaction Scheme III) would be rapid.



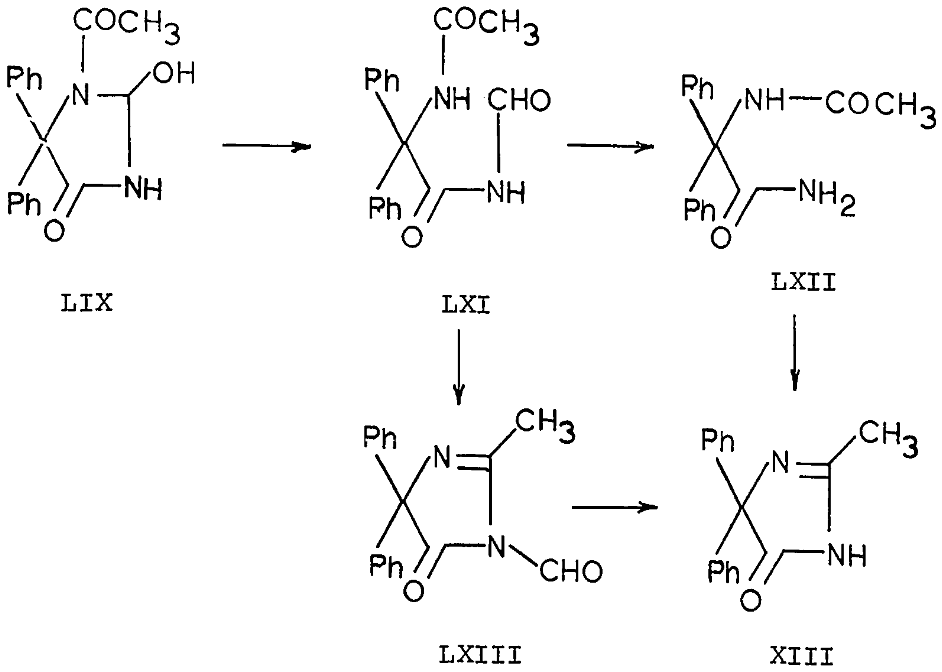
XLI (R=Me) LIX LX XV

Reaction Scheme III

Chromic acid oxidation of 1-acetyl-5,5-diphenylimidazolid-4-one.

We have found that the latter compound is rapidly hydrolyzed to 5,5-diphenylhydantoin XV by hot acetic acid. The hydrolysis of a diacylimide is expected to proceed more rapidly than the hydrolysis of an amide, but even when this is taken into account the facility of the hydrolytic removal of the acetyl group from LX is much greater than would be expected in view of the extreme difficulty of its removal from XLI (R = CH_3).

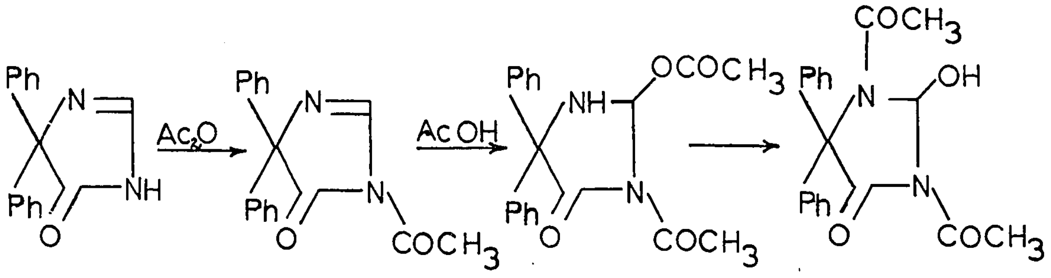
Although potassium permanganate oxidation of alcohols in alkaline medium is rapid (35), the primary oxidation product LIX can undergo a facile base-catalyzed tautomerization to the acyclic N-formyl compound LXI before suffering further oxidation (36). Loss of an N-formyl group to give α-acetamino-α,α-diphenylacetamide (LXII) and the further cyclization of this compound to 2-methyl-4,4-diphenyl- 4H-imidazol-5-one (XIII), (cf. ref. 37, 38) would be expected to be rapid under alkaline conditions.



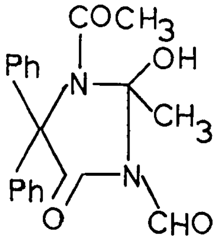
Reaction Scheme IV

Permanganate oxidation of 1-acetyl-5,5-diphenylimidazolid-4-one.

Support for this reaction sequence comes from the fact that the $N_{(3)}$-acetyl derivative (LXVI) of the primary oxidation produc LIX has been prepared and shown to give the postulated intermediates LXI and LXII as well as the final product under varying conditions. The diacetyl compound LXVI



IIIa LXIV LXV LXVI



LXVII

was prepared from 4,4-diphenyl-4H-imidazol-5-one (IIIa) by treatment with acetic anhydride containing 10% acetic acid, or from 1-acetyl-4,4-diphenyl-4H-imidazol-5-one (LXIV) by treatment with acetic acid. It was first prepared by Biltz and Seydel (8), along with the monoacetyl derivative (LXIV), from the reaction of the imidazolone IIIa with acetic anhydride. We have been unable to repeat their preparation, and it is possible that their acetic anhydride contained some acetic acid.

A plausible mechanism for the formation of LXVI, involving the addition of acetic acid to the double bond of LXIV, followed by O→N acyl migration (cf. ref. 39), is shown.

Biltz _et al_ (13) formulated their reaction product as LXVII rather than LXVI. Their structure can be rejected from a consideration of the n.m.r. spectrum of the compound in deuterated dimethyl sulphoxide (Figure 4). This shows singlets (3H) at 2.05 and 2.34 p.p.m. which can be assigned to the methyls of the $N_{(1)}$ and $N_{(3)}$ acetyl groups respectively (40). In the structure LXVII one of these methyl peaks would be expected at a higher field because it is linked to a saturated carbon atom. The broad peak for the phenyl protons is observed at 7.35 p.p.m., slightly split, and a doublet at 8.25 p.p.m. (J = 5.0 c.p.s.) disappears upon addition of deuterium oxide to the solution. This indicates a secondary alcoholic group (41), which is present in LXVI but not in LXVII. The $C_{(2)}$-H, which is spin-coupled with the hydroxyl proton, is not resolved from the phenyl protons, but causes the splitting observable in the peak at 7.35 p.p.m. No deuterium oxide resistant single peak is observed at about 8 p.p.m., such a peak would be observed in this region if an N-formyl group were present, as in LXVII (cf. Table I).

Treatment of the diacetyl compound LXVI with alkali would be expected to cause rapid hydrolysis to the monoacetyl derivative LIX, followed by further transformation via LXI and LXII to XIII. In fact, in 1N sodium hydroxide the conversion of LXVI into XIII was very rapid, and a milder reagent was required to convert it into the intermediate products LXI and LXII. A 1:1 mixture of acetic acid and acetic anhydride was found suitable for this purpose. When the imidazolone IIIa was refluxed in this mixture for six hours, the diacetyl derivative LXVI was not obtained but rather a mixture of the compounds LXI and LXII resulting from its acetolysis. When the reaction time was extended to 18 hours the second compound became the chief product of the reaction.

The structure of the first compound (LXI) followed from its analysis ($C_{17}H_{16}O_3N_2$) and its n.m.r. spectrum (Fig. 5). This showed a singlet (3H) at 2.10 p.p.m. arising from the N-acetyl group, a singlet (10H) at 7.20 p.p.m. from the two phenyl groups, and a singlet peak (1H) at 8.04 p.p.m. caused by the formyl group. Two broad signals at 8.95 and 10.25 p.p.m. disappeared on treatment of the solution with deuterium oxide and are, therefore, assigned to the amide and imide protons respectively.

The N-formyl compound (LXI) was also prepared by pyrolysis of LXVI. It was converted into the imidazolone XIII within five minutes by treatment with hot 1N sodium hydroxide.

The second product of the acetolysis of LXVI was α-acetamino-α,α-diphenylacetamide (LXII), identical with the compound prepared by treating α-amino-α,α-diphenylacetamide with acetyl chloride in pyridine. On treatment with alkali it was converted into the imidazolone XIII more slowly than expected (37), perhaps because of its very slight solubility in aqueous alkali. By contrast, the conversion of both LXVI and LXI was rapid, perhaps because of the greater solubility of these weakly acidic compounds. It is possible that besides LXII the more alkali-labile intermediate LXIII is involved in the conversion of LXI into XIII.

<u>Figure 1</u>

Mass spectral fragmentation of 5,5-diphenylimidazolid-4-one (IV) (only fragments having 2% or higher relative intensity of the most intense peaks are shown).

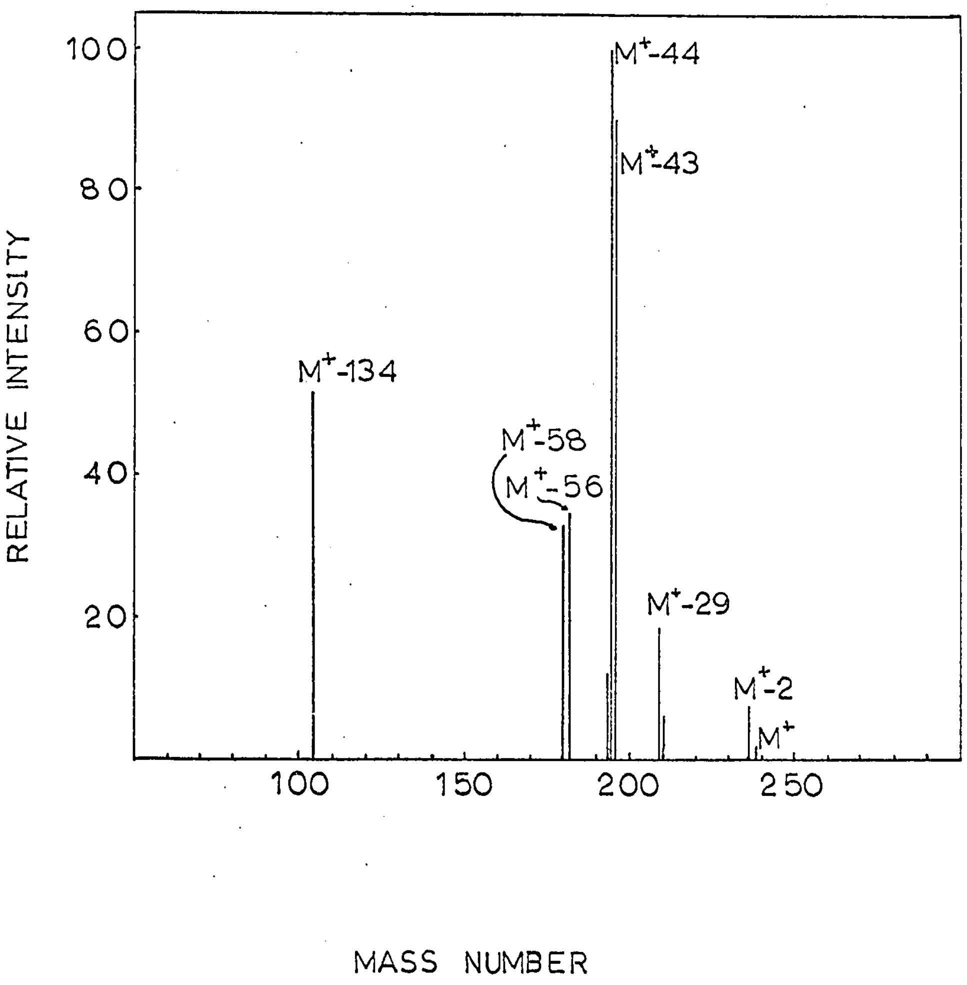
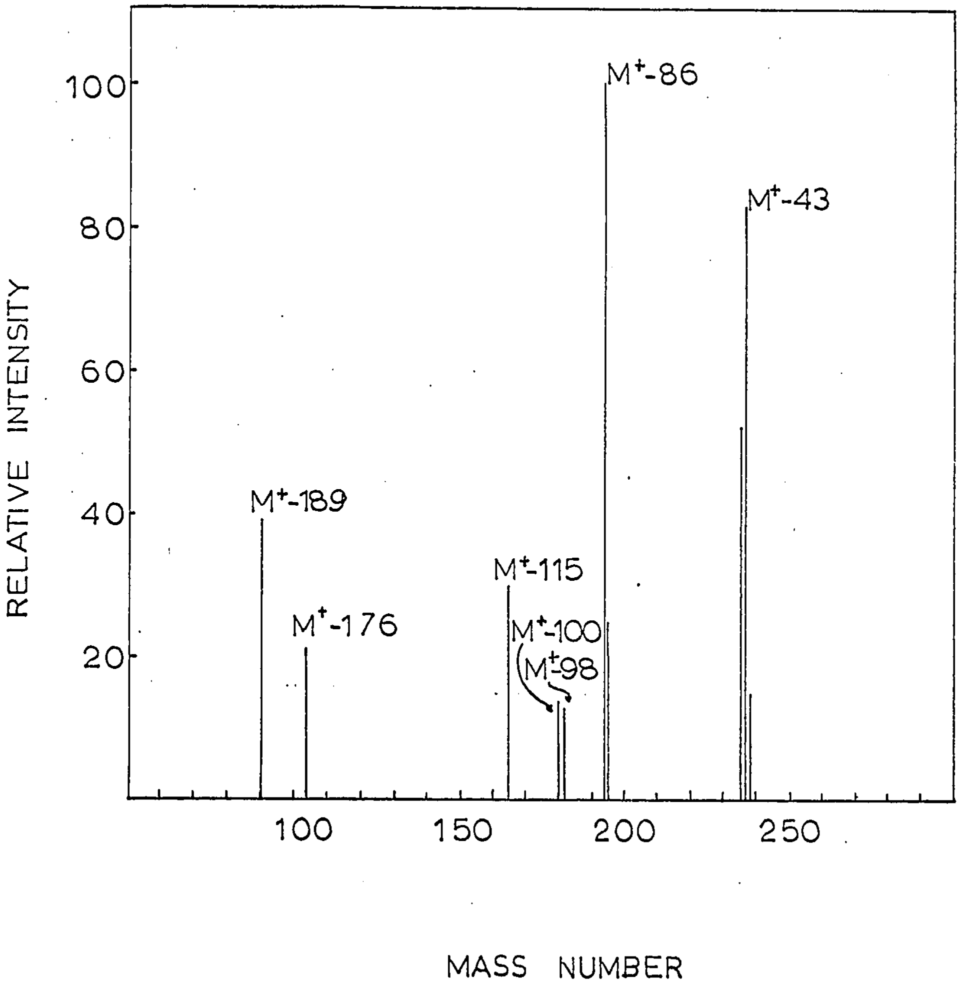

RELATIVE INTENSITY
100
80
60
40
20
100
150
200
250
MASS NUMBER
M⁺-44
M⁺-43
M⁺-134
M⁺-58
M⁺-56
M⁺-29
M⁺-2
M⁺

Figure 2

Mass spectral fragmentation of 1-acetyl-5,5-diphenylimidazolid-4-one XLI (R = Me; = XLVI; R = H). (Only fragments having 2% or higher relative intensity of the most intense peaks are shown.)

Figure 2

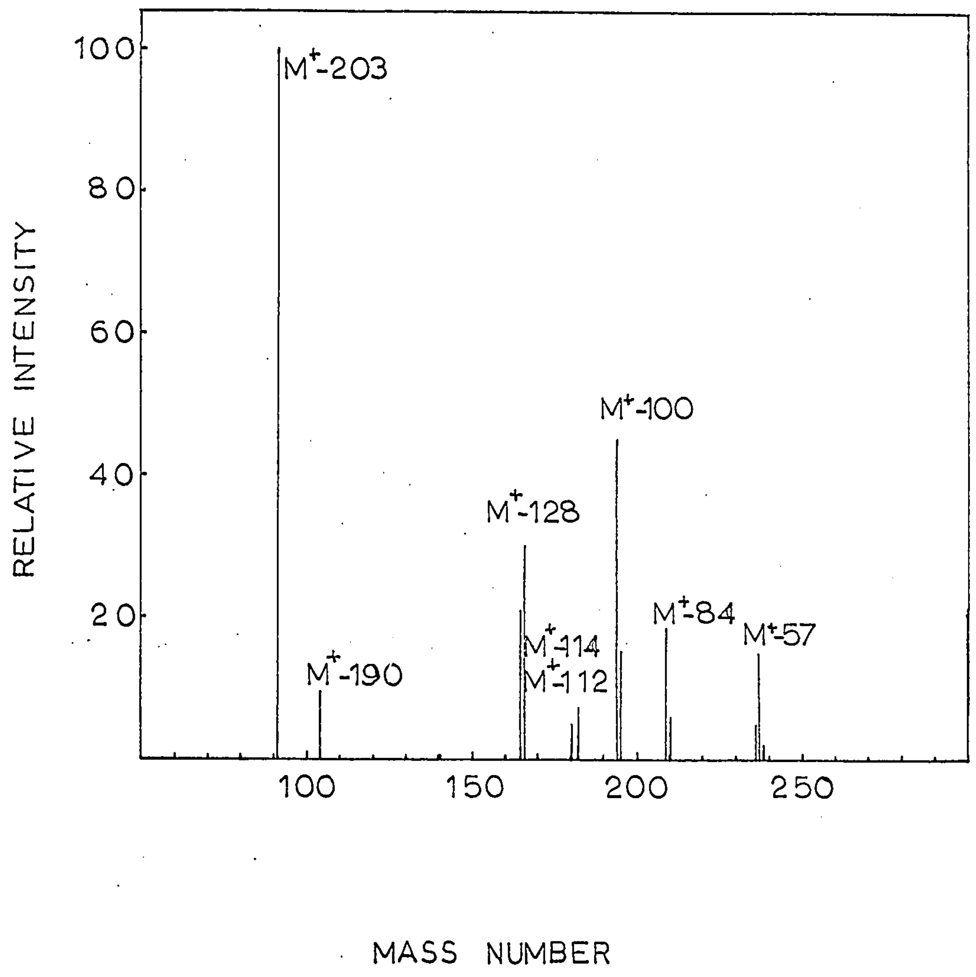
Mass spectral fragmentation of 1-acetyl-5,5-diphenylimidazolid-4-one XLI (R = Me; = XLVI; R = H). (Only fragments having 2% or higher relative intensity of the most intense peaks are shown.)



RELATIVE INTENSITY
100
80
60
40
20
M+-86
M+-43
M+-189
M+-176
M+-115
M+-100
M+-98
100
150
200
250
MASS NUMBER

Figure 3

Mass spectral fragmentation of 1-acetyl-5,5-diphenyl-3-methylimidazolid-4-one (XLVI; R = Me). (Only fragments having 2% or higher relative intensity of the most intense peak are shown).



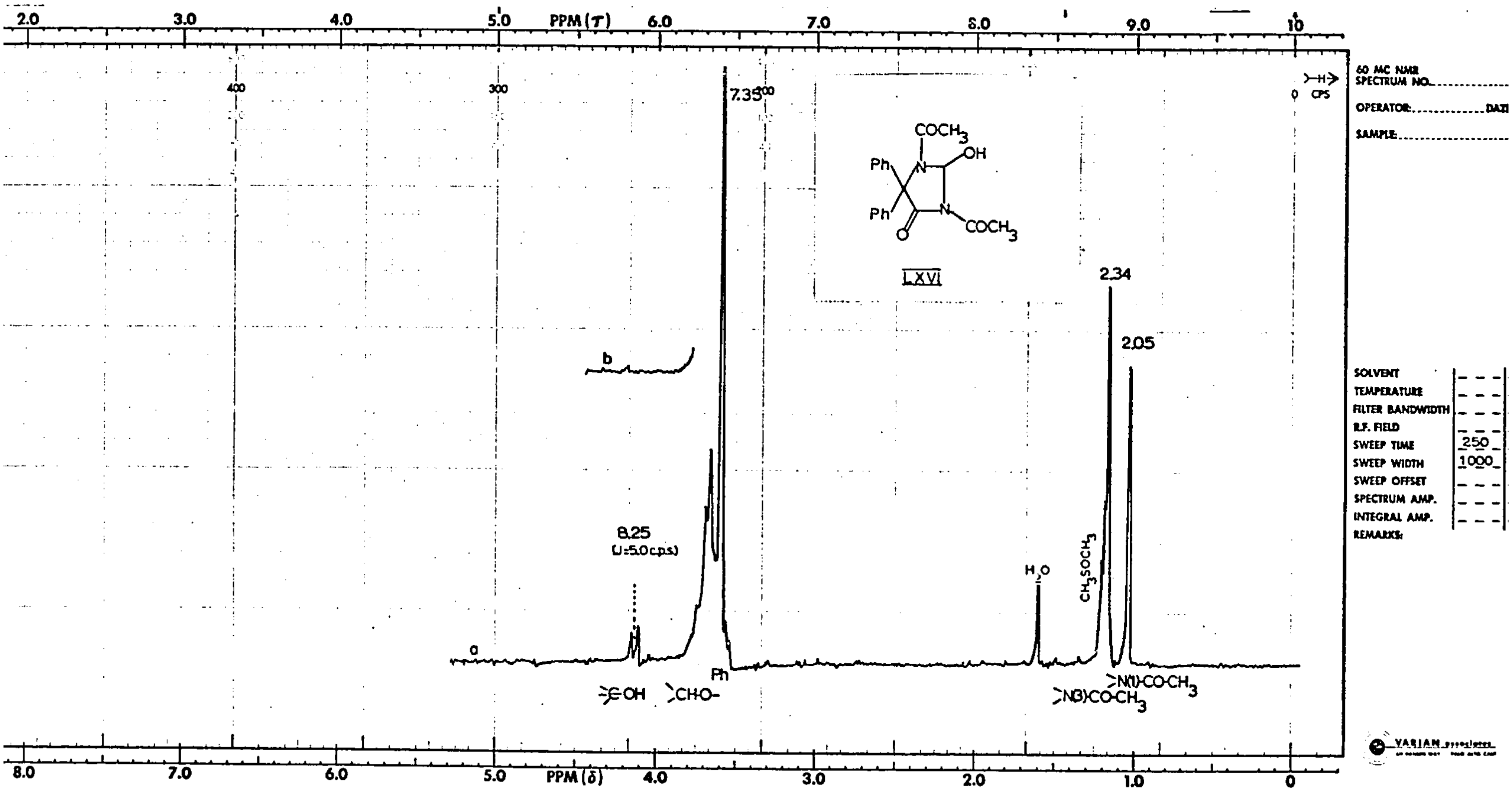
100
80
60
40
20
RELATIVE INTENSITY
M^+-203
M^+-190
M^+-128
M^+-114
M^+-112
M^+-100
M^+-84
M^+-57
100
150
200
250
MASS NUMBER

Figure 4

Nuclear magnetic resonance spectrum of 1,3-diacetyl-5,5-diphenyl-2-hydroxyimidazolid-4-one (LXVI) in CD_3SOCD_3

a) before D_2O exchange

b) after D_2O exchange.



60 MC NMR SPECTRUM NO.

OPERATOR: DATE

SAMPLE:

SOLVENT

TEMPERATURE

FILTER BANDWIDTH

R.F. FIELD

SWEEP TIME 250

SWEEP WIDTH 1000

SWEEP OFFSET

SPECTRUM AMP.

INTEGRAL AMP.

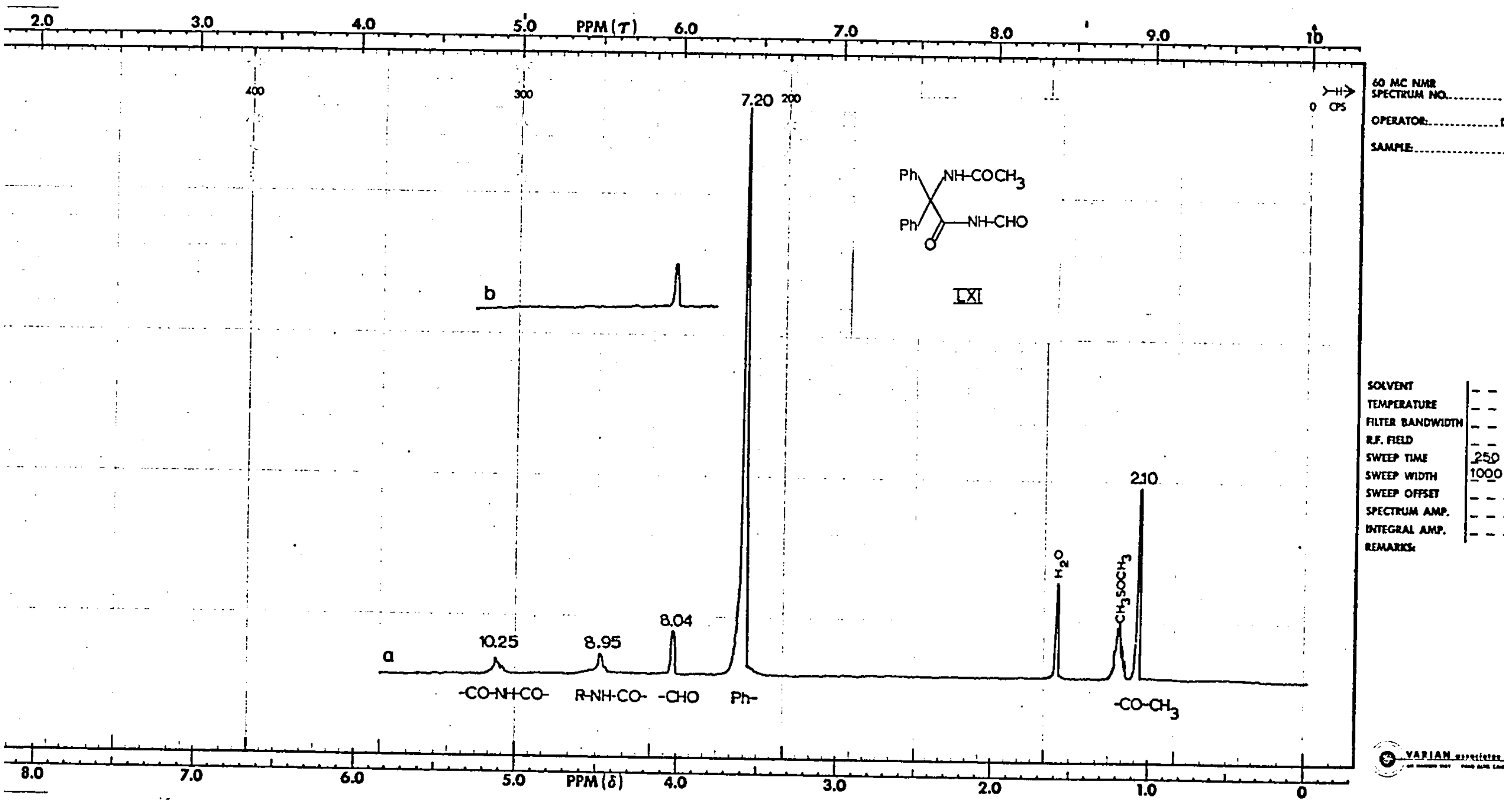
REMARKS:

Figure 5

Nuclear magnetic resonance spectrum of α,α-diphenyl-α-acetamino-N-formylacetamide (LXI) in CD_3SOCD_3

a) before D_2O exchange

b) after D_2O exchange.


PPM (τ)
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
400
300
200
0 CPS
7.20
b
a
10.25
8.95
8.04
2.10
-CO-NH-CO-
R-NH-CO-
-CHO
Ph-
H$_2$O
CH$_3$SOCH$_3$
-CO-CH$_3$
Ph
NH-COCH$_3$
Ph
NH-CHO
O
LXI
60 MC NMR SPECTRUM NO.
OPERATOR:
SAMPLE:
SOLVENT
TEMPERATURE
FILTER BANDWIDTH
R.F. FIELD
SWEEP TIME 250
SWEEP WIDTH 1000
SWEEP OFFSET
SPECTRUM AMP.
INTEGRAL AMP.
REMARKS:
VARIAN associates
PPM (δ)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0

EXPERIMENTAL

Raney Nickel Desulphurization of 5,5-Diphenyl-2-thiohydantoin

(a) Using "W_7" Nickel

5,5-Diphenyl-2-thiohydantoin (20 g.) in ethanol (560 ml.) was treated with Raney nickel of "W_7" activity (43). The product was chromatographed on neutral alumina. Elution with benzene-ether 1:1 (v/v) yielded 5,5-diphenylimidazolid-4-one (IV) (8.0 g.), m.p. 182-184°. Elution with ether-ethanol 1:1 (v/v) yielded 4,4-diphenylimidazol-5-one (III) (8.2 g.), m.p. 164-166°. Carrington et al (10) reported obtaining IV only in 64% yield. Attempts to prepare the imidazolone III by the method of H. Bohringer and K. Schneidt (12) resulted in isolation of 5,5-diphenylimidazolid-4-one (IV) in about 35% yield.

(b) Using "W_4" Nickel

5,5-Diphenyl-2-thiohydantoin, treated in similar fashion with "W_4" Raney nickel (43), gave bis(4,4-diphenyl-5-oxoimidazolid-2-yl) sulphide in 60% yield, m.p. 188-190°. This compound was obtained by Whalley et al (11) as a minor product of the desulphurization of 5,5-diphenyl-2-thiohydantoin with three week old Raney nickel.

Treatment of this compound with hydrogen peroxide according to Whalley et al (11) gave a 60% yield of 4,4-diphenyl-4H-imidazol-5-one (IIIa).

Acylation Products of 5,5-Diphenylimidazolid-4-one (IV)

(a) 5,5-Diphenyl-1-formylimidazolid-4-one XI (= XLI; R = H)

This compound, prepared according to the procedure of Biltz *et al* (13), crystallized from ethanol as colourless plates, m.p. 256-258° (reported m.p. 260°), ν_{max}^{KBr}: 1720 (s), 1650 (s) cm^{-1}.

(b) 1,3-Diacetyl-5,5-diphenylimidazolid-4-one VIII (= XL; R = Me)

The compound, prepared according to ref. 13, crystallized from ethyl acetate as colourless prisms, m.p. 199-200° (reported: 203-204°), ν_{max}^{KBr}: 1750, 1720, 1650 cm^{-1}.

Calc. for $C_{19}H_{18}O_3N_2$: C, 70.79; H, 5.63; N, 8.69%

Found: C, 71.04; H, 5.52; N, 9.37%.

(c) 1,3-Dipropionyl-5,5-diphenylimidazolid-4-one (XL; R = Et)

5,5-Diphenylimidazolid-4-one (4 g.) was heated with propionic anhydride (20 ml.) for 4 hours. The excess anhydride was evaporated at reduced pressure, and the residual white solid was crystallized from ethyl acetate, yielding white crystals (4.6 g.), m.p. 173-175°, ν_{max}^{KBr} : 1750, 1710, 1650 cm^{-1}.

Calc. for $C_{21}H_{22}O_3N_2$: C, 71.98; H, 6.33; N, 8.00%.

Found: C, 72.16; H, 6.24; N, 8.34%.

(d) 1,3-Dibenzoyl-5,5-diphenylimidazolid-4-one (XL; R = Ph)

5,5-Diphenylimidazolid-4-one (4 g.) was refluxed with benzoyl chloride (20 ml.) for 3 hours, and the product worked up as above. Crystallization from ethyl acetate gave a white solid (6.10 g.), m.p. 209-210°, ν_{max}^{KBr}: 1760, 1700, 1670 cm^{-1}.

Calc. for $C_{29}H_{22}O_3N_2$: C, 78.01; H, 4.97; N, 6.27%.
Found: C, 77.90; H, 5.39; N, 6.49%.

Hydrolysis of 1,3-Diacyl-5,5-diphenylimidazolid-4-ones (XL)

The diacyl compound (4 g.) was refluxed for about 3 hours in 1N sodium hydroxide (25 ml.), during which time it dissolved completely. The hot solution was cooled and neutralized with concentrated hydrochloric acid. A colourless precipitate formed and was removed by filtration and crystallized from ethanol. Essentially quantitative yields were obtained. The properties of the products are given in Table IV.

Table IV

Properties of 1-acyl-5,5-diphenylimidazolid-4-ones (XLI)

Acyl group	m.p. (°C)	Formula	Analysis	%C	%H	%N
Acetyl	202-4*	$C_{17}H_{16}O_2N_2$	Calc:	72.84	5.75	10.00
			Found:	73.25	5.73	10.34
Propionyl	203-5	$C_{18}H_{18}O_2N_2$	Calc:	73.45	6.16	9.52
			Found:	73.32	6.06	10.00
Benzoyl	236-8	$C_{22}H_{18}O_2N_2$	Calc:	77.17	5.30	8.18
			Found:	77.57	5.19	8.16

* Biltz *et al* (13) report - m.p. 204-205°

Lithium Aluminum Hydride Reduction of 1-Acyl-5,5-diphenylimidazolid-4-ones (XLI)

The 1-acyl-5,5-diphenylimidazolid-4-one (1 g.) in anhydrous tetrahydrofuran (50 ml.) was slowly added to a slurry of lithium aluminum hydride (1 g.) in tetrahydrofuran (50 ml.). After the vigorous reaction had subsided the mixture was refluxed for one hour. The mixture was cooled, diluted with water, and extracted with chloroform (3 x 50 ml.). The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol. The properties of the white crystalline compounds are given in Table V.

Table V

Properties of 1-Alkyl-5,5-diphenylimidazolid-4-ones (XLII)

Alkyl Group	m.p. (°C)	Formula		Analysis %C	%H	%N
Methyl	204-6*	$C_{16}H_{16}ON_2$	Calc:	76.16	6.39	11.10
			Found:	76.43	6.40	10.44
Ethyl	206-8	$C_{17}H_{18}ON_2$	Calc:	76.66	6.81	10.52
			Found:	76.28	6.52	10.07
Propyl	183-4	$C_{18}H_{20}ON_2$	Calc:	77.11	7.19	9.99
			Found:	77.00	7.25	10.40
Benzyl	212-4	$C_{22}H_{20}ON_2$	Calc:	80.46	6.14	8.53
			Found:	79.97	6.04	8.38

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*Carrington _et al_ (10) reported m.p. 215-216°.

4,4-Diphenyl-1-methylimidazolid-5-one

The following procedure is more convenient than the catalytic reduction over Adam's catalyst carried out by Carrington, Vasey, and Waring (10).

Sodium borohydride (1 g.) was added to a solution of 4,4-diphenyl-1-methyl- 4H -imidazol-5-one (0.7 g.) (13,15) in absolute ethanol (50 ml) and the reaction mixture was stirred for 1 hour. The excess borohydride was destroyed by adding 0.1 N hydrochloric acid until effervescence ceased; the solution was then made alkaline by the addition of sodium carbonate. Deposited white needles of 5,5-diphenyl-3-methylimidazolid-4-one (0.3 g.), m.p. 88-90° (lit. 87-88°(13)), ν_{max}^{KBr} 1690 cm^{-1}, when left standing overnight.

Preparation of 1-Acetyl-5,5-diphenyl-3-methylimidazolid-4-one (XLVI; R = Me)

A mixture of 4,4-diphenyl-1-methylimidazolid-5-one (0.2 g.) and acetic anhydride (5 ml.) was refluxed for three hours. The anhydride was removed under reduced pressure and the residue was crystallized from ethanol, yielding white needles (0.2 g.), m.p. 175-177°, ν_{max}^{KBr}: 1710, 1660 cm^{-1}. Biltz et al (13) prepared this compound, m.p. 177°, by methylating 1-acetyl-5,5-diphenylimidazolid-4-one (XLI; R = Me).

1,3-Dimethyl-5,5-diphenylimidazolid-4-one (XLIII; R = H)

(a) From methylation of 5,5-diphenylimidazolid-4-one (IV)

A mixture of 5,5-diphenylimidazolid-4-one (0.5 g.) and dimethyl sulphate (2 g.) was left overnight. After addition of 0.1 N sodium hydroxide (10 ml.) the solid which separated was removed by filtration and crystallized from ethanol: white crystals (0.6 g.), m.p. 112-113°, (lit. 113-115°, (10)), ν_{max}^{KBr}: 1715 cm^{-1}.

Calc: for $C_{17}H_{18}ON_2$: C, 76.66; H, 6.81; N, 10.52%.
Found: C, 76.23; H, 6.45; N, 10.32%.

(b) From methylation of 5,5-diphenyl-1-methylimidazolid-4-one (XLII; R = H)

5,5-Diphenyl-1-methylimidazolid-4-one (XLII; R = H) (0.5 g.) was warmed gently with dimethyl sulphate (2 ml.) until dissolved (10 minutes). The solution was left overnight and then 0.1 N sodium hydroxide solution (10 ml.) was added. A white crystalline precipitate was collected and crystallized from ethanol. It proved to be identical (infrared spectrum, mixed m.p.) to the methylation product of 5,5-diphenylimidazolid-4-one described above.

1-Acetyl-5,5-diphenylhydantoin (LX)

5,5-Diphenylhydantoin (5 g.) was refluxed in a mixture of pyridine (50 ml.) and acetic anhydride (50 ml.) for three hours. The solvent was removed by evaporation at reduced pressure. Treatment of the oily residue with water gave a white solid (2.5 g.), which crystallized with difficulty from ethyl acetate to give 1-acetyl-5,5-diphenylhydantoin, m.p. 217-220°, ν_{max}^{KBr} 1795, 1740, 1700 cm^{-1}.

Calc: for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80%.
Found: C, 69.36; H, 4.66%.

A solution of 1-acetyl-5,5-diphenylhydantoin (1 g.) in acetic acid (10 ml.), after boiling under reflux for 90 minutes, yielded on cooling and dilution with water 5,5-diphenylhydantoin (0.7 g.) identified by its infrared spectrum.

1-Acetyl-5,5-diphenyl-3-methylhydantoin

1-Acetyl-5,5-diphenylhydantoin (1 g.) dissolved in dimethyl sulfate (5 ml.) when the mixture was heated on the steam-bath for 30 minutes. The cooled solution was diluted with water (50 ml.) and after standing overnight was extracted with ether (3 x 50 ml.). The ether solution after drying (Na_2CO_3) and concentration yielded colourless plates of 1-acetyl-5,5-diphenyl-3-methylhydantoin (0.4 g.), m.p. 170-172°, ν_{max}^{KBr}: 1745, 1720 cm^{-1}.

Calc: for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09%.
Found: C, 70.05; H, 5.50; N, 9.17%.

Treatment of 1-acetyl-5,5-diphenyl-2-methyl hydantoin (0.2 g.) with 5% potassium carbonate solution (5 ml.) for 5 minutes on the steam-bath yielded 5,5-diphenyl-2-methylhydantoin (0.1 g.), m.p. 214-216° (lit. m.p. 216-217° (13)), ν_{max}^{KBr}: 3200 (broad), 1715 (broad) cm^{-1}.

1-Acetyl-4,4-diphenyl-4H-imidazol-5-one (LXIV)

A solution of 4,4-diphenyl-4H-imidazol-5-one (2.5 g.) in acetic anhydride (15 ml.) was boiled under reflux for three hours. The resultant solution was concentrated under reduced pressure to about 10 ml. When cooled it deposited white crystals of 1-acetyl-4,4-diphenyl-4H-imidazol-5-one (1.5 g.), m.p. 134-136° (lit. m.p. 138-139° (13)), ν_{max}^{KBr}: 1750, 1720, 1625 cm^{-1}.

Calc: for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07%.

Found: C, 73.69; H, 5.13%.

1,3-Diacetyl-5,5-diphenyl-2-hydroxyimidazolid-4-one (LXVI)

(a) From 4,4-diphenyl- 4H -imidazol-5-one (IIIa)

A mixture of 4,4-diphenyl- 4H -imidazol-5-one (2 g.) acetic anhydride (13.5 ml.) and acetic acid (1.5 ml.) was boiled under reflux for two hours. The solution was cooled and placed in an evacuated desiccator for 24 hours. Filtration removed white crystals of 1,3-diacetyl-5,5-diphenyl-2-hydroxyimidazol-4-one (0.5 g.), m.p. 243-245° (lit. m.p. 224-225° (8)), ν_{max}^{KBr}: 3100 (broad), 1760, 1720, 1650 cm^{-1}.

Calc: for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36%.

Found: C, 67.38; H, 5.37%.

(b) From 1-Acetyl-4,4-diphenyl- 4H -imidazol-5-one (LXIV)

A solution of 1-acetyl-4,4-diphenylimidazol-5-one (1 g.) in acetic acid (5 ml.) was refluxed for 30 minutes. The solution on cooling deposited crystals of 1,3-diacetyl-5,5-diphenyl-2-hydroxyimidazol-4-one (0.4 g.), identical by m.p. and infrared spectrum with the material obtained above.

α-Amino-α,α-diphenylacetamide

The following procedure is more convenient than those in the literature (44,45). A solution in dioxane (150 ml.)

of crude α-chlorodiphenylacetyl chloride, prepared from benzilic acid (10 g.) (46), was saturated with a slow stream of ammonia for three hours. It was filtered to remove ammonium chloride. The filtrate was placed in a pressure flask and further saturated with a stream of ammonia for 90 minutes. The flask was then closed and heated on a steam bath for 24 hours. The solution was cooled, filtered, and diluted with 10% ammonium hydroxide (150 ml.). The precipitate was crystallized from ethanol, yielding α-amino-α,α-diphenylacetamide (5 g.), m.p. 143-145°, (lit. m.p. 143-144° (44,45)), ν_{max}^{KBr}: 3400 (broad), 1695, 1570 cm^{-1}.

Calc: for $C_{14}H_{14}ON_2$: C, 74.31; H, 6.24; N, 12.38%.

Found: C, 74.40; H, 5.91; N, 12.06%.

The same compound was prepared by refluxing 4,4-diphenyl-4H-imidazol-5-one (1 g.) in 1% sodium hydroxide (25 ml.) for 30 minutes (cf. ref. 47). A 50% yield was obtained as crystals when the solution was cooled.

α-Acetamino-α,α-diphenylacetamide (LXII)

(a) From α-amino-α,α-diphenylacetamide

Acetyl chloride (5 ml.) was added slowly with stirring to α-amino-α,α-diphenylacetamide (1 g.) in pyridine (5 ml.). After 24 hours at room temperature, the solution was diluted with water (100 ml.) and extracted with chloroform (3 x 50 ml.). The extract was dried and evaporated to yield an oily solid which crystallized from ethanol:(0.6 g), m.p. 276-278°,

ν_{max}^{KBr}: 3250, 1675, 1530, 1510 cm^{-1}.

Calc: for $C_{18}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44%.

Found: C, 71.40; H, 5.87; N, 10.86%.

(b) From 4,4-diphenyl- 4H -imidazol-5-one (IIIa)

A solution of 4,4-diphenyl- 4H -imidazol-5-one (2.0 g.) in acetic acid (7.5 ml.) and acetic anhydride (7.5 ml.) was refluxed for 18 hours. The solution was cooled and after seeding deposited crystals (1 g.) shown to be α-acetamino-α,α-diphenylacetamide by m.p., mixed m.p., and infrared spectrum. When the solution was refluxed for six hours, it deposited only 100 mg. of α-acetamino-α,α-diphenylacetamides. Dilution of the filtrate with ethanol (15 ml.) precipitated an amorphous solid, shown by n.m.r. to be an approximately 1:2 mixture of α-acetamino-α,α-diphenylacetamide (acetyl peak at 1.85 p.p.m.) and α-acetamino-α,α-diphenyl-N-formylacetamide (see below) (acetyl peak at 2.10 p.p.m., Fig. 5).

α-Acetamino-α,α-diphenyl-N-formylacetamide (LXI)

1,3-Diacetyl-5,5-diphenyl-2-hydroxyimidazolid-4-one (1 g.) was heated in a sublimation apparatus under a pressure of 3 mm. up to a bath temperature of 240°. After melting frothing took place, and white crystals of α-acetamino-α,α-diphenyl-N-formylacetamide (0.5 g.), m.p. 189-190°, ν_{max}^{KBr}: 3300 (doublet) 1750, 1665, 1520 cm^{-1} collected on the upper part of the apparatus.

Calc. for $C_{17}H_{16}N_3O_2$: C, 68.90; H, 5.44; N, 9.45%.

Found: C, 68.87; H, 5.52; N, 9.30%.

4,4-Diphenyl-2-methylimidazol-5-one (XIII)

α-Acetamino-α,α-diphenyl-N-formylacetamide (0.5 g.) dissolved in 1 N sodium hydroxide (5 ml.) at 70-80° after a few minutes. After 10 minutes the solution was neutralized with hydrochloric acid, and the colourless precipitate was recrystallized from ethanol, yielding (0.3 g.), m.p. 218-220°, identified as 4,4-diphenyl-2-methyl-4H-imidazol-5-one by comparison by mixed melting point and infrared spectrum with an authentic specimen (m.p. 218-220°), prepared according to Biltz _et al_ (13). The latter report a melting point of 228-229°.

1,3-diacetyl-5,5-diphenyl-2-hydroxyimidazolid-4-one (1 g.) treated with aqueous alkali under the same conditions, gave a clear solution only after one hour, which on acidification and crystallization of the precipitate yielded 0.5 g. of 4,4-diphenyl-2-methyl-4H-imidazol-5-one. α-Acetamino-α,α-diphenylacetamide (0.5 g.) did not dissolve completely after two and a half hours. Acidification of the filtrate yielded 50 mg of crude 4,4-diphenyl-2-methyl-4H-imidazol-5-one.

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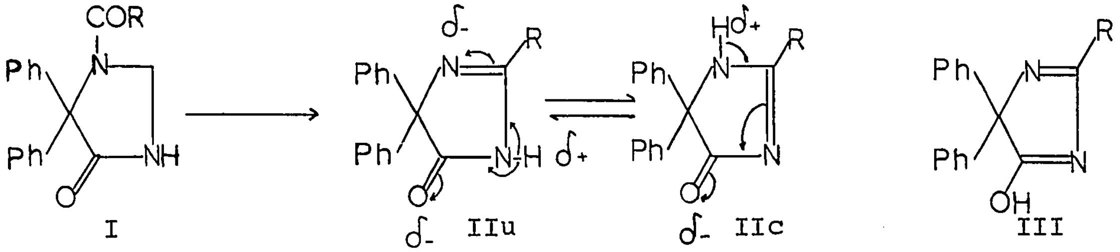
PART II

Tautomeric Equilibria of 5,5-Disubstituted Imidazol-4-ones

The oxidation of 1-acyl-5,5-diphenylimidazolid-4-ones (I) with alkaline potassium permanganate yields compounds which may be formulated as 4,4-diphenyl-4H-imidazol-5-ones (IIu) or 5,5-diphenyl-5H-imidazol-4-ones. Biltz and coworkers (1) applied this oxidation procedure to 1-acetyl-5,5-diphenylimidazolid-4-one (I; R = Me) and isolated the 2-methylimidazolone whose structure they postulated as IIu (R = Me) (cf. X→XIII; Part I) without taking account of the tautomeric possibility IIc.



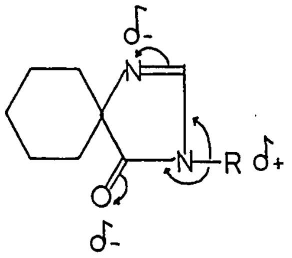
I IIu IIc III

Tautomers of form III can be excluded to a large extent in the imidazolone series for tautomerization of the amide group in IIu to the hydroxy-imino form as in III is an energetically unfavourable process resulting in the loss of the difference in the bond energies of the C=O and C=N bonds (approx. 9.6 Kcal/mole) (2,3) and is not accompanied by appreciable gain in the delocalization energy of the system. Experimental evidence that is shown in the sequel also supports the absence of this tautomeric form. The tautomeric equilibrium

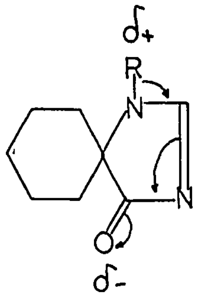
IIu ⇄ IIc can be best investigated by the use of physicochemical methods, for investigations based on chemical evidence are now known to be suspect (2,4,5).

(i) Infrared Spectral Studies

Schipper and Chinnery (6) found that the carbonyl and C=N stretching vibrations of the non-conjugated imidazolones occurred at 1740-1725 and 1612-1609 cm^{-1}, respectively, while for the conjugated imidazolones these absorptions were shifted towards lower frequencies (1710-1695 and 1550-1540 cm^{-1}). This is confirmed by our own studies.



IV



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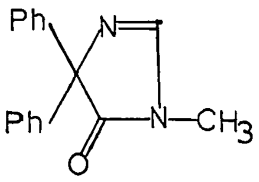

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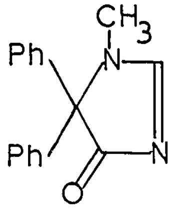

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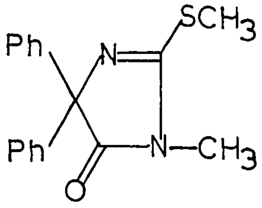


VIII

of the compounds IV (R = Me), VI and VIII (compounds 1, 2 and 3, Table I) and V (R = Me) and VII (compounds 4 and 5, Table I), although these studies with a greater variety of structural type indicate a somewhat greater latitude for the positions of the spectral maxima.

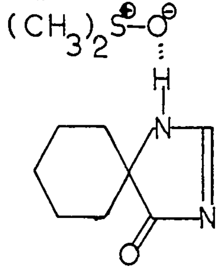
The spectrum of the spiroimidazolone IV or V (R = H) in chloroform shows it to be almost completely in the unconjugated form IV (R = H) (a fact already noted by Schipper and Chinnery (6)). However, in dimethyl sulphoxide the spectrum shows weak peaks at 1720 (shoulder) and 1550 cm^{-1}, indicative of the conjugated tautomer V (R = H), as well as strong peaks at 1740 and 1620 cm^{-1} indicative of the unconjugated tautomer (R = H). By a very rough estimate, based on the intensities of the peaks, the proportion of unconjugated: conjugated tautomer is about 75:25. Evidently, solvation by

Table I

Infrared Absorption Maxima of "Fixed" Imidazolones

Compound	Phase	$\nu_{C=O}$ cm^{-1}	ϵ_A	$\nu_{C=N}$ cm^{-1}	ϵ_A
Unconjugated					
1. IV; R = Me	KBr	1730	s	1620	s
2. VI	KBr	1720	s	1605	s
	Me_2SO	1730	600	1625	350
3. VIII	KBr	1730	s	1570	s
	Me_2SO	1735	610	1580	350
Conjugated					
4. V; R = Me	KBr	1705	s	1560	s
	Me_2SO	1710	540	1560	630
5. VII	KBr	1705	s	1550	s
	Me_2SO	1725	770	1550	700

the dimethyl sulphoxide preferentially stabilizes the conju-



Va (R=H)

gated tautomer as shown in Va (R = H).

Replacement of the cyclopentamethylene group by two phenyl groups displaces the equilibrium, even in dimethyl sulphoxide, almost completely to the unconjugated form IIu.

Table II

Infrared Absorption Maxima of Tautomeric Imidazolones

		$\nu_{C=O}$		$\nu_{C=N}$	
Compound	Phase	cm^{-1}	ϵ_A	cm^{-1}	ϵ_A
6. IV - V; R = H	KBr	1710	s	1530	s
	Me_2SO	(1740	600	1620	330
		(1720	130^a	1560	130
7. II; R = H	KBr	1725	s	1610	s
	Me_2SO	1745	480	1620	220
8. II; R = Me	KBr	(1740	s	1650	s
		(1705	s		
	Me_2SO	1740	520	1650	260
9. II; R = Et	KBr	(1740	s	1630	s
		(1720	s	1550	s
	Me_2SO	1740	550	1645	320
10. II; R = Ph	KBr	1690	s^b	1610 1550	s s
	Me_2SO	1745	940	1630	500
11. II; R = SMe	KBr^c	(1720	s^a	1500	s
		(1690	s^b		
	KBr^d	1720	s^b	1570	s
	Me_2SO	1740	470^b	1580	350

a, shoulder; b, broad; c, crystallized from pyridine-water (6); d, crystallized from chloroform-petroleum ether.

Thus the infrared spectra of solutions of the compounds II (R = H, Me, Et, Ph, and SMe) (compounds 7, 8, 9, 10 and 11 of Table II) show no appreciable amounts of the conjugated forms IIc. This may be explained on either steric or electronic grounds or both. Chemical evidence discussed in Part I of this thesis indicates that the geminal phenyl groups lead to severe steric hindrance in their neighbourhood; this may prevent hydrogen bonding by the bulky dimethyl sulphoxide molecule as occurred in Va (R = H), so that the conjugated tautomer can not be stabilized by solvation. Alternatively, phenyl groups, because of their strong electron-attraction (7), should stabilize the tautomer IIu, in which the nearer nitrogen atom has a partial negative charge, and destabilizes the conjugated tautomer IIc, in which it has a partial positive charge.

The infrared spectra of the crystalline solids in potassium bromide discs show them sometimes to be made up of the unconjugated tautomer (Table II; compounds 7 and 8), sometimes of the conjugated tautomer (compound 6) and sometimes of a mixture (compounds 9 and 10). It is apparent that the tautomeric form crystallizing from solution is not necessarily the more abundant form in solution.

In confirmation of the findings of Lempert et al (8), we obtained the solid II (R = SMe) (compound 11, Table II) in the form IIu or IIc, according to the solvent from which it was crystallized. However, the spectrum of the solution obtained by dissolving either form in dimethyl sulphoxide indicated the presence of the unconjugated form IIu (R = SMe) only. Evidently the proton transfer involved in the change IIc → IIu is rapid in this solvent, which was shown by its n.m.r. spectrum to contain small traces of water. Attempts to isolate the two tautomeric forms of II (R = H, Me, Et, or Ph) by crystallizing from Lempert's solvents were unsuccessful.

(ii) Nuclear Magnetic Resonance Spectra

The n.m.r. spectra of the imidazolones also indicate the unconjugated tautomer to be the stable form in deutero chloroform. The signal arising from the C(2) proton of the unconjugated form is at a higher field than that of the conjugated form, in agreement with calculations of electron densities at C(2) by the L.C.A.O. method.* Thus for IV (R = Me)

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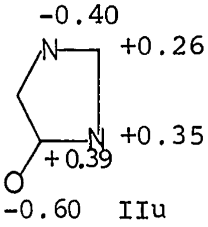
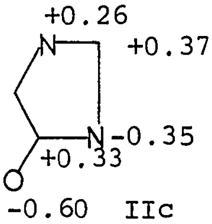
* L.C.A.O. calculations were carried out on an I.B.M.-7040 computer by application of a program available from reference (9). Overlap integral was not included (S=O), and the various coulomb integrals were adjusted to describe the differences of the electronegativities of the atoms in the system (10). Thus the values 0.00, 0.50β_C, 1.50β_C, and 1.00β_C were taken as the coulomb integrals of Sp^2 hybridized carbon (e.g. C(2) and carbonyl), imino-nitrogen, amino-nitrogen, and oxygen atoms, β_C being the resonance integral between two adjacent carbon atoms in unsaturated linkages.



IIu



IIc

Total π Energy: 9.881β 9.961β

Table III

Nuclear Magnetic Resonance Peaks of N-Substituted Imidazolones and Tautomeric Imidazolones in Deutero Chloroform

Compound	Position of Peaks (p.p.m. from T.M.S.)		
	N(1) - R[a]	C(2) - H[a]	Additional Peaks[b]
1. IV; R=Me	3.20	7.70	pentamethylene 1.65
2. VI	3.07	7.78	phenyl 7.30
3. V	3.14	8.03	pentamethylene 1.68
4. VII	3.03	8.35	phenyl 7.33
5. IV-V; R=H	9.77	7.75	pentamethylene 1.67
6. II	4.33	7.75	phenyl 7.30

a) Singlets b) Multiplets

it is at 7.70 p.p.m. (downfield from tetramethylsilane), and for V (R=Me) it is at 8.03 p.p.m. (Table III compounds 1 and 3 respectively); for compound IV-V (R=H) it is at 7.75 p.p.m. (compound 5), indicative of the tautomer IV (R=H).

Similarly, for compound VI it is at 7.78 p.p.m., for VII at 8.35 p.p.m., and for II at 7.75 p.p.m.: again indicative of the unconjugated tautomer IIu (compounds 2,4 and 6 in Table III). However the small differences between the chemical shifts of the C(2) protons render the above conclusions approximations only. The 2-substituted-4,4-or 5,5-diphenyl tautomers show additional signals due to the 2-substituent: methyl, 2.20 p.p.m. (s); ethyl, 2.87 (q) and 1.05 (t) p.p.m.

(J=7.2 c.p.s.); phenyl, 7.10 (s) p.p.m., in deuterated dimethyl sulphoxide.

(iii) Ultraviolet Spectra and Basicity Measurements of Spiroimidazolones IV-V.

The infrared and n.m.r. spectra indicate the non-conjugated tautomer to be predominant in non-polar solvents. For investigating the tautomeric equilibrium in more polar solvents such as ethanol and water it is convenient to use ultraviolet spectroscopy. Schipper and Chinnery (6) noted that the spectrum of the conjugated imidazolone V (R = Me) (Table IV: compound 4) had a peak at longer wavelength than the spectrum of the non-conjugated compound IV (R = Me) (compound 1); these spectra are shown in Figure 1. The spectrum of the potentially tautomeric compound IV-V (R = H) (compound 6) had two peaks at about the positions expected for the conjugated and the non-conjugated tautomer (Figure 2). In an attempt to analyze the last spectrum more quantitatively, we have taken account of the bathochromic effect of substituting methyl groups for hydrogen on chromophores (11,12). As an example of this effect, the absorption peaks of the methylated cations IX (R_1=H, R_2=Me and R_1=Me, R_2=H) are at 9 mμ higher wavelength than the peak of the cation IX (R_1=R_2=H).

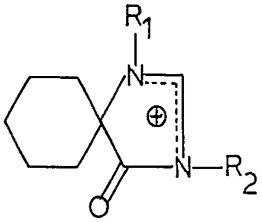
Table IV

Ultraviolet Absorption Maxina or Imidazolones

Compound	Ethanol		Water		IN HCl		0.1N NaOH	
	λ_{max}	ϵ_{max}	λ_{max}	ϵ_{max}	λ_{max}	ϵ_{max}	λ_{max}	ϵ_{max}
Unconjugated								
1. IV; R=Me	234	(5090)[a]	231	5100	240	6350(780)[a]		
2. VI	243	3860	243	4200	247	5180		
3. VIII	242	3820	242	3800	b			
Conjugated								
4. V; R=Me	269	8500(8040)[a]	267	9070	240	7300(6890)[a]		
5. VII	275	5620	275	5510	240	5890		
Tautomeric								
6. IV-V; R=H	228	5220(4670)[a]	228	3480	231	6380(7220)[a]	250	5850(6800)[a]
	256	2630(1440)[a]	255	3270				
7. II; R=H	260	1850	250[c]	~3000	e		262	4500
			265[c]	~2000	e			
8. II; R=Me	257	2680	255	3720	e		258	5250
9. II; R=Et	257	2650	255	3700	e		257	5150
10. II; R=PH	230	16.900	230-240[d]	14.300	258[b]	19700	238	21600
	255	10.200	258	15.400				
11. II; R=SMe	240	13.400	246	17.600	b		b	
	261	6.000						

[a] Values from ref.5; [b] Decomposes rapidly [c] Shoulder
[d] Plateau [e] No peaks or shoulders above 220 mμ .

We have assumed that the absorption peaks of the tautomers

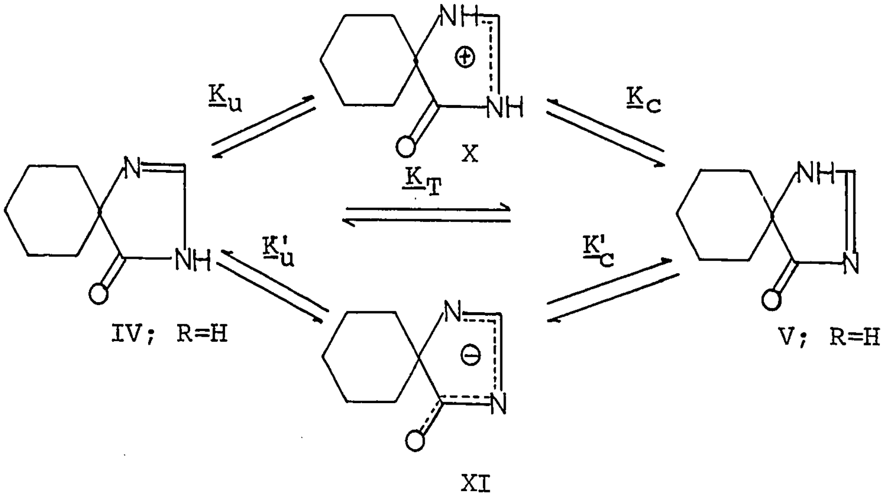


IX

IV (R=H) and V (R=H) have the same shape and intensity as those of the fixed methyl derivatives IV (R=Me) and V(R=Me), but are shifted 8 mμ and 12 mμ , respectively, to shorter wavelength. With the further assumption that the tautomeric mixture is made up of 65% of IV (R=H) and 35% of V (R=H), the absorption curve shown as a dotted line in Figure 2 may be calculated. The agreement is good enough to show that the assumptions cannot be grossly in error.

This composition for the tautomeric mixture in water was confirmed by basicity measurements (2,5,13) carried out by conventional spectrophotometric methods and are recorded in Table V.

When both tautomers are protonated to form a common



cation (in this instance, X*), the tautomeric equilibrium constant K_T (= [IV; R=H]/[V; R=H]) is related to the acid ionization constants Ku and Kc of the cation X, ionizing to yield a proton and the unconjugated or conjugated tautomer respectively, by the equation

$$(1) \quad K_T = Ku/Kc$$

However, in practice the separate ionization constants are not available, but rather an apparent ionization constant K_1 obtained by conventional methods (14) applied to the tautomeric mixture. This is related to Ku and Kc by the equation

$$(2) \quad K_1 = Ku + Kc$$

Combining equations (1) and (2) yields

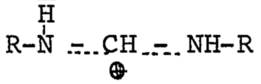
$$(3a) \quad K_T = \frac{K_1 - Kc}{Kc} = K_1/Kc - 1$$

$$(3b) \quad = \frac{Ku}{K_1 - Ku} = \frac{1}{K_1/Ku - 1}$$

---

[*] The simple amidine systems a protonate on the imino-nitrogen

R-N = CH-NH-R



$$\overset{H}{R\text{-}N} \cdots \underset{\oplus}{CH} \cdots NH\text{-}R$$

a b

to form conjugated acidic species b where the positive charge is delocalized over the entire molecule (15). This property is probably sustained in the protonation of acyl-amidines. Experimental proof comes from the similar ultraviolet spectra of the protonated N-methyl spiroimidazolones IX (R_1=Me_1, R_2=H) and IX (R_1=H, R_2=Me) (compounds 4 and 1, Table IV).

While *Ku* and *Kc* are not experimentally determinable, their values can be approximated by the ionization constants *Ku*(Me) and *Kc*(Me) of the methyl derivatives IX (R_1=H, R_2=Me) and IX (R_1=Me, R_2=H) (2,12), so that

(4) $\underline{Ku} \approx \underline{Ku}(\mathrm{Me}) = ([\mathrm{IV};\ R{=}\mathrm{Me}][H^+]/[\mathrm{IX};\ R_1{=}H,\ R_2{=}\mathrm{Me}])$

(5) $\underline{Kc} \approx \underline{Kc}(\mathrm{Me}) = ([\mathrm{V};\ R{=}\mathrm{Me}][H^+]/[\mathrm{IX};\ R_1{=}\mathrm{Me},\ R_2{=}H])$

This latter approximation implies that the effect of methyl substitution on the basicities of compounds IV and V (R=H) will be of similar magnitude and direction. While substitution of a methyl group for a proton is usually considered base strengthening by both inductive and mesomeric effects (7, p. 608), several examples can be found where methyl substitution is base weakening (13) (e.g. the N-methyl derivatives of cyclic imines are considerably weaker bases than the parent imines (16)). Such would be the case if a particularly strong hydrogen bond was broken as a result of alkyl substitution.

Comparing by equation 2, the ionization constant for the cation X ($R_1 = R_2 = H$) with those of its methyl derivatives (IX; $R_1 = H$, $R_2 = \mathrm{Me}$; and IX; $R_1 = \mathrm{Me}$, $R_2 = H$) (compounds 6, and 1,4 in Table V, respectively) indicates that methyl substitution has not increased the basicity of the imidazolone system. Clearly the base increasing effect of the substituent has in this instance been counteracted by the loss of hydrogen bonding.

Application to the experimental data (Table V) to equation 1 in the form

$$(1a)\quad \underline{K}_T \approx \underline{Ku}(Me) / \underline{Kc}(Me)$$

Table V

Acid Dissociation Constants of Protonated Imidazolones

Compound	pK
Unconjugated	
1. IV; R=Me	3.72
2. VI	1.72
Conjugated	
4. V; R=Me	4.21
5. VII	2.32
Tautomeric mixture	
6. IV-V: R=H	3.65
7. II; R=H	2.13
8. II; R=Me	2.73
9. II; R=Et	2.80

yields K_T = 3.09, indicating a ratio of unconjugated to conjugated compounds in water of 75:25. Use of equation (3a), and substituting Kc(Me) for Kc indicates a ratio of 74:26, and of equation (3b) a ratio of 85:15.

In the less polar solvent ethanol, the intensity of the peak at lower wavelength increases, and that of the peak at higher wavelength decreases (Fig. 2). This indicates an increase in the ratio of unconjugated : conjugated tautomer, since effects of solvent on the absorption spectra of these compounds are slight (see compounds 1 and 4 in Table IV).

(iv) Ultraviolet Spectra and Basicity Measurements of Diphenylimidazolones (II)

The diphenylimidazolones VI and VII contain the acylamidine chromophores of IV (R=Me) and V (R=Me), and two geminal phenyl groups separated from those chromophores by a saturated carbon atom. Some interaction between the phenyl and acylamidine chromophores might be anticipated (17), and indeed VI and VII show absorption peaks at considerably longer wavelength than do IV (R=Me) and V (R=Me), as well as a very intense peak at about 210 mμ due to the benzene rings (18). Consequently, any attempt to treat the spectra of the diphenyl compounds as being the sum of the contributions of isolated chromophores can have only limited success. However, an attempt has been made in Fig. 3 to indicate the peaks of VI and VII. It is noteworthy that on such an analysis the acylamidine peak of VI in water is at about 248 mμ , compared with a wavelength of 231 for IV (R=Me) in this solvent.

It is apparent, qualitatively, that the spectrum of II (R=H) shown in Fig. 4, has too low an intensity at about 245 mμ to be made up wholly of IIu (R=H), although the absence of a strong peak between 260 and 270 mμ indicates that it is not made up wholly of IIc (R=H). A spectrum of II (R=H) calculated on the assumption that the tautomeric mixture contains 60% of IIu (R=H), having an absorption curve identical with that of VI but shifted 15 mμ to shorter wavelength, and 40% of IIc (R=H), having an absorption curve identical with that of VII but also shifted 15 mμ, is shown as a broken line in Fig. 4. The agreement is as good as can be expected in view of the limitations of the assumptions involved. While no great weight should be attached to the exact numerical result, it does show that in water the compound II (R=H) exists **preponderately** but not completely as the unconjugated tautomer IIu (R=H).

The same conclusion emerges, again somewhat tentatively, from a consideration of basicity measurements. Application of equation (1a) to the data in Table V indicates a ratio of 81:19 for the unconjugated:conjugated form of II (R=H) in water. However, while pKc(Me) is probably fairly accurate, since the spectral change on protonation of VII is large, pKu(Me) and pK, are probably less accurate because the spectral changes on protonation of VI and of II (R=H) (Table VIII; compounds 5,2 and 7 respectively) are small. It is noteworthy that VI is a weaker base than II (R=H), probably because the methylation of the unconjugated tautomer excludes the possibility of the formation of strongly hydrogen bonded species of increased basicity. Hydrogen bonding is expected to be more important with the diphenyl compounds, because of the electron withdrawing effect of the geminal phenyl groups, than with the spiroimidazolone analogues.

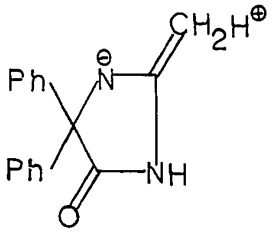
The greater acidity of the protonated forms of VI and VII over those of IV (R=Me) and V (R=Me) (Table V) is expected because of the electron pull of the geminal phenyl groups. For the same reason, II (R=H) proves to be considerably stronger acid (pK_2 = 9.60, Table VIII) than IV-V (R=H) (pK_2 = 10.61, Table VII). (K_2 is an experimental dissociation constant of the tautomeric mixture, related to Ku' and Kc' [see reaction Scheme I] by the equation $K_2 = Ku'Kc'/$

(Ku' + Kc') (4,12)). The difference between the dissociation constants of the diphenyl and spiroimidazolones (1.0 pK units) is close to the difference between the constants of diphenylacetic acid and acetic acid (0.8 pK units) (7, p. 579).

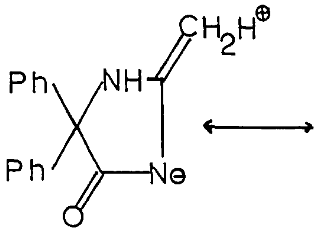
The ultraviolet and basicity data indicate the presence of some of the conjugated tautomer IIc (R=H) in water solutions of II (R=H), while it had been previously shown by infrared studies that in dimethyl sulphoxide the conjugated form V (R=H) of the spiroimidazolone was found in both water and dimethyl sulphoxide solution. This difference may be related to the steric effects of the phenyl groups, which prevent the stabilization of the conjugated form by solvation by the bulky dimethyl sulphoxide molecule, as in Va (R=H), but do not prevent solvation by the smaller hydroxyl groups of water or alcohols.

Substitution of an electron-donating group R for hydrogen in the 2-position of the diphenyl-imidazolone II increases the relative stability of the conjugated form IIc. This is shown by the enhancement of peak at about 250 mμ, due to the conjugated form, of the methyl derivative (II; R=Me) (Figure 5) and, more markedly, of the methylthio derivative (II; R=SMe) (Figure 6). Also noteworthy are the large solvent effects, the conjugated form being favoured by the more polar solvent. (The change in the spectrum of the fixed compound VIII with solvent, shown in Fig. 6, is small in comparison.) This is illustrated in Fig. 7 for the phenyl derivative (II; R=Ph), whose intense absorption makes it possible to examine the effect of several solvents.

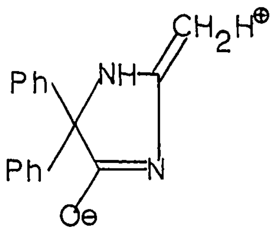
2-Alkyl substituents increase the basicity of the diphenyl imidazolone system by about <u>0.6</u> pK units (compounds 8 and 9 as compared to 7, in Table V). Since the magnitude of the base strengthening effect of the alkyl substituent is comparable to that observed when pyridine is alkylated in the 2- or 4-positions (19), it is likely that hyperconjugated structures XIa and XIb have important contributions.



XIa



XIb



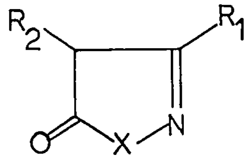
XIc

Canonical forms such as XIb can also explain the increased proportions of the conjugated form IIc (II; R=Me) for the negative charge on the nitrogen is stabilized by the adjacent carbonyl group as in XIc.

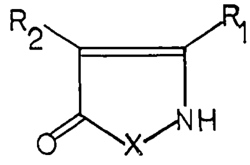
(v) Summary

The results indicate (a) a greater intrinsic stability of the unconjugated systems (IIu and IV; R=H), but (b) a greater polarity of the conjugated systems, because the mesomeric electron shifts are in the same and not in opposite directions (cf. IV and V). This results in some stabilization of the conjugated systems in more polar solvents. Substitution of electron-donating substituents in the 2-position increases the stability of the conjugated forms more than that of the unconjugated because of the more extensive conjugation available for the former tautomers (cf. XIb and XIc).

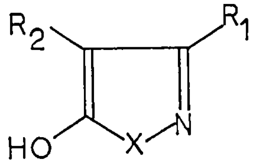
These results parallel the findings of Katritzky and coworkers on the tautomerism of related heterocyclic 5 membered rings (20). These workers found that isoxazol-5-ones (XIIa → XIIc; X=O) and 1-substituted pyrazol-5-ones (XIIa → XIIc; X=N-Ph or N-Me) existed in tautomeric forms



XIIa



XIIb



XIIc

XIIa (unconjugated) XIIb (conjugated) and XIIc (hydroxy) depending on the extent of substitution and the polarity of the media. Increasing substitution at R_1 and R_2 resulted in higher concentration of the conjugated tautomer XIIb, which tautomer was also favoured in polar solvents. Non-polar solvents or fewer substituents favoured the unconjugated tautomeric form XIIa. The hydroxy form XIIc, which now forms an aromatic system, was present in the solid phase only. The hydroxy tautomers of the imidazolones under study in this thesis cannot form an aromatic six π-electron system, and so are not observed.

Experimental

Preparation of Compounds

Compounds prepared according to existing methods in literature are listed in Table VI.

Table VI

Physical Constants and Literature References of some Imidazolones

Compounds	M.p.°(found)	M.p.°(reported)	Reference
1. IV; R=Me	51-51.5	51-52	6[a]
2. VI	175-177	176-178	21[b]
3. VIII	170-172	175	22
4. V; R=Me	120-121	120-121	6
5. VII	———	231	21[b]
6. IV-V; R=H	164-165	165-166	6
7. II; R=H	165-166	166-167	21
11.II; R=SMe	210-212	213	22

a), For preparation of α-aminocyclohexyl-N-methyl carboxamide, see ref. 23;

b), We are gratefull to Dr. Carrington for providing authentic samples of these compounds.

2-Substituted 4,4/5,5-diphenyl-4H/5H-imidazol-5/4-ones (IIu/IIc)

The 1-acyl-5,5-diphenylimidazolid-4-one (0.0035 moles) was dissolved in 1 N sodium hydroxide solution (20 ml) at 70-80°. A solution of aqueous potassium permanganate (0.0025 moles in 5 ml water) of the same temperature was added with constant stirring. The reaction proceeded to completion in a few minutes and the hot mixture was filtered. The pH of the cooled filtrate was adjusted to 0.5-1.00 with hydrochloric acid (10%), and the solution was filtered again. The filtrate was neutralized with sodium hydroxide (solid pellets) and sodium bicarbonate. The precipitate was filtered and crystallized from ethanol.

1-Acetyl-5,5-diphenylimidazolid-4-one gave 4,4/5,5-diphenyl-2-methyl-4H/5H-imidazol-5/4-one (IIu/IIc; R=Me compound 8) in 30% yield. M.P.: 218-220° (lit. 228-229°).

Calculated for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19%.

Found: C, 77.00; H, 5.98; N, 11.00%.

1-Propionyl-5,5-diphenylimidazolid-4-one gave 4,4/5,5-diphenyl-2-ethyl-4H/5H-imidazol-5/4-one (IIu/IIc; R=Et, compound 9) in 50% yield. M.p.: 208-209°; molecular weight 264 (mass spectrum).

Calculated for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60%.

Found: C, 78.00; H. 6.13; N, 11.03%.

1-Benzoyl-5,5-diphenylimidazolid-4-one gave 4,4/5,5-diphenyl-2-phenyl-4H/5H-imidazol-5/4-one (IIu/IIc; R=Ph, compound 10) in 60% yield. M.P.: 238-240°, molecular weight 312 (mass spectrum).

Calculated for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97%.
Found: C, 81.20; H, 5.69; N, 9.17%.

Spectral Measurements

All spectra were obtained on a Perkin-Elmer 350 recording instrument. Stock solutions of approximately 10^{-4} molar were prepared in abs. ethanol and 0.5-1 ml aliquots were diluted to 25 ml with sodium phosphate buffers of ionic strength 0.01. pH measurements were taken on a Radiometer titrimeter using standard calomel and glass electrodes.

Calculations of the ionization constants were done at 3 different wavelengths for each solution according to equation 6 and their average was calculated. These calculations are summarized in Tables VII and VIII.

$$(6) \quad pK^M = pH + \log \frac{\epsilon_B - \epsilon}{\epsilon - \epsilon_{BH^+}}$$

where pK^M is the measured (mixed (19, p.13)) ionization constant, ϵ_B is the molar extinction coefficients of the basic form, ϵ_A is the molar extinction coefficient of acidic form, and ϵ is the molar extinction coefficient of the solution where partial ionization is occuring. The pK^M obtained by equation 6 is related to the thermodynamic constant pK^T by equation 7:

$$(7) \quad pK^T = pK^M + \frac{0.5\ I^{\frac{1}{2}}}{1 + 1.6I^{\frac{1}{2}}}$$

where I is the ionic strength of the solution. The ionization constants calculated this way are about 0.05 pK units larger than the values shown in Tables VII and VIII. However, the difference is within the experimental error.

Table VII

Ionization Constants of the Spiroimidazolones

pH	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK
IV-V; R=H (compound 6)						
0.00	6.40[a,c]		0.655[a,d]		.328[a,e]	
3.05	5,85[c]	3.70	1.09[d]	3.75	.765[e]	3.75
3.48	5.30[c]	3.72	1.75[d]	3.63	1.420[e]	3.63
4.05	4.32[c]	3.76	2.63[d]	3.57	2.30[e]	3.57
6.57	3.39[b,c]		3.27[b,d]		2.95[b,c]	
			Average . , ...			3.65 ± 0.10
IV-V; R=H (compound 6)						
8.47	2.95[a,f]		3.17[d,g]		3.28[a,d]	
10.45	4.00[f]	10.61	4.26[g]	10.61	4.18[d]	10.63
10.85	4.58[f]	10.62	4.87[g]	10.61	4.76[d]	10.57
12.20	5.53[b,f]		5.85[b,g]		5.53[b,d]	
			Average			10.61 ± 0.05
IV; R=Me (compound 1)						
1.2	6.35[d,h]		5.85[d,f]		4.55[a,g]	
3.15	5.90[h]	3.67	5.25[f]	3.75	3.95[g]	3.68
3.82	5.05[h]	3.73	4.20[f]	3.73	3.00[g]	3.73
6.88	4.00[b,h]		2.85[b,f]		1.75[b,g]	
			Average			3.72 ± 0.05

Table VII (cont'd)

pH	$\epsilon x10^{-3}$	pK	$\epsilon x10^{-3}$	pK	$\epsilon x10^{-3}$	pK	$\epsilon x10^{-3}$	pK
V; R=Me (compound 4)								
1.30	$7.10^{a,i}$		$7.15^{a,j}$		$0.85^{a,k}$		$6.40^{a,l}$	
3.42	6.15^{i}	4.10	6.25^{j}	4.11	1.60^{k}	4.36	1.15^{l}	4.42
4.10	4.15^{i}	4.12	4.55^{j}	4.12	4.00^{k}	4.29	3.70^{l}	4.30
5.00	1.70^{i}	4.09	2.45^{j}	4.10	7.35^{k}	4.36	7.35^{l}	4.35
6.95	$1.05^{b,i}$		$1.85^{b,j}$		$8.85^{b,k}$		$8.90^{b,l}$	

Average . . . . 4.21 ± .15

---

a, ϵ_A; b, ϵ_B; c, at 230mμ ; d, at 255 mμ ; e, at 260 mμ; f, at 245 mμ; h, at 240 mμ; i, at 237.5 mμ; j, at 242.5 mμ, k, at 265 mμ; l, at 270 mμ.

Table VIII

Ionization Constants of the Diphenylimidazolones

pH	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK
II; R=H (compound 7)						
0.30	$4.80^{a,d}$		$4.37^{a,e}$		$3.94^{a,f}$	
1.85	4.54^{d}	2.13	4.10^{e}	2.09	3.68^{f}	2.10
2.28	4.40^{d}	2.22	3.95^{e}	2.16	3.52^{f}	2.15
3.19	4.18^{d}	$(2.51)^{e}$	3.71^{e}	$(2.27)^{c}$	3.31^{f}	$(2.39)^{c}$
4.07	$4.05^{b,d}$		$3.63^{b,e,}$		$3.21^{b,f}$	

Average . . . . 2.13 ± 0.10

Table VIII (Cont'd)

pH	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK
II; R=H (compound 7)						
6.75	$2.28^{a,g}$		$2.05^{a,h}$		$1.65^{a,i}$	
8.97	2.69^{g}	9.60	2.52^{h}	9.56	2.08^{i}	9.60
9.18	2.89^{g}	9.58	2.72^{h}	9.57	2.28^{i}	9.60
9.78	3.57^{g}	9.53	3.45^{h}	9.60	2.95^{i}	9.65
10.38	4.06^{g}	9.70	4.00^{h}	9.66	3.59^{i}	9.62
12.50	$4.43^{b,g}$		$4.37^{b,h}$		$3.93^{b,i}$	

Average . . . . . 9.60 ± 0.10

pH	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK
VI (compound 2)						
0.12	$4.14^{a,f}$		$5.15^{a,k}$		$4.90^{a,l}$	
1.12	5.00^{f}	1.82	4.95^{k}	1.80	4.58^{l}	1.69
1.66	4.79^{f}	1.84	4.68^{k}	1.82	4.23^{l}	1.76
1.83	4.63^{f}	1.60	4.50^{k}	1.72	3.97^{l}	1.63
2.13	4.45^{f}	1.59	4.31^{k}	1.70	3.79^{l}	1.69
6.57	$4.25^{b,f}$		$4.00^{b,k}$		$3.39^{b,l}$	

Average . . . . . 1.72 ± .100

Table VIII (Cont'd)

pH	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK
VII (compound 5)						
0.36	$5.90^{a,e}$		$1.90^{a,i}$		$0.87^{a,m}$	
1.05	5.60^{e}	(2.11)[c]	2.27^{i}	(2.00)[c]	1.13^{m}	(2.28)[c]
1.82	5.03^{e}	2.34	2.90^{i}	2.23	2.05^{m}	2.30
2.17	4.50^{e}	2.40	3.29^{i}	2.37	2.63^{m}	2.39
2.35	3.66^{e}	(2.18)[c]	3.90^{i}	2.25	3.21^{m}	2.35
3.15	2.71^{e}	2.40	5.13^{i}	(2.19)[c]	5.05^{m}	2.25
6.59	$2.14^{b,e}$		$5.48^{b,i}$		$5.58^{b,m}$	

Average . . . . . 2.32 ± 0.10

pH	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK	$\epsilon \times 10^{-3}$	pK
II; R=Me (compound 8)						
0.50	$2.44^{a,g}$		$2.07^{a,h}$		$1.67^{a,i}$	
2.05	2.68^{g}	2.63	2.29^{h}	2.71	1.83^{i}	2.63
3.10	3.20^{g}	2.82	2.87^{h}	2.82	2.20^{i}	2.75
6.05	$3.60^{b,g}$		$3.29^{b,h}$		$2.44^{b,i}$	

Average . . . . . 2.73 ± 0.100

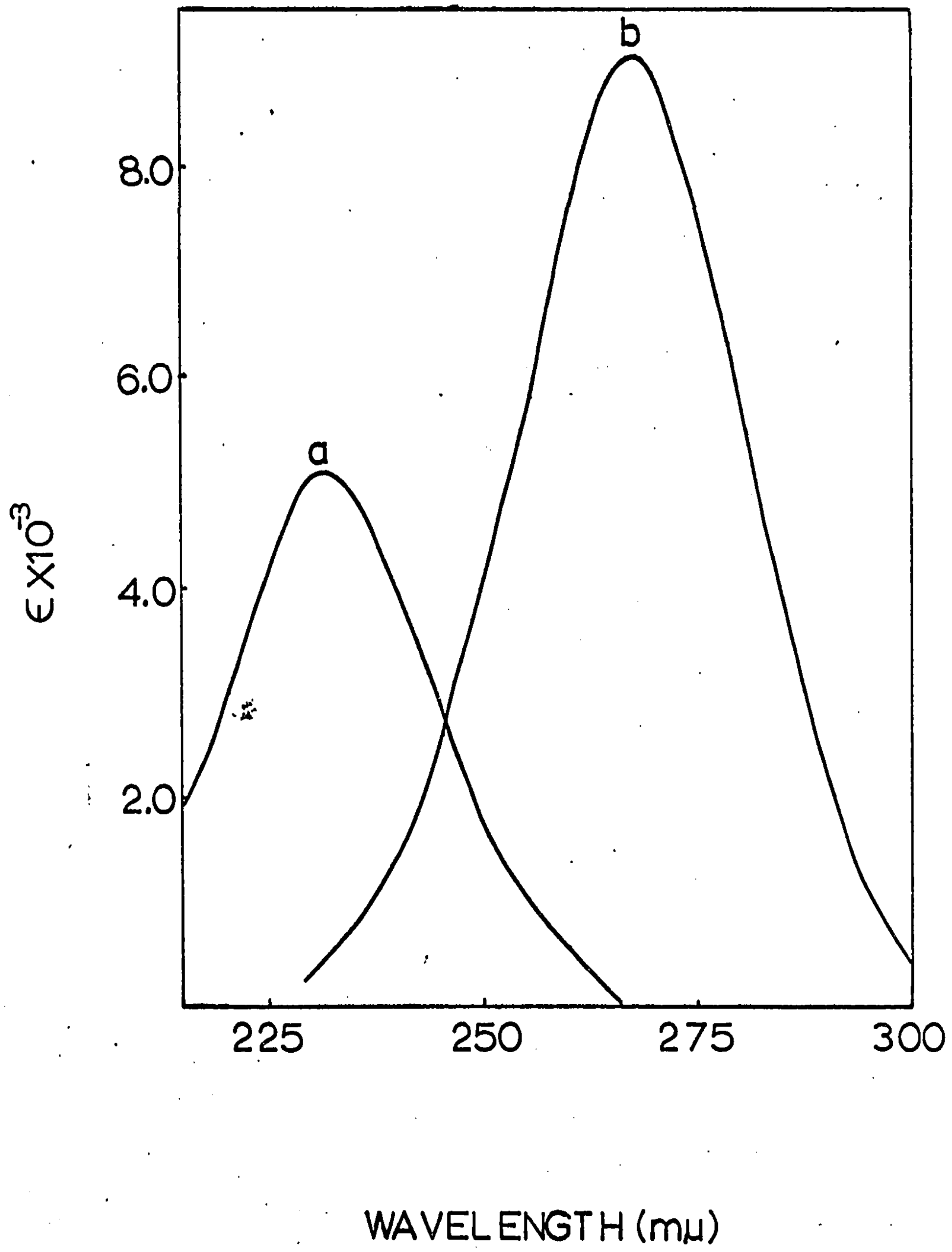
Table VIII(Cont'd)

pH	ϵ	pK	ϵ	pK	ϵ	pK
II; R=Et (compound 9)						
0.50	$2.77^{a,l}$		$2.29^{a,g}$		$1.98^{a,h}$	
2.05	2.98^{l}	2.89	2.48^{g}	2.74	2.10^{h}	2.92
3.10	3.40^{l}	2.78	3.06^{g}	2.76	2.68^{h}	2.76
6.05	$3.70^{b,l}$		$3.41^{b,g}$		$3.00^{b,h}$	
			Average		2.80 ± 0.10	

a, ϵ_A; b, ϵ_B; c, values not included in average; d, at 235 mμ; e, at 240 mμ; f, at 245 mμ; g, at 260 mμ; h, at 265 mμ; i, at 270 mμ; k, at 250 mμ; l, at 255 mμ; m, at 280 mμ.

Figure 1

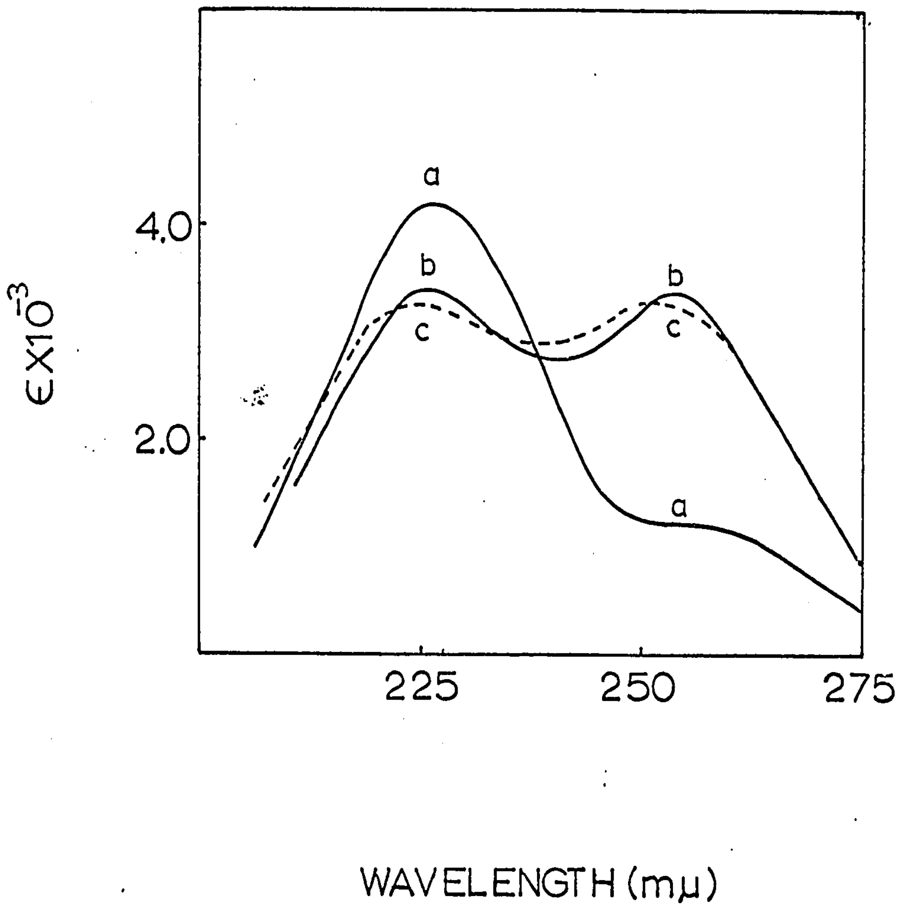
Ultraviolet absorption spectra of (a) 1-methyl-4,4-pentamethylene-4H-imidazol-5-one (IV; R=Me) and (b) 1-methyl-5,5-pentamethylene-5H-imidazol-4-one (V; R=Me) in water.



b
a
8.0
6.0
4.0
2.0
$\epsilon \times 10^{-3}$
225
250
275
300
WAVELENGTH (mμ)

Figure 2

Ultraviolet absorption spectra of the tautomeric pentamethyleneimidazolone (IV-V, R=H) in (b) water and (a) ethanol; (c) spectrum calculated from the spectra of the N-methyl compounds.



a
b
c
b
c
a
4.0
2.0
∈ X 10⁻³
225
250
275
WAVELENGTH (mμ)

Figure 3

Ultraviolet absorption spectra of (a) 1-methyl-4,4-diphenyl-4H-imidazol-5-one (VI), (b) 1-methyl-5,5-diphenyl-5H-imidazol-4-one (VII), and (c) the diphenylmethane chromophore in water.

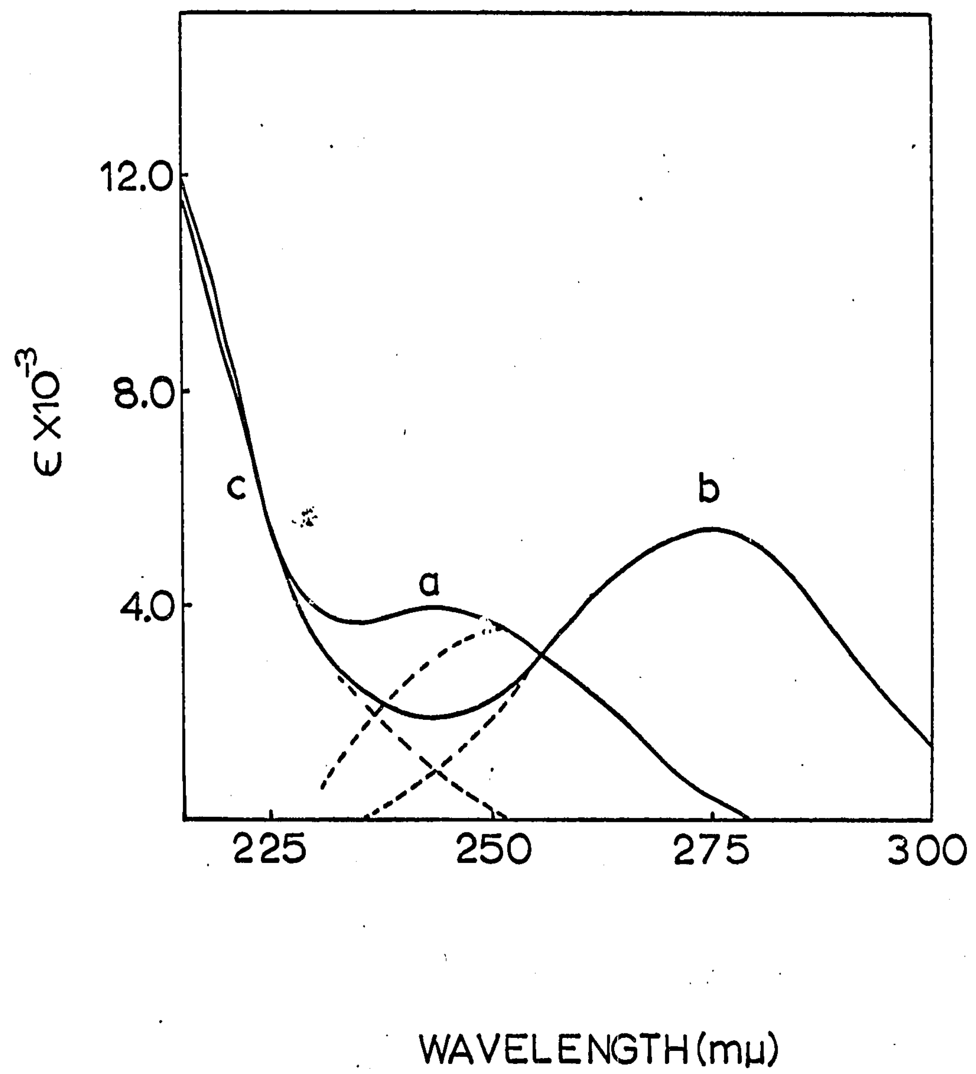

12.0
8.0
4.0
ϵ X10^{-3}
c
a
b
225
250
275
300
WAVELENGTH (mμ)

Figure 4

Ultraviolet absorption spectra of the tautomeric diphenyl-imidazolone (II; R-H) in water, (a) observed, (b) calculated from the spectra of the N-methyl derivatives.

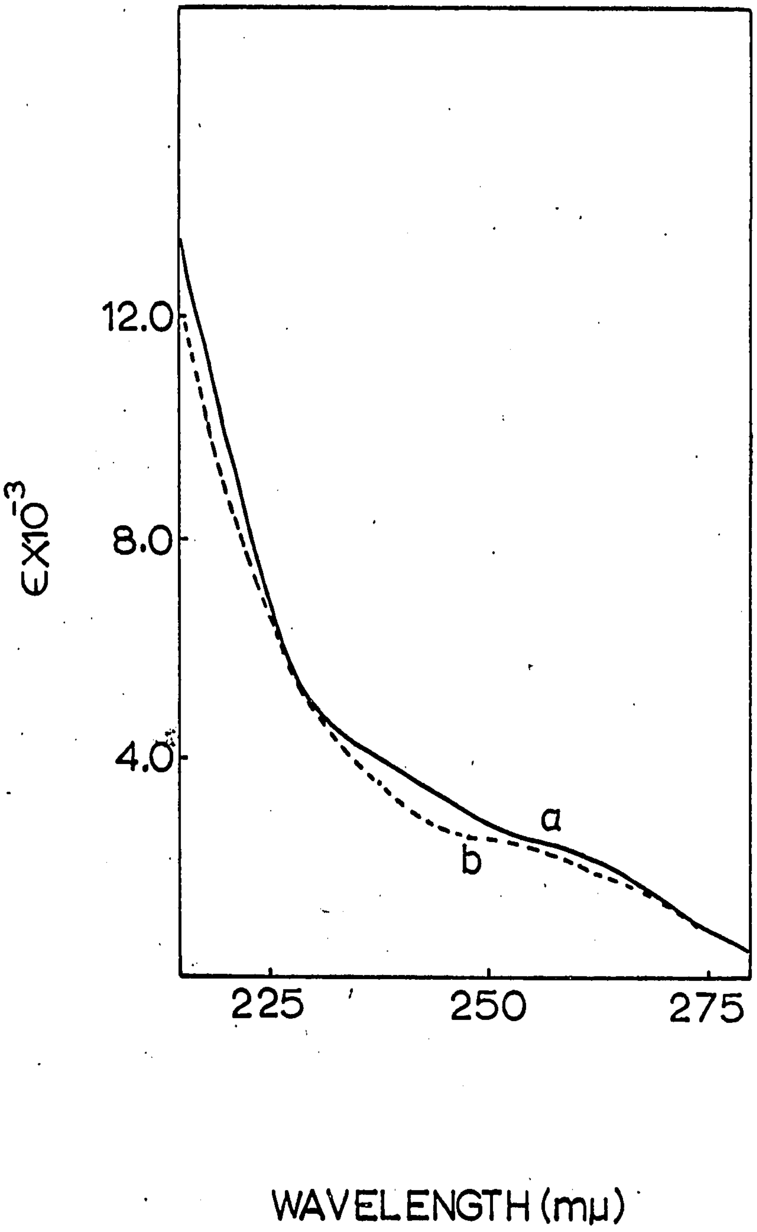

12.0
8.0
4.0
€X10^{-3}
a
b
225
250
275
WAVELENGTH (mμ)

Figure 5

Ultraviolet absorption spectra of the tautomeric diphenylimidazolones: (a) Compound II (R=Me) in in water, (b) in ethanol. (c) Compound II (R=H) in water, (d) in ethanol.

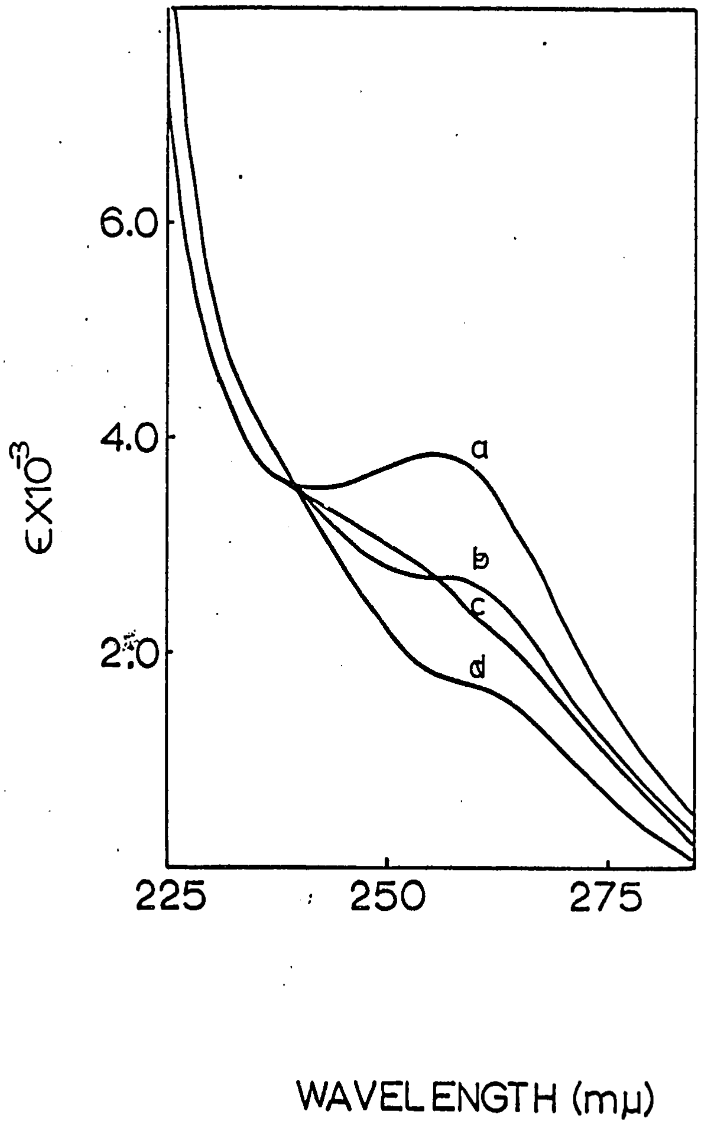

6.0
4.0
2.0
∈X10⁻³
a
b
c
d
225
250
275
WAVELENGTH (mμ)

Figure 6

Ultraviolet absorption spectra of the tautomeric diphenyl-imidazolones:

(a) Compound II(R=SMe) in water, (b) in ethanol.

(c) Compound VIII in water, (d) in ethanol.

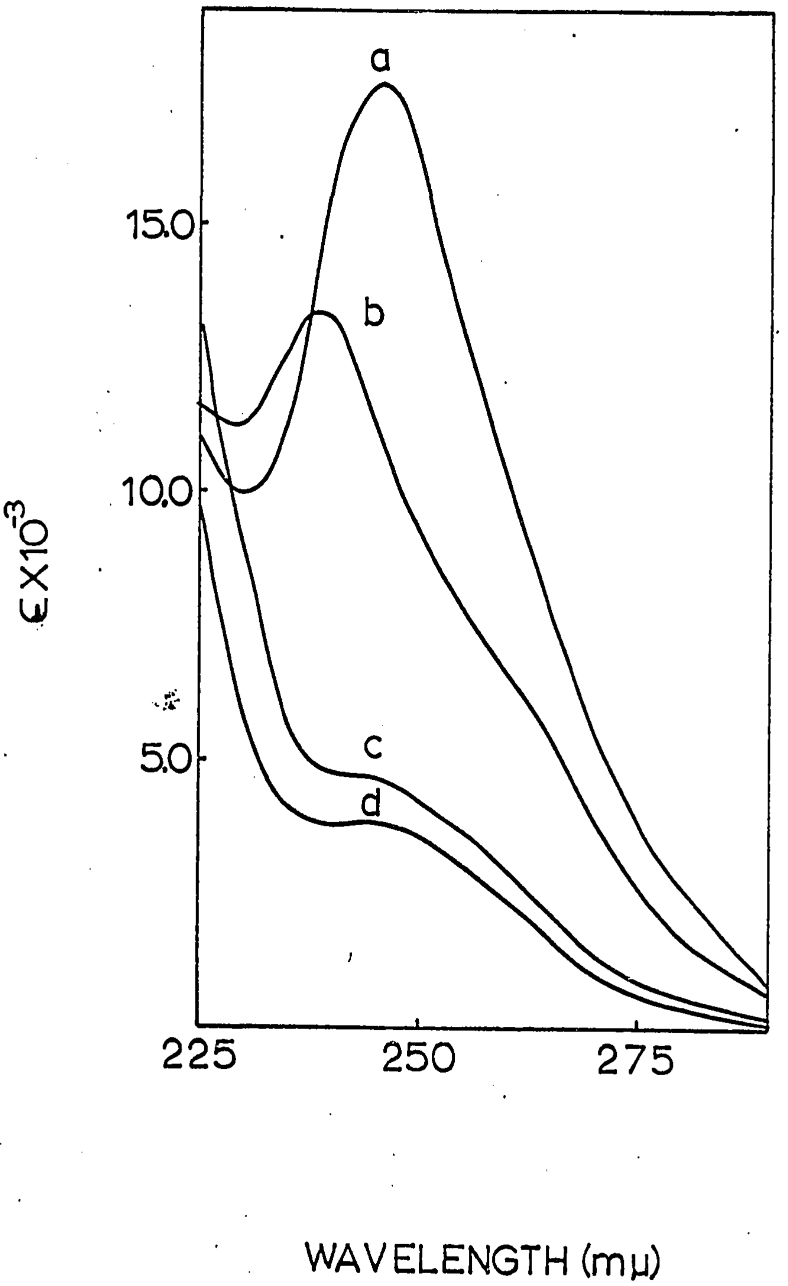
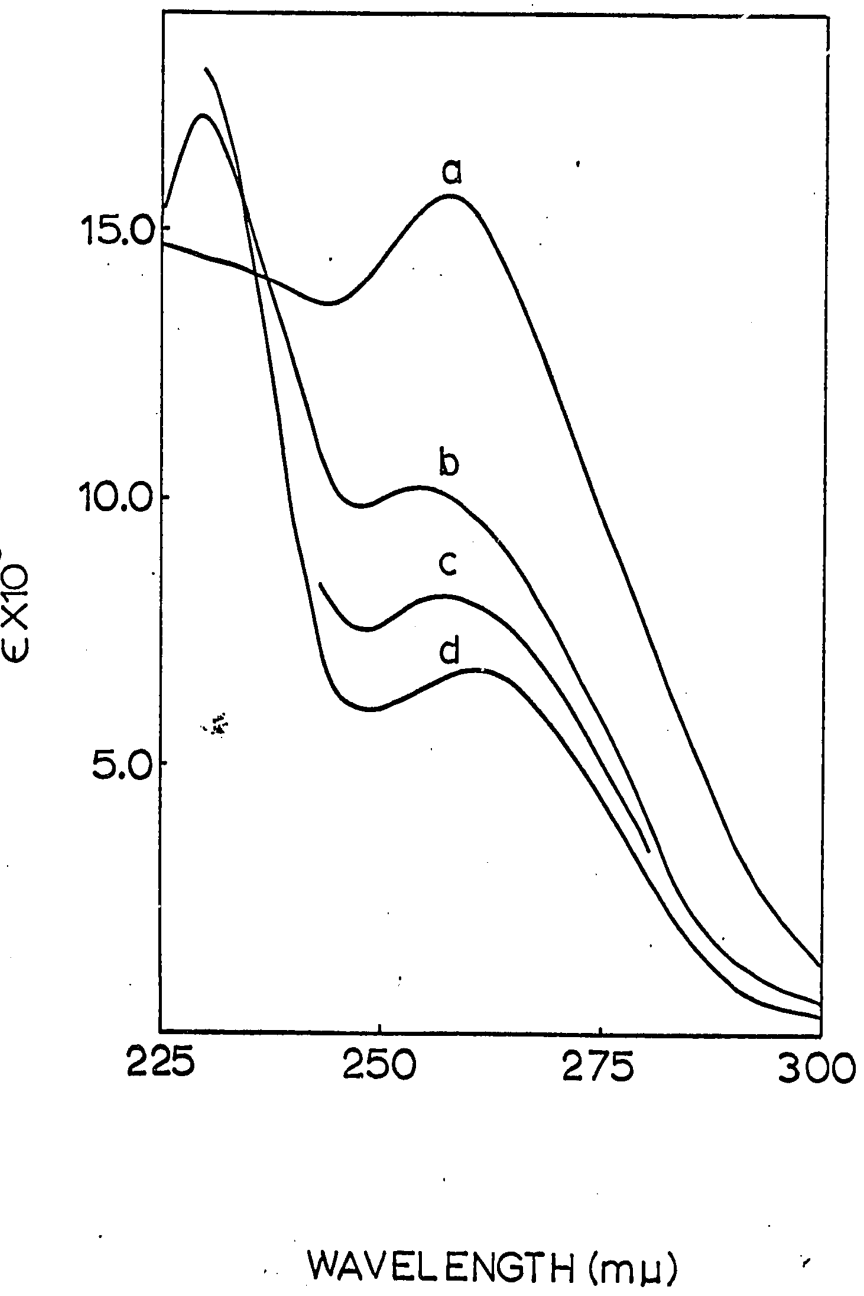

a
b
c
d
15.0
10.0
5.0
ϵ X10^{-3}
225
250
275
WAVELENGTH (mμ)

Figure 7

Ultraviolet absorption spectra of the tautomeric imidazolone II (R=Ph) in (a) water, (b) ethanol, (c) chloroform, and (d) dioxane.


a
b
c
d
15.0
10.0
5.0
ϵ X10^{-3}
225
250
275
300
WAVELENGTH (mμ)

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Part III

Protonation of 2-Thiohydantoins and Analogous Thio Bases in Aqueous Sulphuric Acid

The ionization of weak organic Bronsted bases in aqueous sulphuric acid can be expressed by the protolytic equilibrium (neglecting the concentrations of solvent and counter ion (1)):

$$(1) \quad BH^+ \rightleftharpoons B + H^+$$

for which the thermodynamic equilibrium constant may be written:

$$(2) \quad \underline{K}_{BH^+} = \frac{\underline{a}_{H^+} \underline{f}_B}{\underline{f}_{BH'}} \cdot \frac{[B]}{[BH]}$$

The quantities in square brackets refer to molar concentrations, $\underline{a}_{H^+}$ is the activity of the solvated proton, $\underline{f}_B$ and $\underline{f}_{BH^+}$ are activity coefficients and $\underline{K}_{BH^+}$ is the thermodynamic protonation constant. Based on studies of the protonation of a series of primary amine indicators, Hammett and coworkers (2) advanced the postulate that the activity coefficient ratio $\underline{f}_B/\underline{f}_{BH^+}$ in equation 2 is independent of the nature of the organic base, therefore its combination with the activity of the proton can serve as a unique definition of the acidity of the medium. The Hammett acidity function $\underline{H}_o$

$$(3) \quad \underline{H}_o = -\log(\underline{a}_{H^+} \cdot \underline{f}_B/\underline{f}_{BH^+})$$

has been found for many years exceedingly useful in treating the ionization of organic bases in aqueous sulphuric acid solutions (3). Adherence to the Hammett postulate requires that plots of the logarithms of the experimentally determinable ionization ratios $\underline{I}$ (=$[BH^+]/[B]$) of the compounds against the acidity function $\underline{H}_o$ should yield straight lines with unit slopes (1), according to the equation:

$$(4) \quad pK_{BH^+} - \log I = \underline{H}_o$$

In recent years it has been found that most organic bases (3-16), other than the primarily aromatic amines, do not obey this equation. Some, like tertiary aromatic amines (11), ionize more rapidly with increase of acid concentrations (i.e. plots of log I against - H_o have slopes greater than unity); some, like amides, ionize more slowly (i.e. have slopes less than unity).

Thermodynamic protonation constants could be obtained for these organic bases by the acidity function approach when members of a series showed sufficient differences in basicity to permit the application of the "overlap principle" of Hammett (2), so that the strongest bases could be studied in dilute aqueous solutions (the standard state). However, this treatment has produced a host of new acidity functions (7-12), and it is now apparent that the simplicity of the early Hammett treatment is erroneous.

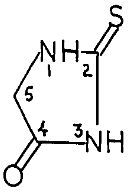
When none of the compounds is basic enough to be studied in dilute aqueous solutions, we can obtain thermodynamic protonation constants for a group of newly investigated bases by either (1) relating their ionization behaviour to one of the already existing acidity functions, or (2) by making use of Bunnett's (15) relation, from which one calculates protonation behaviour in dilute aqueous solution. The difficulties and limitations of these procedures are discussed later in this chapter.

In the present work we have studied the protonation behaviour of several bases related to 2-thiohydantoin and thiourea. We also reevaluated the data for thioureas and thiolactams. It was known that the extent of protonation of these latter compounds increased with acid concentration more rapidly than expected from the $\underline{H}_o$ functions (13,16). By a careful selection of compounds, a new acidity function $\underline{H}_{Th}$ is proposed for the range 20-70% sulphuric acid; which shows marked similarity to the present $\underline{H}_o'''$ function.

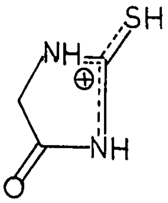
I. Ultraviolet spectra of thioureas and thiohydantoins, and the structure of their conjugate acids

The peaks in the ultraviolet spectra of 2-thiohydantoins have been classified (17) in the light of Janssen's (18) studies of the thiocarbonyl chromophores. Of the three bands that comprise the spectrum the long wavelength, small intensity band (Type I, λ max = 300-360 mμ, ϵ max = 20-150) can be assigned to an $n \rightarrow \pi^*$ transition (19) of one of the lone pair of electrons of the sulphur atom. The assignment is supported by the hypsochromic shifts induced by polar solvents and by molecular orbital calculations (20).

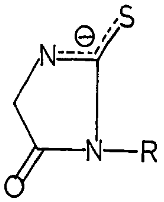
Type II bands occur between 260-290 mμ with extinction coefficients 15.000-20.000 and were assigned to $n \rightarrow \sigma^*$ transitions. This assignment was based on the hypsochromic effect of polar solvents, the extensive blue shift of the band in concentrated sulphuric acid (assuming that protonated species Ib are formed as proven in the sequel), and the blue shift observable in the position of the band in the spectrum of ionic species Ic. However, against this assignment, Janssen (20) has found that molecular orbital calculations did not exclude the possibility that the absorption has $\pi \rightarrow \pi^*$ origin.



Ia



Ib



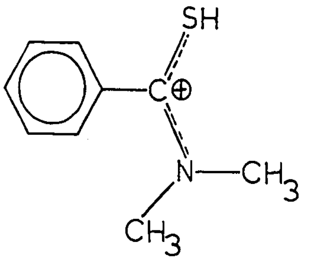
Ic

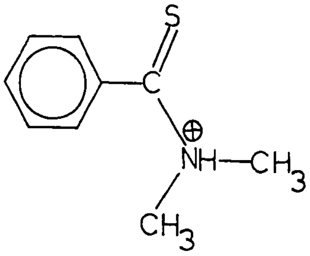
This possibility is also advanced by Sandstrom (21), who applied a self-consistent L.C.A.O. calculation to thiobenzamide, thioacetamide, and the protonated thioacetamide.

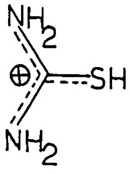
In the spectrum of thiobenzamide no peak is observable at 267 mμ (the position of Type II peak in the spectrum of thioacetamide) but a peak of comparable intensity appears at 298 mμ. The bathochromic effect of conjugation is also predicted for the spectrum of thioacrylamide, not available in the literature. The calculations of Sandstrom indicate that if the absorbance originates from $\pi \rightarrow \pi^*$ transitions, conjugation would have a bathochromic effect on the position of the peak.

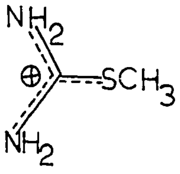
We do not feel that these treatments are rigorous enough to override the assignment of the Type II band based on solvent effects, especially because Sandstrom did not consider the possibility that an electron withdrawing substituent on the thiocarbonyl group should cause a bathochromic shift in an $n \rightarrow \sigma^*$ absorption band (22).

The structure of the protonated forms of thioamides, thioureas, and thiohydantoins is best considered together on the grounds of their structural similarities. Sandstrom (21) obtained compelling evidence for structure IIa for the conjugate acid of N,N-dimethylthiobenzamide from the n.m.r. spectrum of the compound in sulphuric acid. The spectrum showed two distinct peaks separated by 10 c.p.s. caused by the hydrogens of the methyl groups. This indicates restricted rotation about the carbon-nitrogen bond, and excludes IIb as a structural possibility.


IIa

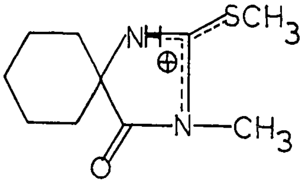

IIb

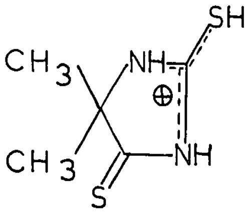

IIIa

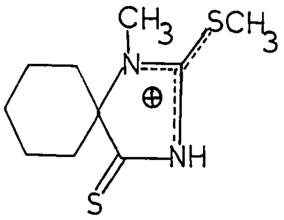

IIIb

Janssen (23) discussed the site of protonation of the thioureas by comparing the ultraviolet and infrared spectra of thiourea and S-methylisothiourea in strong enough sulphuric acid solutions to assure protonation. The spectral similarities unambigously assign structures IIIa and IIIb, respectively, to the protonated forms of the compounds. The same conclusion was reached independently by Wang (16).

Analogously, protonation of the 2-thiohydantoins can be expected to take place on the sulphur atom, as in structure Ib.


IV


Va


Vb

Support for this structure can be obtained by comparing its ultraviolet spectrum with that of the methylmercaptoimidazolone IV in sulphuric acid solution (Fig. 1), when account is taken of the bathochromic effect of the S-methyl group

(24,25). Similarly, the spectra of Va and Vb* also bear a close resemblance (the S-methyl substituent again resulting in a bathochromic shift), showing that protonation of 2,4-dithiohydantoins also takes place on the thiourea sulphur.

II. Protonation of 2-thiohydantoins and 2,4-dithiohydantoin in varying concentrations of sulphuric acid.

The Type II bands were found to be most suitable for following the protonation of these compounds because of these hypsochromic shifts. Solvent effects (2) resulting in lateral shifts of the absorption peaks without appreciable change in the intensity, are also present; however, ionization ratios were calculated by methods (11, 12, 26) which minimize these effects, using the equation:

$$(5) \quad \underline{I} = \frac{\epsilon_B - \epsilon}{\epsilon - \epsilon_{BH^+}}$$

Over the range of acid concentrations in which protonation changes are appreciable, medium effects are small, as shown by the fact that absorption curves for these acidities passed through fairly well defined isosbestic points. This is shown in Figs. 12 and 13, which are representative of the rest.

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* We are grateful to Mr. Joseph K. Liu for the spectra of these latter compounds.

Plots of log I (within values of 1.0 and -1.0) against the acidity of the solution (expressed on the $\underline{H}_o'''$ acidity scale) gave straight lines with slopes varying between 0.95 and 1.00 (Fig. 2). On the assumption that the protonation of these compounds follow $\underline{H}_o'''$ the thermodynamic ionization constants were obtained from the intercepts of these plots. These values were checked by obtaining sigmoid plots of the extinction coefficients of the solutions against the H_o''' function (Fig. 8-11). The ionization ratios, slopes and protonation constants for the thiohydantoins are listed in Table I.

Table I

Ionization ratios of thiohydantoins at different acidities

% H_2SO_4	$\epsilon \times 10^{-4}$	log I	%H_2SO_4	$\epsilon \times 10^{-4}$	log I
1.2-thiohydantoin[a]			2. 5,5-diphenyl-2-thiohydantoin[b]		
0	1.61	--	0	1.88	--
40.4	1.57	-1.46	47.8	1.87	--
48.2	1.54	-1.29	58.3	1.80	-1.25
55.1	1.43	-0.873	62.0	1.61	-0.678
58.8	1.33	-0.648	63.0	1.58	-0.635
62.0	1.03	-0.217	65.7	1.21	-0.128
63.5	0.812	0.047	67.0	1.04	0.055

Table I (Cont'd)

$\%H_2SO_4$	$\epsilon \times 10^{-4}$	log I	$\%H_2SO_4$	$\epsilon \times 10^{-4}$	log I
64.1	0.669	0.202	68.7	0.766	0.200
66.3	0.414	0.545	70.3	0.583	0.671
67.7	0.287	0.791	71.1	0.487	0.864
71.4	0.114	1.55	75.4	0.322	1.914
93.6	0.072	--	80.2	0.307	--
pK_{BH^+}		-6.40±0.1			-7.00±0.1
slope		1.00			1.00
3. 5-benzal-2-thiohydantoin[c]			4. 5-benzyl-2-thiohydantoin[d]		
0	7.47	--	0	1.76	--
47.3	7.45	--	43.0	1.75	--
58.8	7.45	--	54.7	1.66	-1.23
63.9	6.28	-0.610	57.1	1.54	-0.800
67.2	4.94	-0.140	57.7	1.50	-0.700
68.4	4.47	0.00	59.8	1.41	-0.540
69.2	3.68	0.230	62.2	1.015	-0.030
71.8	2.42	0.715	66.4	0.667	0.380
75.2	1.65	1.442	67.8	0.239	0.670
81.7	1.44	--	72.0	0.218	--
			76.8	0.212	--
pK_{BH^+}		-7.25±0.1			-6.45±0.1
slope		0.95			0.95
5. 5,5-dimethyl-2-thiohydantoin[e]			6. 5,5-dimethyl-2,4-dithiohydantoin[f]		
0	1.60	--	0	2.92	--

Table I (Cont'd)

$\%H_2SO_4$	$\epsilon \times 10^{-4}$	log I	$\%H_2SO_4$	$\epsilon \times 10^{-4}$	log I
31.8	1.58	--	45.5	2.95	--
52.7	1.53	-1.48	54.9	2.90	-1.42
57.1	1.38	-0.83	57.7	2.71	-0.637
61.0	1.075	-0.32	58.8	2.59	-0.422
62.2	0.858	0.031	60.75	2.46	0.220
65.4	0.572	0.260	62.9	2.21	0.110
71.9	0.118	1.160	65.8	1.93	0.512
76.1	0.017	--	80.5	1.61	--
pK_{BH^+}		-6.45±0.1			-6.30±9.1
slope		0.95			0.98

The ionization was measured at the following wavelength: a, 260 mμ; b, 269 mμ; c, 290 mμ; d, 265 mμ; e, 260 mμ; f, 294 mμ.

It is apparent from Fig. 2 and the calculated slopes that over the range of acidities in which measurable changes of I take place, the thiohydantoins follow $\underline{H}_o$''' fairly well.

The following questions then arise:

A. Can we conclude that the $\underline{H}_o$''' values of the sulphuric concentrations for half-ionization give the thermodynamic ionization constants for these compounds?

B. Why do these compounds behave like the structurally dissimilar tertiary anilines in following $\underline{H}_o'''$ rather than $\underline{H}_o$ on protonation?

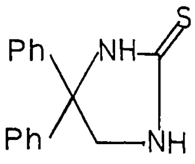
We shall now consider the answers to these questions in turn.

III. Thermodynamic Ionization constants by the overlap principle of Hammett

As it was indicated in the introduction, thermodynamic ionization constants for a group of newly investigated bases can be obtained if there is enough variation in their basicity to apply the overlap treatment of Hammett. Unfortunately the thiohydantoins protonate in a limited region of sulphuric acid concentration and therefore to extend the scale more basic compounds of similar structure and increased basicity are required.

The protonation behaviour of other thio compounds, such as thiolactams (13) and thioureas (16), has been investigated by Edward and co-workers. Reexamination of their data for the thiolactams indicates that they follow the $\underline{H}_I$ acidity function (based on the protonation of indole bases (9)), and therefore the deviation from the Hammett $\underline{H}_o$ function is in the same direction as that of the thio-hydantoins, but less.

The thioureas behave in a diverse manner. In Fig. 3 we have plotted the logarithmic ionization ratios from Wang's data (16) against $\underline{H}_o$. It can be seen that the slopes vary between 0.90 and 1.50 depending on the nature of the substituent: N,N'-di-t-butylthiourea had a slope of 0.90; N-allyl-, N-phenyl- and thiourea itself had slopes of about unity; while all the rest had slopes greater than unity. N,N-Diphenylthiourea had a slope of 1.25 against $\underline{H}_o$ and 1.00 against $\underline{H}_o'''$. Its behaviour thus was very similar to that of the thiohydantoins, and it was therefore selected as the most basic compound for the "overlap" treatment. Advantageously, it was a strong enough base to allow a fairly accurate basicity determination by the Bunnett treatment (discussed below), and its low solubilities allowed its activity coefficients in various concentrations of acid to be determined. Bases of intermediate strength were found in N-acetylthiourea and in 4,4-diphenylimidazolid-2-thione (VI), the latter obtained from the lithium aluminum hydride reduction of 5,5-diphenyl-2-thiohydantoin. The protonation of both of these compounds followed $\underline{H}_o'''$, as seen from Fig. 2.



VI

Their ionization ratios for different sulphuric acid concentrations are listed in Table II, together with the experimental data of Wang for N,N-diphenylthiourea (16).

By plotting the logarithmic ionization ratios of compounds 1,2,7,8, and 9 against the sulphuric acid concentration (Fig. 4), it became evident that the compounds indeed form an overlapping set of indicators having identical slopes. To anchore the acidity function to the thermodynamic standard state of dilute aqueous solutions, the protonation constant, $pK_{ThH^+} = -2.40$ was obtained for N,N-diphenylthiourea from Bunnett's extrapolation technique (15). The pK_{ThH^+} values of the other thiobases listed at the bottom of Table III were then obtained from the equation,

$$(6) \quad pK_{Th_1H^+} - pK_{Th_2H^+} = \log I_1 - \log I_2$$

by the stepwise technique of Hammett (2). From these values and the smoothed out values of log I obtained from Fig. 4 for different concentrations of sulphuric acid, values of H_{Th} (the acidity function applying to the protonation of the restricted series of thioureas and thiohydantoins) could be calculated from the equation (4a) (modified from Hammett's original equation (4)):

$$(4a) \quad pK_{ThH^+} - \log I = H_{Th}$$

These values are listed in Table III.

Table II

Ionization ratios of N,N-diphenylthiourea, 4,4-diphenylimidazolid-2-thione and N-acetylthiourea in sulphuric acid solutions

Compound	$\%H_2SO_4$	$\epsilon \times 10^{-4}$	log I
7. N,N-diphenylthiourea[a,d]	0	1.45	--
	20.8	1.40	-1.19
	24.5	1.28	-0.590
	29.1	1.17	-0.295
	32.0	1.05	-0.030
	36.8	0.83	0.470
	39.9	0.73	0.82
	46.6	0.65	1.42
	60.4	0.62	--
slope	1.00		
pK_{BH^+}	-2.65		
8. 4,4-diphenylimidazolid-2-thione[b]	0	1.13	--
	31.3	1.10	--
	36.8	0.865	-0.403
	38.5	0.810	-0.278
	42.2	0.630	0.103
	46.0	0.390	0.738
	50.3	0.330	1.042
	60.0	0.280	1.613
	78.3	0.260	--
slope	1.00		
pK_{BH^+}	-3.55		
9. N-acetylthiourea[c,e]	0	1.34	--
	39.2	1.11	-0.670
	45.4	0.970	-0.410
	48.6	0.720	-0.050
	50.7	0.57	0.150
	50.9	0.480	0.280
	55.3	0.270	0.630
	88.6	0.030	--
slope	0.97		
pK_{BH^+}	-4.45		

The ionization was measured at the following wavelength: a, 245 mμ; b, 239 mμ; c, 267.5 mμ;
d, data taken from reference 16;
e, we wish to thank Mr. Joseph K. Liu for his assistance in the study of this compound.

Table III

The H_{Th} acidity function

$\%H_2SO_4$	$-H_{Th}$	$-H_o'''$	$H_{Th} - H_o'''$
20	1.20^{a}	1.47	0.27
25	1.70^{a}	1.93	0.23
30	2.20^{a}	2.44	0.24
35	$2.75^{a,b}$	2.95	0.20
40	$3.25^{a,b} \pm 0.05$	3.46	0.19
45	$3.84^{b,c} \pm 0.05$	4.00	0.16
50	$4.39^{b,c} \pm 0.03$	4.54	0.15
55	4.94^{c}	5.10	0.16
60	$5.68^{d,c}$	5.91	0.23
65	$6.40^{d} \pm 0.05$	6.75	0.35
70	$7.15^{d,e} \pm 0.05$	7.65	0.50

Values based on: a, compound 7, $pK_{BH^+} = -2.40$; b, compound 8, $pK_{BH^+} = -3.35$ c, compound 9, $pK_{BH^+} = -4.24$; d, compound 1, $pK_{BH^+} = -6.00$, e, compound 2, $pK_{BH^+} = -6.65$.

It is apparent from the data (plotted in Fig. 5) that the two acidity functions behave remarkable similarly. The small difference between the two functions may be due to a systematic error in H_{Th} because of an error in the pK_{ThH^+} of the anchor compound or it may reflect a genuine difference between the protonation behaviour of thio bases and tertiary amines. The latter possibility is considered in the next section.

IV. Dependence of acidity functions on activity coefficients of indicators

We now consider the reason for divergence of different acidity functions as the acid concentration is increased from dilute aqueous acid (in which, by definition, they all become identical to pH).

An acidity function is constructed by measurement of the ionization of a series of bases B_1, B_2, B_3 . . . etc. of decreasing basicity, the first or "anchor" base being sufficiently basic to have its $p\underline{K}_{B_1H^+}$ determined in dilute aqueous acid. The difference in the ionization ratios I_1 and I_2 of a pair of bases in the same concentration of acid is given by,

$$(7)\quad \log I_1 - \log I_2 = p\underline{K}_{B_1H^+} - p\underline{K}_{B_2H^+} + \log \frac{\underline{f}_{B_1}\underline{f}_{B_2H^+}}{\underline{f}_{B_2}\underline{f}_{B_1H^+}}$$

Using a set of indicators which happened to be mostly aromatic primary amines, Hammett found that plots of $\log I_1$ and $\log I_2$ against concentration of sulphuric acid were parallel over the range of acid concentrations in which changes in I_1 and I_2 were measurable, i.e. $\log I_1 - \log I_2$ was constant. This is possible, according to equation (7), only if log $(\underline{f}_{B_1}\underline{f}_{B_2H^+} / \underline{f}_{B_2}\underline{f}_{B_1H^+})$ is invariant with acid concentration. If this parallelism extends down into dilute concentrations of aqueous acid in which $\underline{f}_{B_1} = \underline{f}_{B_2} = \underline{f}_{B_1H^+} = \underline{f}_{B_2H^+} = 1$, then log $(f_{B_1}f_{B_2H^+} / f_{B_2}f_{B_1H^+})$ will be zero. It will also be zero (because of parallelism) in more concentrated acid solutions; i.e. the changes in $f_{B_1} / f_{B_1H^+}$ and $f_{B_2} / f_{B_2H^+}$ as the acid concentration increases must be equal. This is shown more formally by differentiating equation 7 with respect to acid concentration (%).

$$(8)\quad \frac{d \log I_1}{d\ \%} - \frac{d \log I_2}{d\ \%} = \frac{f_{B_2}f_{B_1H^+}}{f_{B_1}f_{B_2H^+}} \frac{d}{d\%} \log \frac{f_{B_1}f_{B_2H^+}}{f_{B_2}f_{B_1H^+}}$$

This shows that at a given acid concentration the slopes of log I_1 and log I_2 will be identical (i.e. the curves will be parallel), only if log $(f_{B_1}f_{B_2H^+} / f_{B_2}f_{B_1H^+})$ is invariant with acid concentration.

Hammett found that changes in I_2 and I_3 could be observed over a range of stronger acid concentrations and that again plots of log I_2 and log I_3 against acid concentration were parallel. This indicated $(f_{B_2}f_{B_3H^+} / f_{B_3}f_{B_2H^+})$ to be invariant over this range of concentrations. The same was found to be true of the acitivty coefficients of the weaker bases, over the acid ranges in which comparison of any two bases was possible. Hammett then made the assumption, which Arnett (1) has termed, Hammett's activity coefficient postulate, that the activity coefficient ratios (f_B / f_{BH^+}) of all bases B_1, B_2. B_3 . . . etc. change to the same extent over the whole range of acid concentration. If this is so, then at any acid concentration the term $h_o = a_{H^+} \cdot f_B / f_{BH^+}$ is valid as a measure of the portonating power of the medium for all the bases, and the constant obtained from ionization ratios using equation (4) is a true thermodynamic constant.

It seems likely that for a closely related series of compounds, such as Hammett's nitroanilines, the activity coefficient postulate is approximately correct, and that the protonation constants determined from equation (4) are thermodynamic constants, referred to dilute aqueous solution as the standard state. However, it is less likely to be true for compounds of different structure. Arnett (1) has considered the case of benzoic acid, whose ionization in 75-90% sulphuric acid follows h_o, and which is given a pK_{BH^+} of -7.2 from the H_o of half-ionization. Such a pK_{BH^+} is a thermodynamic constant if in fact the protonation of this compound follows h_o over the whole range of acidity down to dilute aqueous solution. This is possible if its f_B / f_{BH^+} ratio changes in the same way as that of the Hammett indicators over the whole range of acidity. Arnett argues that while it may do this over the range 75-90% acid, it will not do this in more dilute acids because of strong salting - in effects noted by Hammett and Chapman (27).

Similar arguments may apply to the thio bases. The parallelism of log I for thio bases and for tertiary anilines (B''') shown in Fig. 2, shows that over the range of acid concentrations in which this is observed the changes in (f_{Th} / f_{ThH^+}) and ($f_{B'''} / f_{B'''H^+}$) must be the same (cf. equation (8)). However, it does not follow that over this acid range (f_{Th} / f_{ThH^+}) is equal to ($f_{B'''} / f_{B'''H^+}$); rather, the divergence of the H_o''' and H_{Th} curves (Fig. 5) is explained if $\log (f_{B'''}/f_{B'''H^+}) > \log (f_{Th} / f_{ThH^+})$. This follows from the equation, which must hold for any given acid concentration:

$$(9) \quad H_o''' - H_{Th} = \log (f_{Th}/f_{ThH^+}) - \log (f_{B'''H^+}/f_{B'''})$$

Hence with change of acid concentration from 0% (in which $\log (f_{B'''}/f_{B'''H^+}) = \log (f_{Th}/f_{ThH^+})$) to 20%, $\log (f_{B'''}/f_{B'''H^+})$ must increase more, or decrease less, than $\log (f_{Th}/f_{ThH^+})$.

There are no reliable data on $f_{B'''}$ and $f_{B'''H^+}$, and so the testing of this analysis remains for the future. However, an attempt can be made to explain the divergence of the H_{Th} and H_o curves (Fig. 5) in terms of the similar equation (holding for a fixed acid concentration):

$$(10) \quad H_{Th} - H_o = \log f_B - \log f_{Th} + \log (f_{ThH^+}/f_{BH^+})$$

5,5-Diphenyl-2-thiohydantoin, because of its small solubility in aqueous acid, was chosen as the model thiohydantoin and its activity coefficient (f_{Th}) determined from solubility measurements over the range 0 - 73.4% (cf. refs. 14, 28). These are given in Table IV, in which are listed also activity coefficients (f_B) taken from Boyd (14) of 2,6-dichloro-4-nitroaniline, chosen as the model Hammett indicator. It is evident that, *accepting these models as valid* (see Boyd (14) and Yates and Sweeting (29) for discussion and justification of similar treatments), the difference in H_{Th} and H_o arises because thiohydantoins are salted-out more than Hammett indicators as the acid strength rises (compare f_{Th} and f_B). This may be explained by the highly polar nature of the thiohydantoins (cf. 13), which causes them to be fairly heavily hydrated; such a molecule will be salted-out strongly with increasing strength of acid, in part because of the decreasing water activity of the solutions. Acting in the opposite direction, but less strongly, is the greater tendency of protonated-thiohydantoins than of protonated Hammett indicators to be salted-out with increasing concentration of acid.

These conclusions can only be regarded as highly tentative, and point to the desirability of determining values of $f^{*}_{ThH^{+}}$ and of more values of f_{Th} from suitable models (the former activity coefficients being related to those of tetraethylammonium ion(14,29)), however solubility studies of N,N-diphenylthiourea and N,N'-diphenylthiourea (16) indicate that this marked salting-out behaviour in aqueous sulphuric acid of the thio bases is of a general nature.

Table IV

Solubilities and activity coefficients for 5,5-diphenyl-2-thiolydantoin in aqueous sulphuric acid solutions

$\%H_2SO_4$	O.D (269 m)	O.D (corr)^a	log f_T	log f_B^b	log $(f_{ThH^+}/f_{BH^+})^c$
0	0.695	0.695	0	0	--
9.62	0.373	0.373	0.27	0.039	--
19.03	0.220	0.220	0.50	0.071	+0.18
29.1	0.149	0.149	0.67	0.039	0.18
40.0	0.118	0.118	0.77	-0.143	0.13
50.5	0.120	0.120	0.75	-0.407	0.16
60.2	0.142	0.140	0.70	-0.735	0.25
67.4	0.210	0.145	0.68	-1.035	0.31
70.8	0.230	0.140	0.70	-1.167	0.47
73.4	0.600	0.230	0.48	-1.255	

a) Corrections were applied as calculated from the ionization ratios (Fig. 4), $\epsilon_B = 1.87 \times 10^{-4}$, $\epsilon_{BH^+} = 0.300 \times 10^{-4}$;

b) activity coefficients of 2,6-dichloro-4-nitroaniline (14).

c) calculated from equation 10.

V. Protonation constants from the Bunnett treatment

Bunnett has recently devised a technique (15) whereby thermodynamic ionization constants can be obtained for bases that follow different acidity functions. The advantage of such a technique is that only a single acidity function need to be applied. Equation 11 is suggested as the standard formulation for the L.F.E.R. (Linear Free Energy Relationship) treatment.

$$(11)\quad \log\left([\mathrm{ThH}^+]/[\mathrm{Th}]\right) + \underline{H}_o = \phi\left(\underline{H}_o + \log[\mathrm{H}^+]\right) + \underline{pK}_{\mathrm{ThH}^+}$$

Plots of the left hand terms of this equation against ($\underline{H}_o$ + log [H^+]) yield straight lines whose intercepts (when $\underline{H}_o$ = - log [H^+]) gives the thermodynamic acidity constants. The slope ϕ is considered to represent the average hydration change for the hypothetical reaction,

$$(12)\quad \mathrm{ThH}^+(\mathrm{H_2O})_p + \mathrm{B}(\mathrm{H_2O})_b = \mathrm{Th}(\mathrm{H_2O})_s + \mathrm{BH}^+(\mathrm{H_2O})_a + (p-s-a+b)\,\mathrm{H_2O}$$

the separate terms refer to the hydrated species of different bases Th and B and their conjugate acids ThH^+ and BH^+. Numerically it is equal to

$$(13)\quad \phi = \frac{(p-s) - (a-b)}{b+n-a} = \frac{(p-a) - (s-b)}{b+n-a}$$

where n is equal to the hydration number of the proton (customarily taken as 4.0 in sulphuric acid concentrations up to 65% (29)).

Application of equation 11 to the experimental data for N,N-diphenylthiourea, 2-thiohydantoin, and 5,5-diphenyl-2-thiohydantoin yielded the results summarized in Table V.

Table V

Ionization constants and slopes of the Bunnett plots (Fig. 7)

Compounds	ϕ	$pK^{a}_{ThH^+}$	$pK^{b}_{ThH^+}$	$pK^{c}_{ThH^+}$
N,N-diphenylthiourea	-0.42	-2.40	-2.40	-2.65
2-Thiohydantoin	-0.40	-6.40	-6.00	-6.40
5,5-Diphenyl-2-thiohydantoin	-0.33	-6.60	-6.60	-7.00

The ionization constants were determined a, from Fig. 7; b, from Table III; c, from Tables I and II.

The protonation constants obtained in this way for the 2-thiohydantoins are in reasonable agreement with the values obtained by the overlap method (Table III), considering the long extrapolation needed to get values using equation 11.

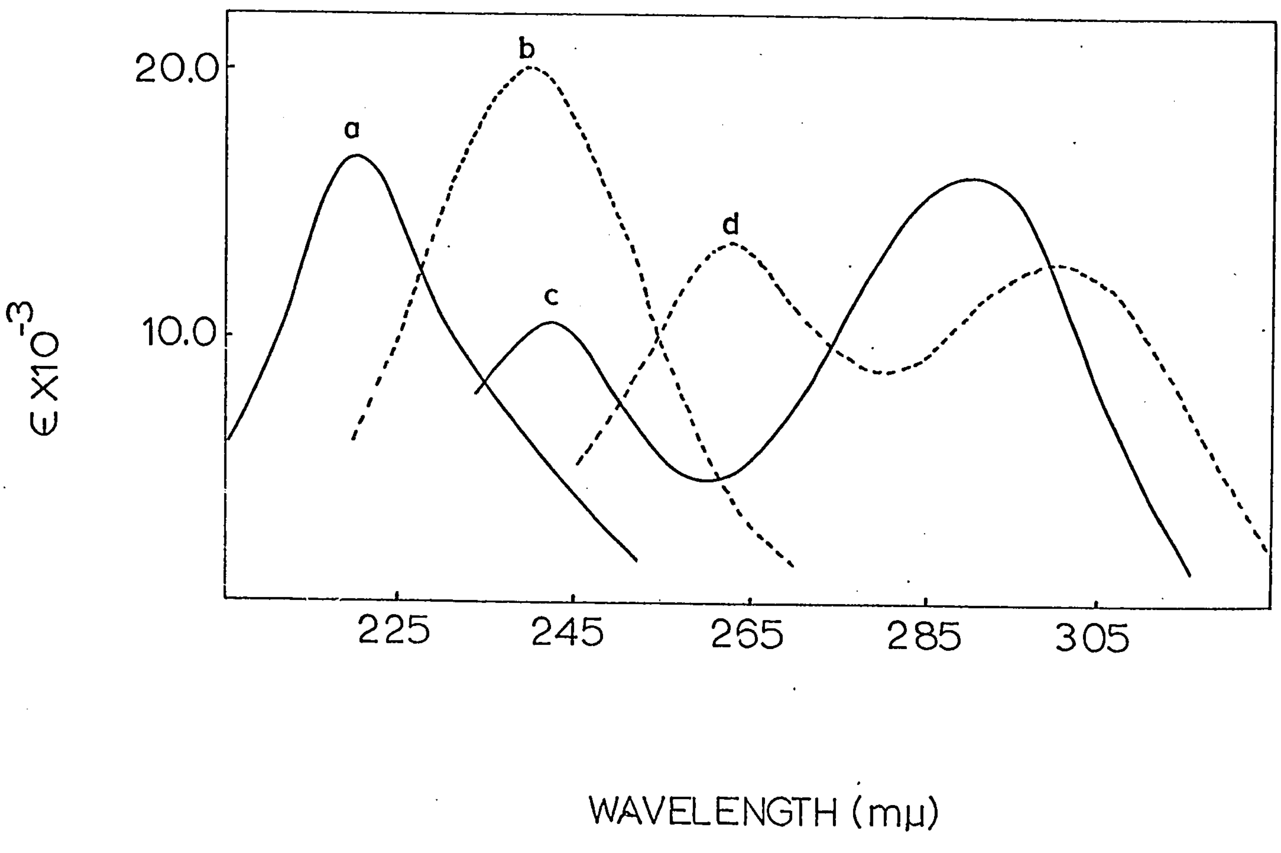
The slopes (ϕ) are within a narrow range, which according to Bunnett, indicates good behaviour as model compounds for acidity function construction, and are very similar to those obtained for the tertiary anilines (-0.33 to -0.48 (15)). The negative value of ϕ is also in a qualitative agreement with our proposed hydration hypothesis presented earlier from activity coefficient studies. Since the proton is more heavily hydrated than the cations of equation 12, $b+n-a > o$. However, the numerator in equation 13 will be negative if $p > a$ but $s >> b$ as suggested above.

VI. Correlations between the thermodynamic ionization constants

The basicities of the 2-thiohydantoins (Tables I, III and V) show the expected substituent effects. Substitution of the two phenyl groups in the 5-position has a marked base weakening inductive effect (0.60 pK unib) in agreement with the similar effect found in Part II of this thesis. It is interesting to observe that the 2,4-dithio-compound has ionization constant comparable to 2-thiohydantoin, although it has been shown from the ionization of this compound as an acid, that the thiocarbonyl group withdraws electron density to a higher extent than the carbonyl group (30). Qualitatively this could be explained, that while the latter ionization takes place on the 3-position of the 2,4-dithiohydantoin molecule, neighbouring the thiocarbonyl groups, the former basic ionization takes place on the sulphur atom, three atoms removed from the second thiocarbonyl group and therefore its electron withdrawing effects are not observed to the same extent. Zahradnik (31) determined the basicity of 1-acetylthiourea assuming it followed $\underline{H}_o$ his value of -3.20 corresponds to -4.20 on the $\underline{H}_{Th}$ scale in excellent agreement with our experimental value (-4.24, Table III).

Figure 1

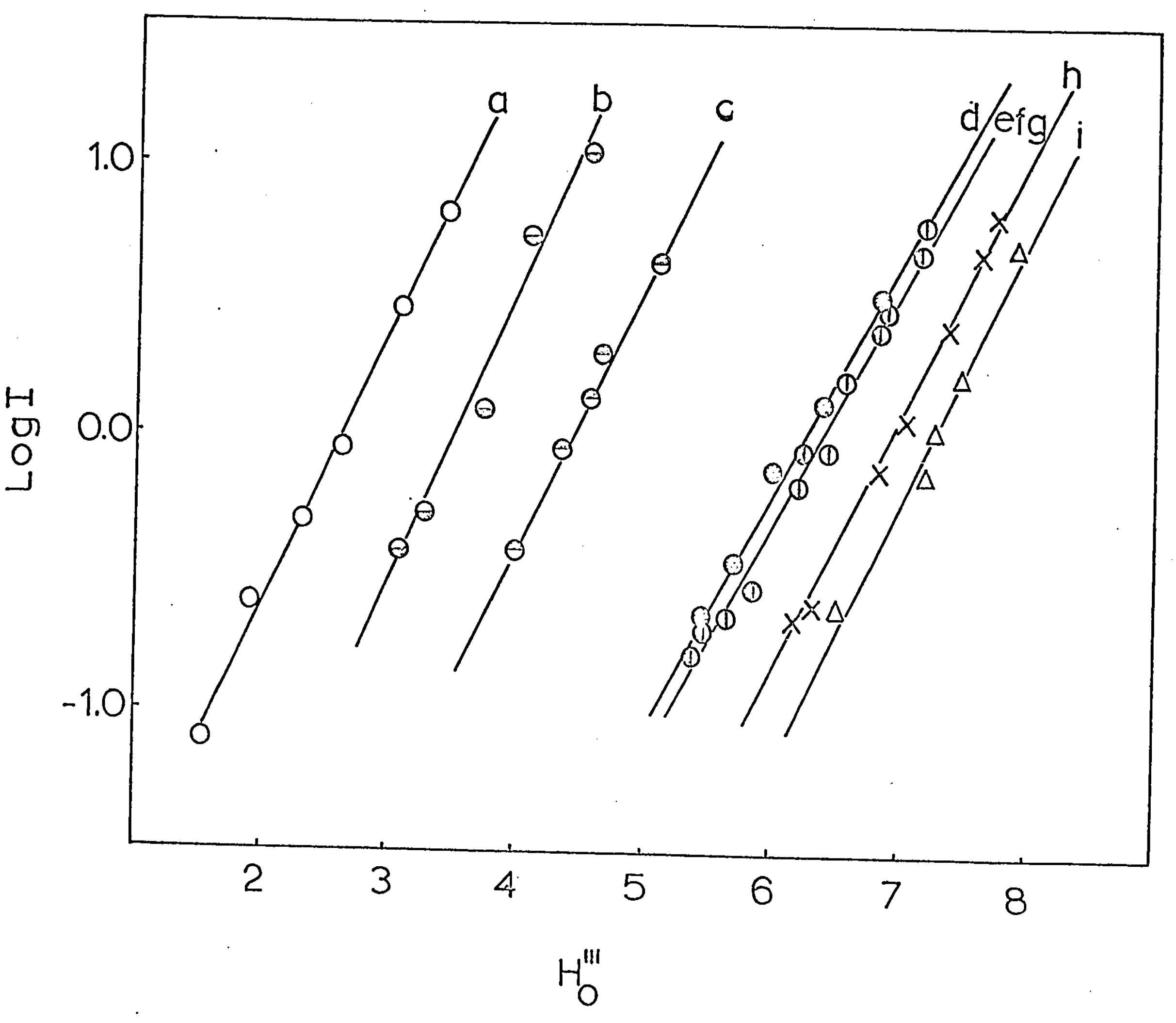
Ultraviolet absorption spectra of a, 5,5-dimethyl-2-thiohydantoin (compound 5) in 76.1% H_2SO_4; b, 1-methyl-2-methylmercapto-4,4-pentamethylene-4H-imidazol-5-one in 83.6% H_2SO_4 (IV); c, 5,5-dimethyl-2,4-dithiohydantoin (compound 6) in 80.5% H_2SO_4; d, 1-methyl-2-methylmercapto-5,5-pentamethylene-5H-imidazol-4-thione in 76.1% H_2SO_4 (Vb).



a
b
c
d
20.0
10.0
ε X10^{-3}
225
245
265
285
305
WAVELENGTH (mμ)

Figure 2

Ionization ratios of thiobases vs. the $\underline{H}_o'''$ acidity function: a, N,N-diphenylthiourea (compound 7); b, 4,4-diphenylimidazolid-2-thione (compound 8); c, N-acetylthiourea (compound 9); d, 5,5-dimethyl-2,4-dithiohydantoin (compound 6); e, 2-thiohydantoin (compound 1); f, 5,5-dimethyl-2-thiohydantoin (compound 5); g, 5-benzyl-2-thiohydantoin (compound 4); h, 5,5-diphenyl-2-thiohydantoin (compound 2); i, 5-benzal-2-thiohydantoin (compound 3).

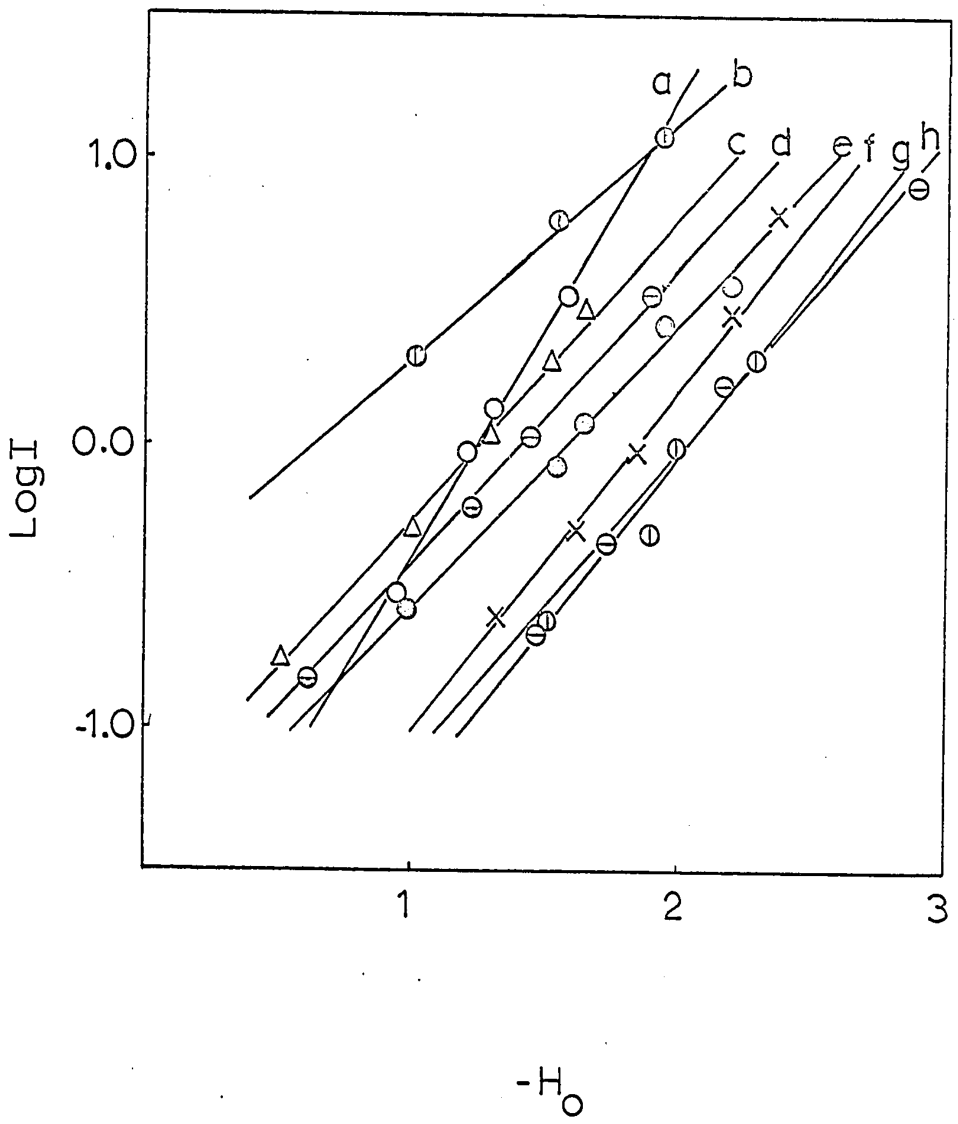


a
b
c
d
efg
h
i
1.0
0.0
-1.0
Log I
2
3
4
5
6
7
8
H_0'''

Figure 3

Ionization ratios of thioureas against the $\underline{H}_o$ acidity function (ref. 16).

	Compound	Slope
a,	N,N'-diethylthiourea	1.50
b,	N,N'-di-t-butyl-	0.90
c,	thiourea	1.01
d,	N-allyl-	1.05
e,	N-phenyl-	1.00
f,	N,N-diphenyl-	1.25
g,	N,N'-diphenyl-	1.20
h,	ethylene-	1.10



a
b
c
d
e
f
g
h
1.0
0.0
-1.0
LogI
1
2
3
-Ho

Figure 4

Ionization ratios of thiobases in aqueous sulphuric acid solucions:

a, N,N-diphenylthiourea (compound 7); b, 4,4-diphenylimidazolid-2-thione (compound 8); c, N-acetylthiourea (compound 9); d, 2-thiohydantoin (compound 1); e, 5,5-diphenyl-2-thiohydantoin (compound 2).

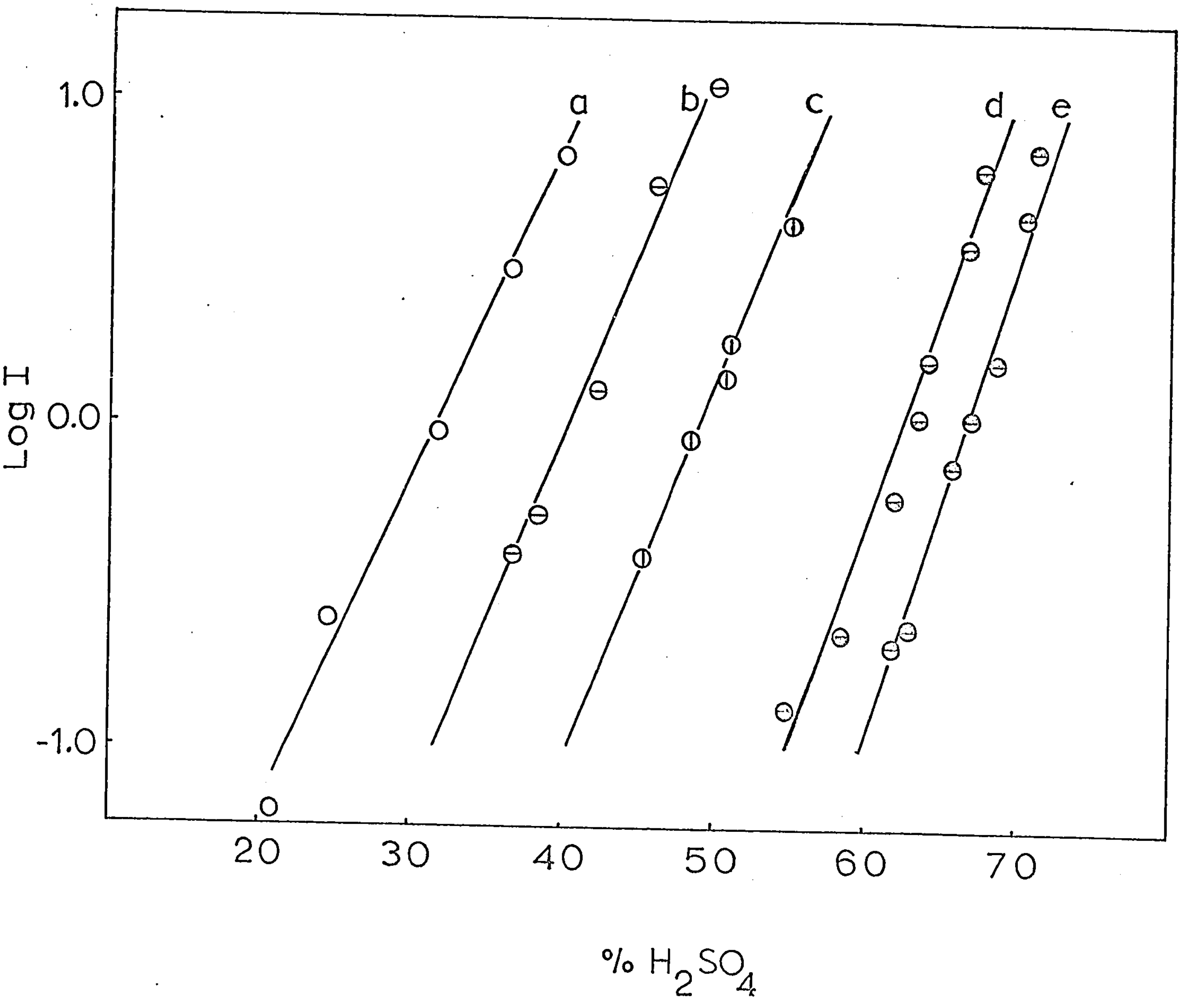

a
b
c
d
e
1.0
0.0
-1.0
Log I
20
30
40
50
60
70
% H_2SO_4

Figure 5

The $\underline{H}_o$, $\underline{H}_o'''$, and $\underline{H}_{Th}$ acidity functions in sulphuric acid.

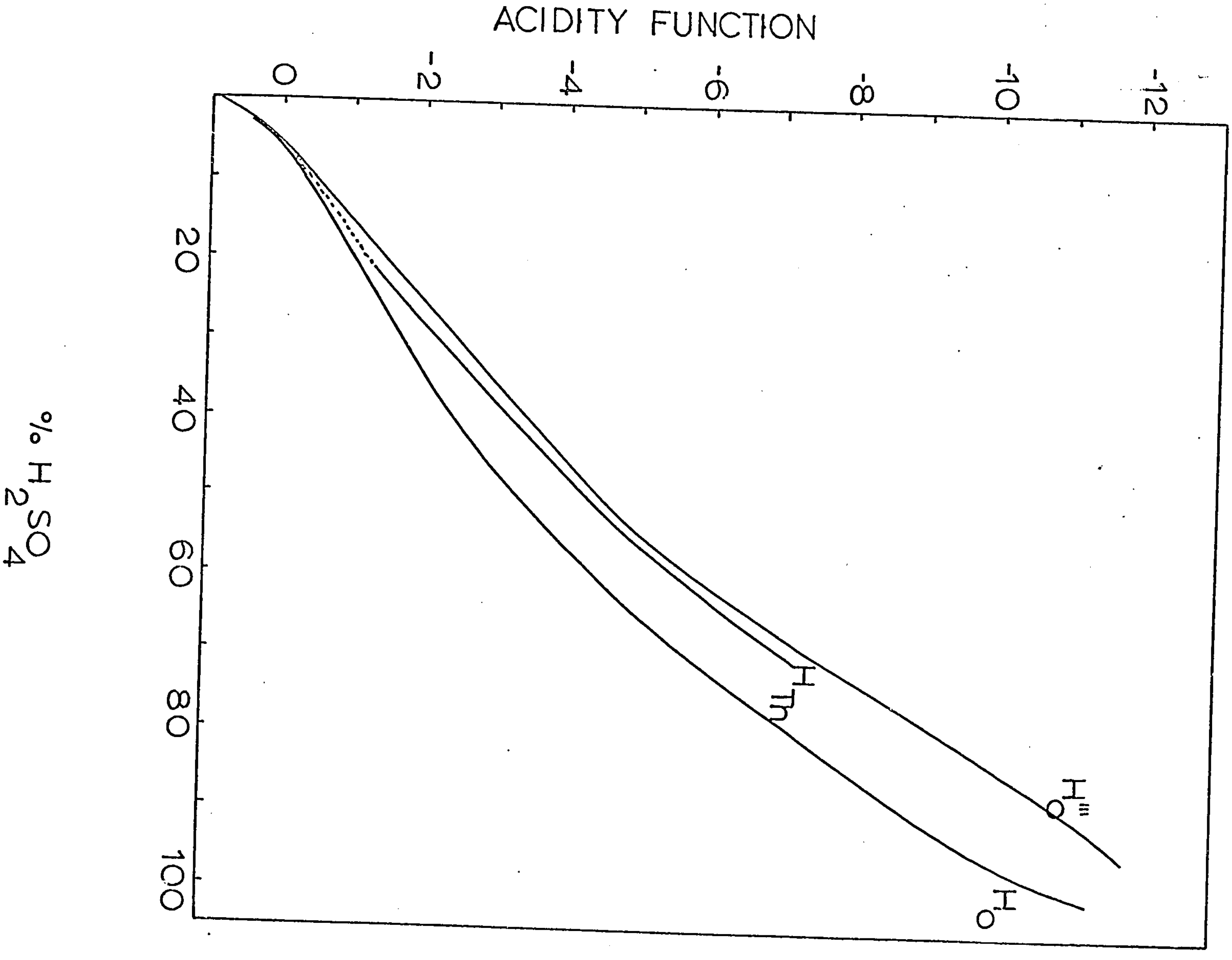

ACIDITY FUNCTION
0
-2
-4
-6
-8
-10
-12
20
40
60
80
100
% H_2SO_4
H_m
H_0'''
H_0

Figure 6

Activity coefficients of a, 5,5-diphenyl-2-thiohydantoin and b, 2,6-dichloro-4-nitroaniline (ref. 14) in aqueous sulphuric acid.

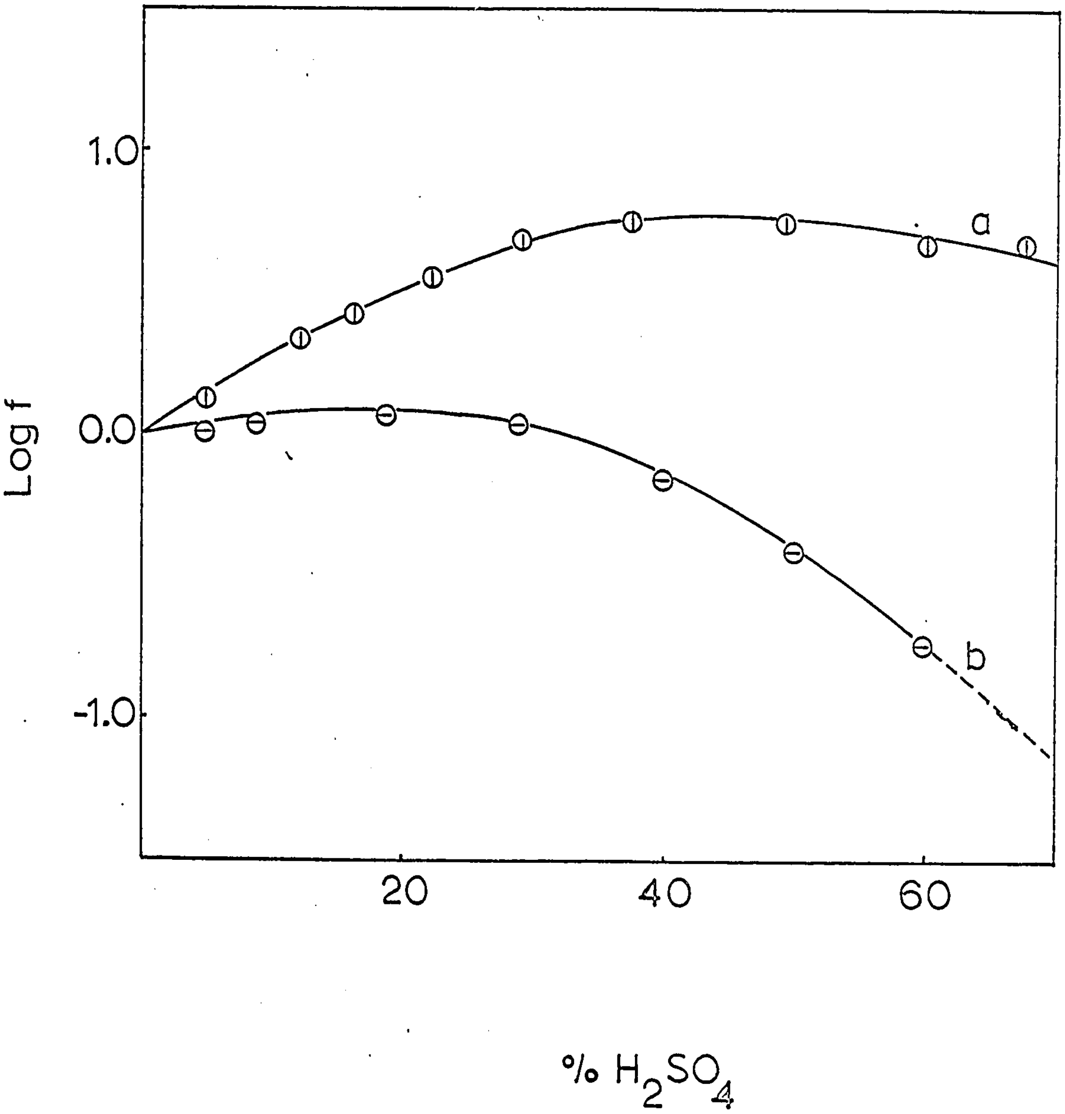

1.0
0.0
-1.0
Log f
20
40
60
a
b
% H_2SO_4

Figure 7

"Bunnett plots" of a, 5,5-diphenyl-2-thiohydantoin, b, 2-thiohydantoin and c, N,N-diphenylthiourea.

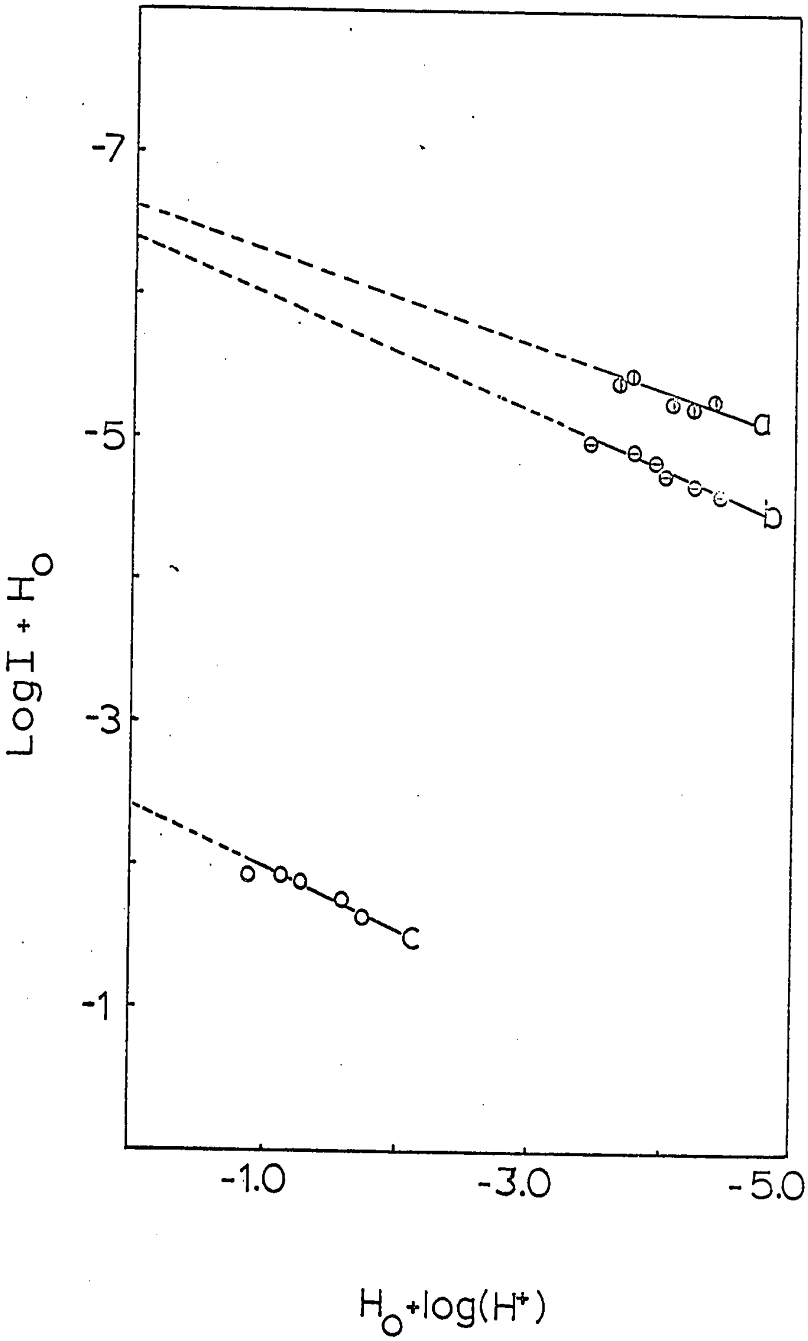

-7
-5
-3
-1
Log I + H_O
-1.0
-3.0
-5.0
H_O+log(H^+)
a
b
c

Figure 8

Ionization of 5,5-diphenyl-2-thio-(A; $\lambda = 269$ mμ) and 2-thio-(B; $\lambda = 260$ mμ) hydantoins in aqueous sulphuric acid.

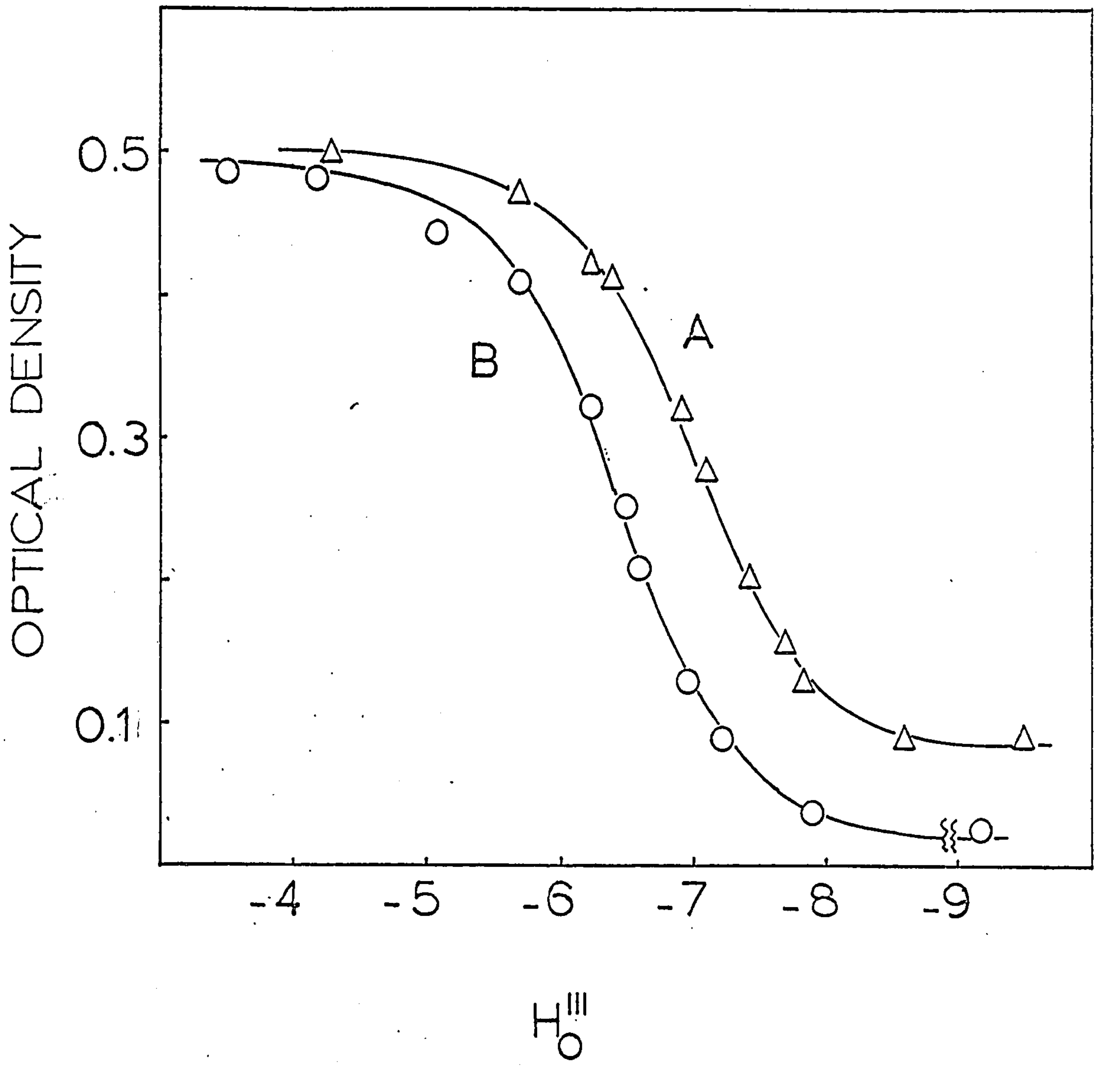

OPTICAL DENSITY
0.5
0.3
0.1
A
B
-4
-5
-6
-7
-8
-9
H_0'''

Figure 9

Ionization of 5,5-dimethyl-2,4-dithio-(C; λ = 294 mμ) and 5-benzal-2-thio-(D; λ = 290 mμ) hydantoins in aqueous sulphuric acid.

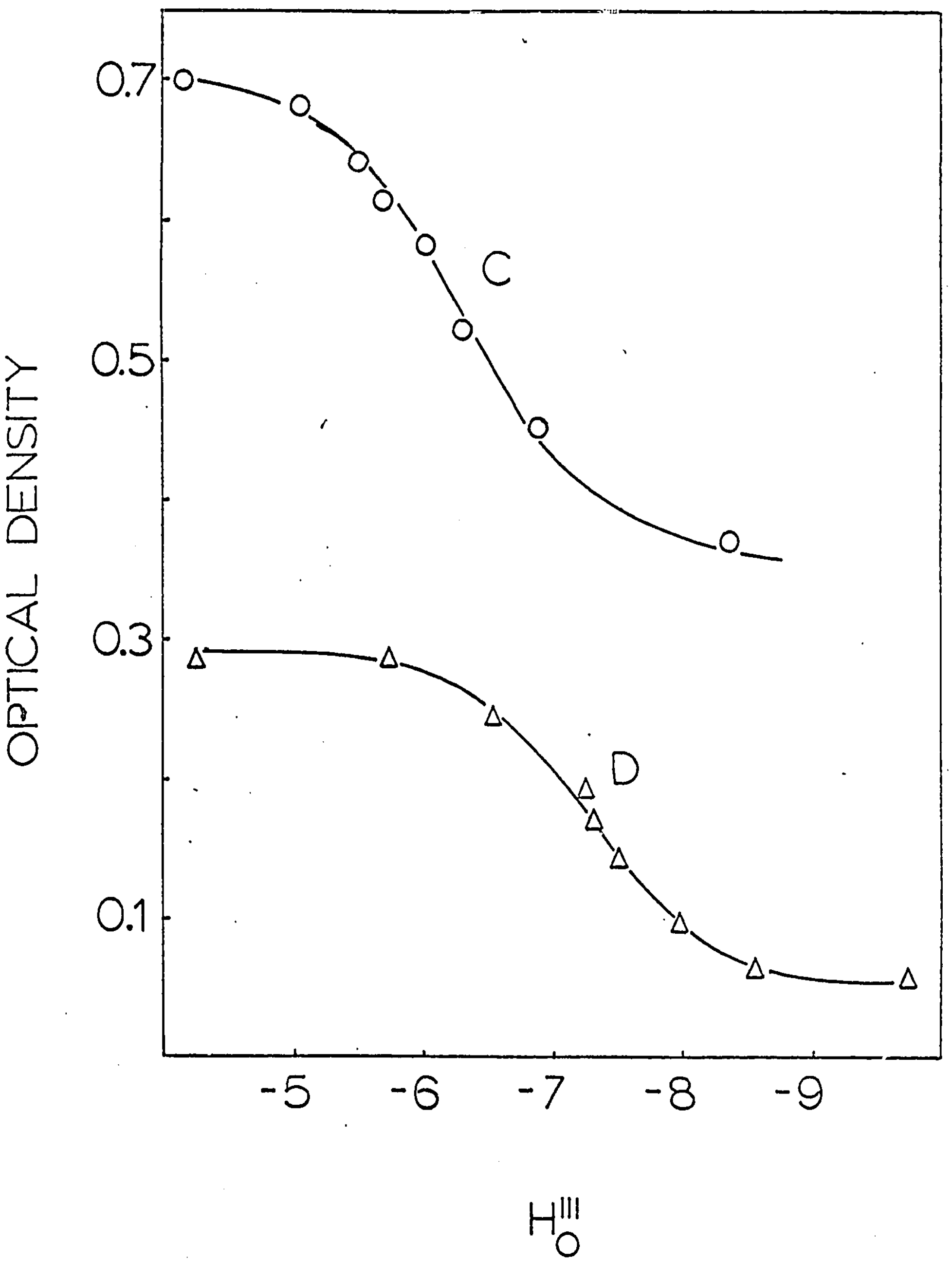

0.7
0.5
0.3
0.1
OPTICAL DENSITY
C
D
-5
-6
-7
-8
-9
H_o^{III}

Figure 10

Ionization of 5-benzyl-2-thiohydantoin (E; λ = 265 mμ) and N-acetylthiourea (F; λ = 267.5 mμ) in aqueous sulphuric acid.

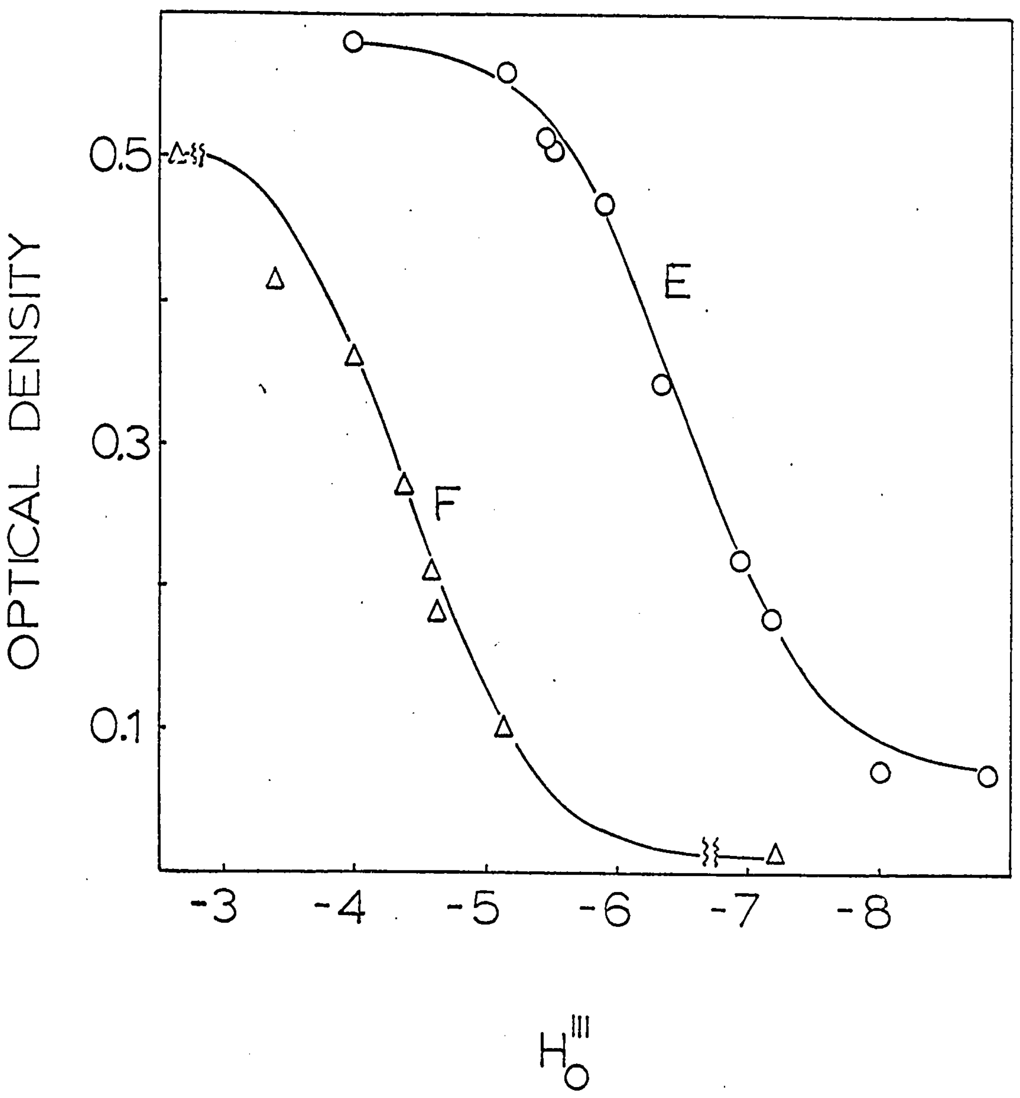

OPTICAL DENSITY
0.5
0.3
0.1
E
F
-3
-4
-5
-6
-7
-8
H_0^{III}

Figure 11

Ionization of 5,5-dimethyl-2-thiohydantoin (G; λ= 260 mμ) and 4,4-diphenylimidazolid-2-thione (H; λ= 239 mμ) in aqueous sulphuric acid.

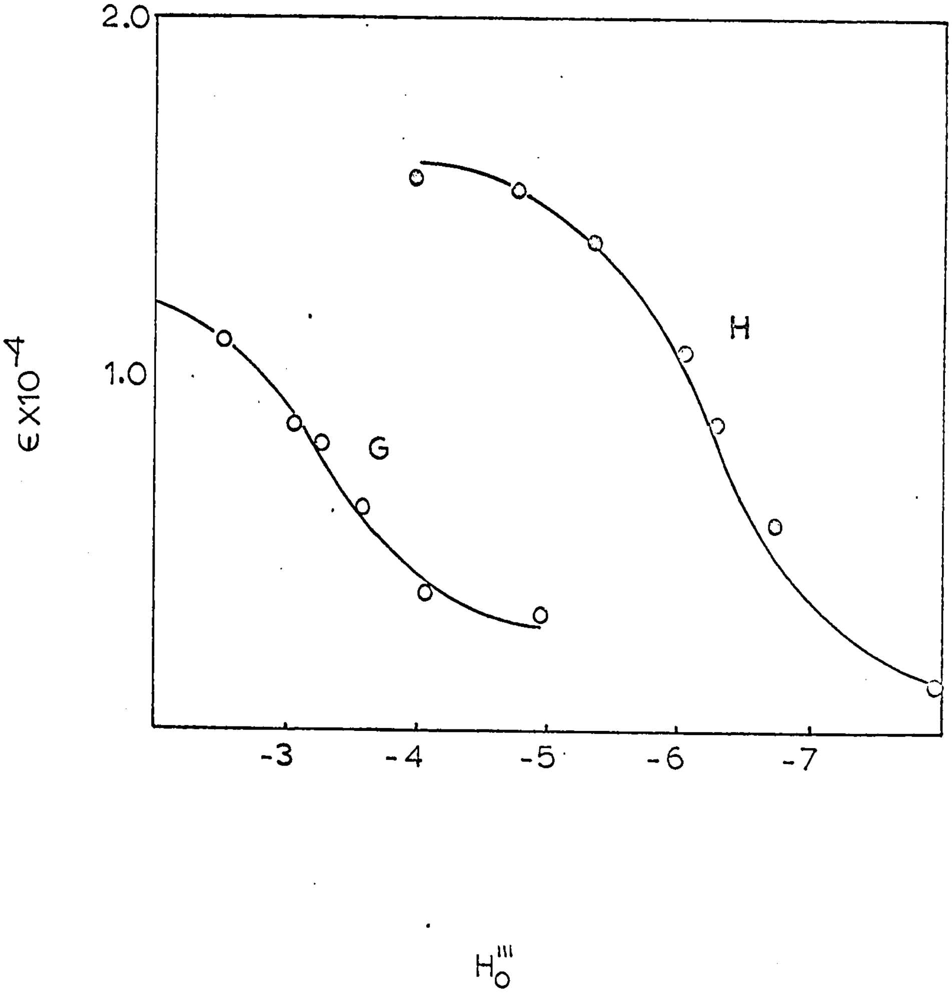

2.0
1.0
$\epsilon \times 10^{-4}$
H
G
-3
-4
-5
-6
-7
H_0'''

Figure 12

Ultraviolet absorption spectra of 5,5-diphenyl-2-thiohydantoin in the following concentrations of aqueous sulphuric acid: a, 47.8; b, 63.0; c, 65.7; d, 67.0; e, 68.7; f, 70.3; g, 80.3%.

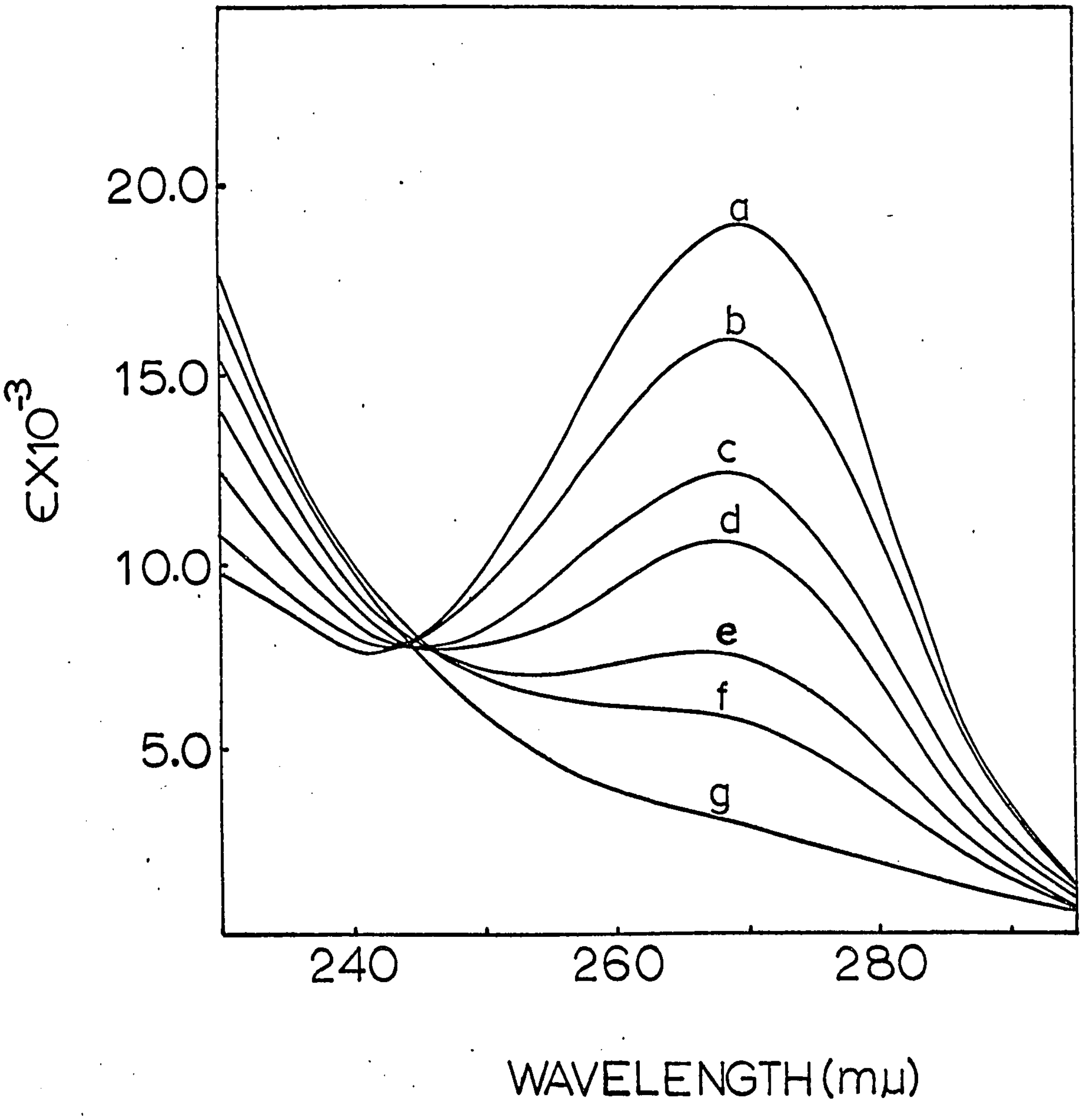
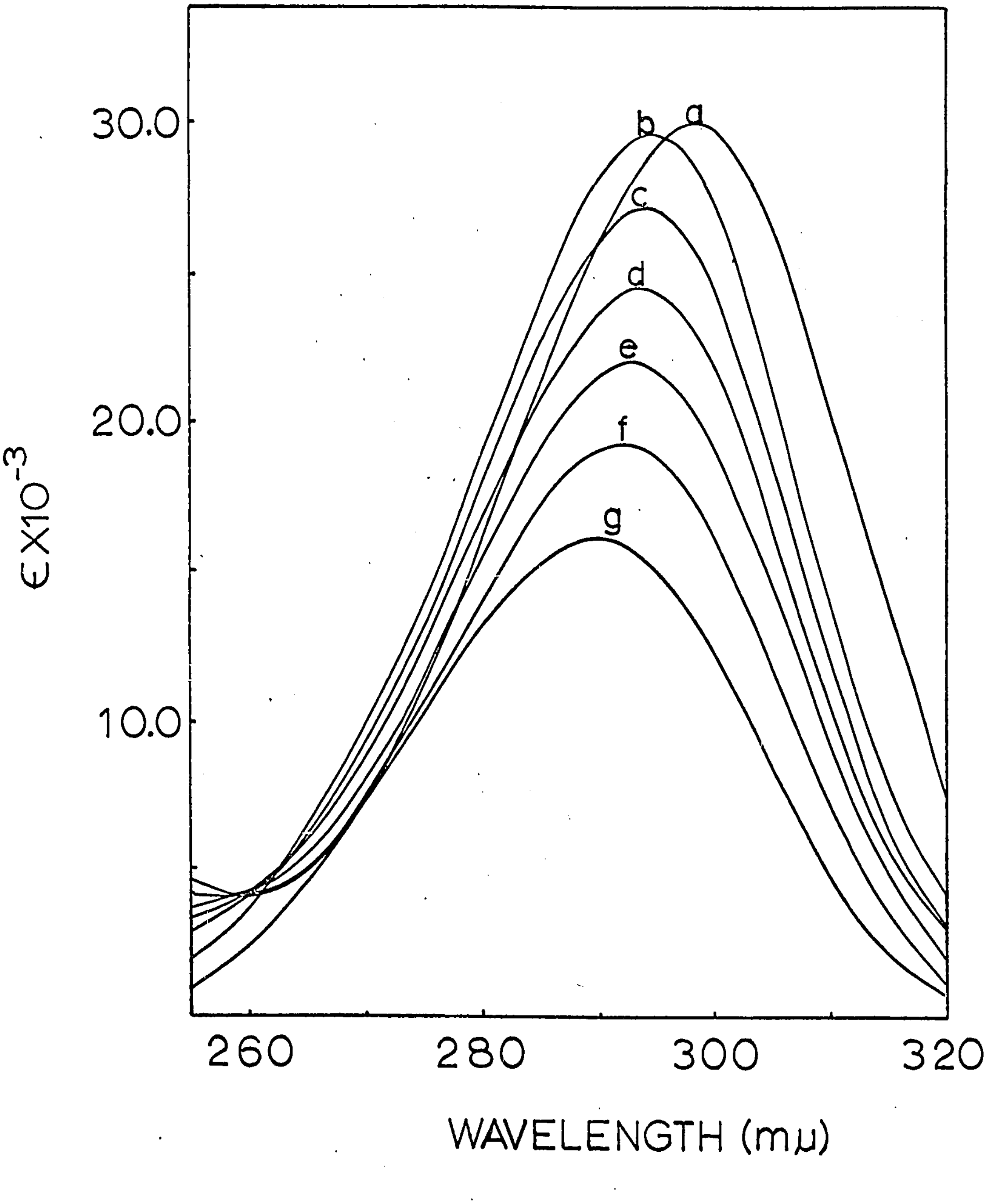

20.0
15.0
10.0
5.0
ЄX10^{-3}
240
260
280
WAVELENGTH (mµ)
a
b
c
d
e
f
g

Figure 13

Ultraviolet absorption spectra of 5,5-dimethyl-2,4-dithiohydantoin in the following concentrations of aqueous sulphuric acid: a, 0; b, 45.5; c, 57.7; d, 60.75; e, 62.9; f, 65.8; g, 80.5%.


30.0
20.0
10.0
ЄX10⁻³
a
b
c
d
e
f
g
260
280
300
320
WAVELENGTH (mμ)

Experimental

Materials: Compounds prepared according to existing methods are listed in Table VI.

Table VI

Compound	Mp. Obs.	Mp. Lit	Reference
2-thio-hydantoin	226-228	227	32
5,5-dimethyl-2-thio-	177-178	178-179	34
5,5-diphenyl-2-thio-	236-238	235	33
5-benzyl-2-thio-	185-185.5	184-184.5	36
5-benzal-2-thio-	254-256	258	32
5,5-dimethyl-2,4-dithio-	142	144	35
N-acetyl-2-thiourea	164.5-165.5	165	37

4,4-Diphenylimidazolid-2-thione (VI)

A suspension of 5,5-diphenyl-2-thiohydantoin (4 gm) and lithium aluminum hydride (1.2 gm) in anhydrous tetrahydrofuran (100 ml) was refluxed for an hour. The reaction mixture was cooled, the excess hydride was destroyed with water (approx. 50 ml), and the mixture was extracted with chloroform (3 x 50 ml). The chloroform layer was dryed over anhydrous sodium carbonabe and evaporated under reduced pressure. The white crystalline material was recrystallized from ethanol, yielding plates of 4,4-diphenylimidazolid-2-thione (2.0 g), m.p. 272-274°.

Anal. Calc. for $C_{15}H_{14}N_2S$: C, 70.86; H, 4.92; N, 11.02; S, 12.59%.
Found: C, 70.61; H, 5.56; N, 11.16; S, 12.61%.

Spectral measurements:

The procedure for the spectral measurements was essentially the same as described earlier (16). Stock solutions of approximately 10^{-3} - 10^{-4} molar concentrations were prepared in absolute ethanol, and 0.5 - 1.0 ml aliquots were diluted to 25 ml. Sulphuric acid of variable strength was prepared from Nichols C.P. reagent grade acid (95.5 - 96.5%). The concentration of acid was determined by titration with standard alkali using phenolphthalein as indicator. The spectral measurements for 2-thiohydantoin, 5,5-diphenyl-2-thiohydantoin, 5-benzal-2-thiohydantoin and N-acetylthiourea were obtained on a Beckman DU Spectrophotometer, and for 5,5-dimethyl-2-thiohydantoin on a Unicam SP 800 spectrophotometer. The cell compartment on these instruments was thermostated at 24.0 ± 0.5°. The spectra for 5,5-dimethyl-2,4-dithiohydantoin and 5-benzyl-2-thiohydantoin were obtained on a Bausch and Lomb Spectronic 505 spectrophotometer. The latter instrument did not have thermostating attachment, however the temperature in the cell compartment was intermittently checked and found constant 24.0 ± 1.0° during each run.

N-acetylthiourea showed hydrolysis during the spectral determinations and therefore measurements were taken at known time intervals and the optical density was extrapolated to zero time at the wavelength maximum.

The activity coefficients of 5,5-diphenyl-2-thiourea were determined according to the procedure of Boyd (14), using a Perkin-Elmer 350 Spectrophotometer.

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Summary and Claims to Original Research

Part I

The acylation products of 5,5-diphenylimidazolid-4-one (IV) were studied. Treatment with acetic anhydride gave 1,3-diacetyl-5,5-diphenylimidazolid-4-one (XL; R=Me) its alkaline hydrolysis product being 1-acetyl-5,5-diphenylimidazolid-4-one (XLI; R=Me). Biltz and coworkers previously assigned the bicyclo structures IX and X, respectively to these compounds. The revised structural assignment is supported by spectroscopic evidence, and by the lithium aluminum hydride reduction of the mono-acetyl derivative to 1-ethyl-5,5-diphenylimidazolid-4-one (XLII; R=Me). The reaction sequence: acylation, hydrolysis, and reduction was extended to the propyonyl and benzoyl derivatives and yielded 1-propyl- and 1-benzyl-5,5-diphenylimidazolid-4-one (XLII; R=Et, Ph). Similarly, the bicyclo structure X proposed by Biltz *et al* for the product of the formylation reaction was shown to be the N-formyl derivative (XLI; R=H), its reduction yielded 5,5-diphenyl-1-methylimidazolid-4-one (XLII; R=H).

Alkaline potassium permanganate oxidation of the mono-acetyl derivative according to the procedure of Biltz *et al* gave the tautomeric 4,4-diphenyl-2-methyl-4H-imidazol-5-one (XIII), the intermediates of the reaction were found as 1-acetyl-5,5-diphenyl-2-hydroxylimidazolid-4-one (LXVI), α-acetamino-α,α-diphenyl-N-formylacetamide (LXI), and α-amino-α,α-diphenylacetamide (LXII). The latter intermediates together with the 3-acetyl derivative of the hydroxy compound were isolated and their structure proved by spectroscopic methods and synthesis.

Part II

The oxidation procedure of Biltz et al was extended to the 1-propionyl and 1-benzoyl derivatives, and the tautomeric equilibrium of the resulting 2-alkyl-4,4/5,5-diphenyl-4H/5H-imidazol-5/4-ones (IIu/IIc; R=Et, Ph) was studied together with several related tautomeric imidazolones prepared by literature methods.

The diphenyl compounds were found to exist in the unconjugated form IIu in non-polar solvent and as a mixture of the unconjugated-conjugated forms, IIu-IIc, in polar solvents. The crystalline solid 2-ethyl and 2-phenyl compounds indicated the presence of both tautomeric forms, while the 2-methyl compound was found as the unconjugated tautomer only.

The basicities of several imidazolones were determined.

Part III

The protonation behaviour of several 2-thiohydantoins and 4,4-diphenylimidazolid-2-thione (VI), prepared from the lithium aluminum hydride reduction of 5,5-diphenyl-2-thiohydantoin, was studied in aqueous sulphuric acid. The ionization of several related thio bases was re-evaluated from the literature and a new acidity function $\underline{H}_{Th}$ is proposed, based on the thiohydantoins and thiourea derivatives. This acidity function shows close resemblance to the $\underline{H}_o'''$ function in the 20-70% acid concentration range, it deviates from $\underline{H}_o$ because of the different activity coefficient behaviour of the model compounds.