THESIS

entitled

STUDY OF HETEROCYCLIC COMPOUNDS

Submitted by
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NOTES

Besides the work carried out in this thesis, the candidate has attended postgraduate course for two years in organic chemistry including the following topics :-

1) Reaction mechanisms.
2) Electronic, Infrared, Raman and n.m.r. Spectroscopy of organic molecules.
3) Instrumentation and Instrumental analysis
4) Micro-Analysis of organic compounds.

He has successfully passed an examination of these topics.

Prof. F.G. Baddar
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SUMMARY

β-Aroylpropionic acids (CXII*a* - *c*) react with hydrazine hydrate to give the corresponding 6-aryl-2,3,4,5-tetrahydropyridazin-3-ones (CXIII*a* - *c*). Similarly β-aroylpropionic acids (CXII*d* and *e*) react with methyl or phenylhydrazine to give the corresponding 6-aryl-2,3,4,5-tetrahydro-2-methyl (CXII*d*)-, and 2-phenyl (CXIII*e*)-pyridazin-3-ones, respectively The structure of the 3-pyridazinones is established by a study of their ultraviolet and infrared spectra.

6-Aryl-2,3,4,5-tetrahydropyridazin-3-ones (CXIV*a* - *o*) condense with benzaldehyde, *o*-chlorobenzaldehyde and *p*-anisaldehyde to give the corresponding 4,6-diaryl-2,3-dihydropyridazin-3-ones (CXV*a* - *o*). The structure of these compounds is established by a study of their infrared, and ultraviolet spectra. Thus their infrared spectra have in common a broad band in the 3 μ region characteristic of the spectra of 3-pyridazones. It also shows the carbonyl stretching frequency in the range 1645 - 1680 cm^{-1} characteristic of the stretching frequency of the carbonyl group of cyclic amides. The ultraviolet spectra show that they absorb at a shorter wavelength than the corresponding

6-aryl-2,3,4,5-tetrahydropyridazin-3-ones (CXIV).

However, when 2,3,4,5-tetrahydro-2-phenyl-6-p-tolylpyridazin-3-one (CXVII) is allowed to condense with benzaldehyde in the presence of sodium ethoxide, the 4-benzylidene derivative (CXVIII) is obtained.

6-Aryl-2,3,4,5-tetrahydropyridazin-3-ones (CXIVa, d, g, j and m) condense with formaldehyde to give the corresponding 6-aryl-2,3-dihydro-4-methylpyridazin-3-ones (LVIIa, d, g, j, and m). The structure of these compounds is established by a study of their infrared and ultraviolet spectra and by comparison with authentic specimens prepared by the action of hydrazine hydrate on β-aroyl-α-methylacrylic acids.

6-Aryl-2,3,4,5-tetrahydropyridazin-3-ones (CXIVa, d, j, and m) and 6-aryl-4-arylidene-2,3-dihydropyridazin-3-ones (CXXa and b) and 6-aryl-2,3-dihydropyridazin-3-one (CXXc) react with formaldehyde and piperidine to give the corresponding N-piperidinomethyl derivatives (CXIXa, d, j, and m), and (CXXIa - c), respectively. The position of the piperidinomethyl group is established by infrared spectrum which shows the absence of the bands characteristic of the NH and OH groups in the 3 micron region.

6-Aryl-2,3,4,5-tetrahydropyridazin-3-ones (CXIV*d* and *g*) react with paraformaldehyde to give the corresponding N-hydromethyl-derivatives (CXXI*d* and *g*). The structure of these compounds is established by a study of their infra-red, and ultraviolet spectra.

Phenylmagnesium bromide reacts with 6-*p*-biphenylyl (CXIV*j*)-, and 6-aryl-2-piperidinomethyl (CXIX*a*, *d*, *j*, and *m*)-2,3,4,5-tetrahydropyridazin-3-ones to give the corresponding 6-*p*-biphenylyl (CXXV)-, and 6-aryl (CXXVII*a*, *d*, *j* and *m*)-3-phenylpyridazines.

On the other hand 6-*p*-biphenylyl-2,3,4,5-tetrahydro-2-methylpyridazin-3-one (CXXVI or CXIII*d*) react with phenylmagnesium bromide to give 6-*p*-biphenylyl-2,3,4,5-tetrahydropyridazin-3-one. The structure is established by comparison with authentic specimen.

6-*p*-Anisyl-2,3-dihydro-4-methylpyridazin-3-one (LVII*a*) reacts with phenylmagnesium bromide to give the corresponding 6-*p*-anisyl-2,3,4,5-tetrahydro-4-methyl-4-phenylpyridazin-3-one (CXXVII) by 1,4-addition to the -C=C-C=N- group. The structure of this compound is established by a study of its infrared spectra and also by its identity with the product of the interaction of methylmagnesium iodide with 6-anisyl-2,3-dihydro-4-phenylpyridazin-3-one (CXXIX).

INTRODUCTION

The present investigation deals with the action of aromatic aldehyde and formaldehyde on 6-aryl-2,3,4,5-tetrahydropyridazin-3-ones. The products obtained are 4,6-diaryl-2,3-dihydropyridazin-3-ones. It also deals with the action of phenylmagnesium bromide on some 3-pyridazinones and 3-pyridazones to give 3,6-diarylpyridazines and 3-pyridaz [illegible]

Accordingly the introduction will, therefore, cover the following sections in the following order:-

Section A : Synthesis of 6-Aryl-2,3,4,5-tetrahydropyridazin-3-ones.

Section B : Synthesis of 6-Aryl-2,3-dihydropyridazin-3-ones.

Section C : Synthesis of pyridazines.

Section D : Properties of 3-pyridazinones and 3-Pyridazones

CHAPTER I

INTRODUCTION

SECTION (A)

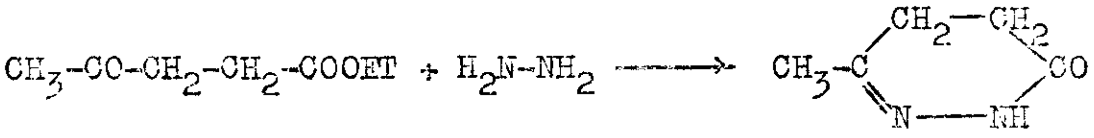
Synthesis of 2,3,4,5-Tetrahydropyridazin-3-ones (3-Pyridazinones)

3-Pyridazinones could be synthesised by any of the following methods :-

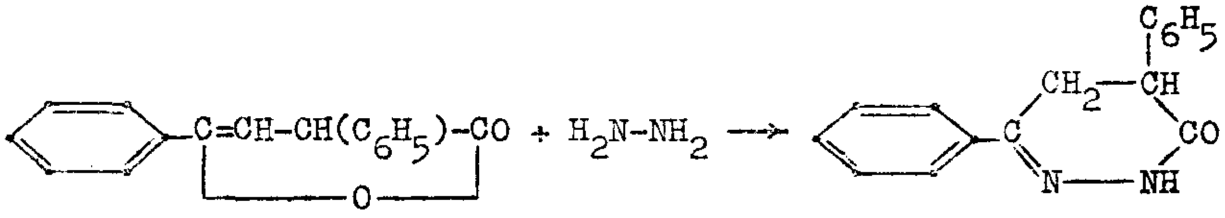
I) From γ-ketoacids, their esters and their lactones.

A- By reaction with hydrazine hydrate .

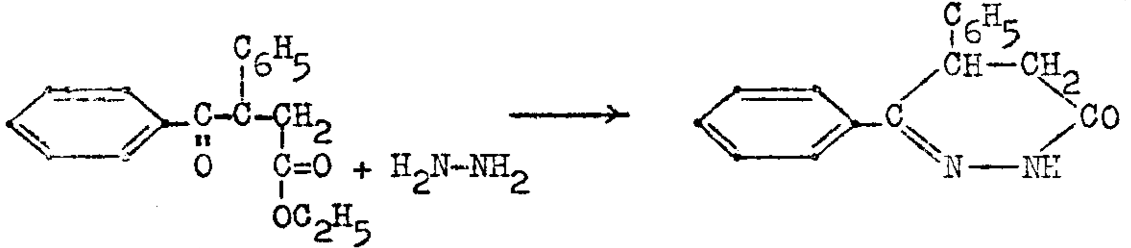
Ethyl laevulate (I), 2,4-diphenyl-4-hydroxy-but-3-enoic lactone (II), and β-benzoyl-β-phenylpropionic ester (III) were condensed with hydrazine hydrate to give 6-methyl (IV),[1] 4,6-diphenyl (V)[2] and 5,6-diphenyl (VI)[3,4] - 2,3,4,5-tetrahydropyridazin-3-ones, respectively.



(I) (IV)

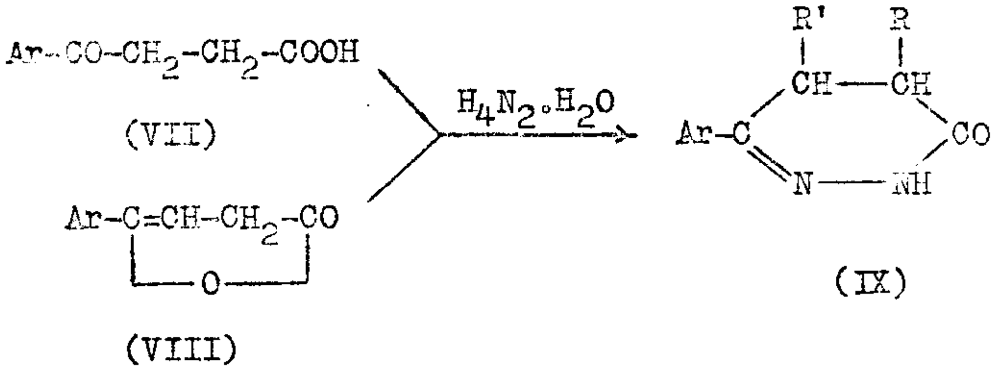


(II) (V)



(III) (VI)

The following 6-aryl-2,3,4,5-tetrahydropyridazin-3-ones (IXa-t) were obtained by the condensation of β-aroylpropionic acids (VII) or their corresponding lactones (VIII) with hydrazine hydrate.

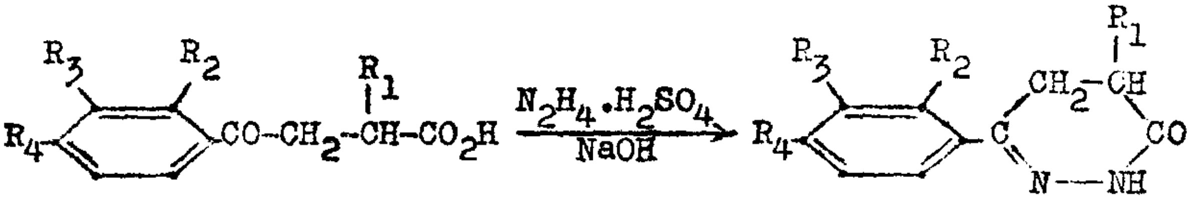


Ar	R	R'	Ref.
IXa; C_6H_5	H	H	4
b; $C_6H_4.CH_3$-p	H	H	
c; $C_6H_4.OCH_3$-p	H	H	
d; $C_6H_4.Cl$-p	H	H	5
e; 3,4,5-$(OCH_3)_3.C_6H_2$	H	H	6
f; 3,4-$(CH_3)_2.C_6H_3$	H	H	7
g; 2,4-$(CH_3)_2.C_6H_3$	H	H	
h; 2,5-$(CH_3)_2.C_6H_3$	H	H	
i; 2-Xanthenyl	H	H	8
j; 2-Fluorenyl	H	H	
k; 3-Chloro-4-methoxyphenyl	H	H	
ℓ; 5-Chlro-2-methoxyphenyl	H	H	
m; 5-Chloro-2-hydroxyphenyl	H	H	

	Ar	R	R'	Ref.
IXn:	2-$C_{10}H_{11}$	CH_3	H	
o:	2-$C_{10}H_{11}$	H	C_6H_5	
p:	2-$C_{10}H_{11}$	C_6H_5	H	
q:	$C_6H_4 \cdot CH_3$-p	H	C_6H_5	9
r:	$C_6H_4 \cdot CH_3$-p	C_6H_5	H	
s:	C_6H_4-CH_3-p	CH_3	H	
t:	2-$C_{10}H_{11}$	H	CH_3	

B- By reaction with hydrazine sulphate in sodium hydroxide solution.

The general scheme employed for the conversion of 4-substituted-4-oxo-butanoic acid (X), into 6-substituted-2,3,4,5-tetrahydropyridazin-3-ones (XIa-g) by the action of hydrazine sulphate in sodium hydroxide solution was essentially that of Curtius.[11] The following 3-pyridazinones were obtained by this procedure almost in quantitative yield.

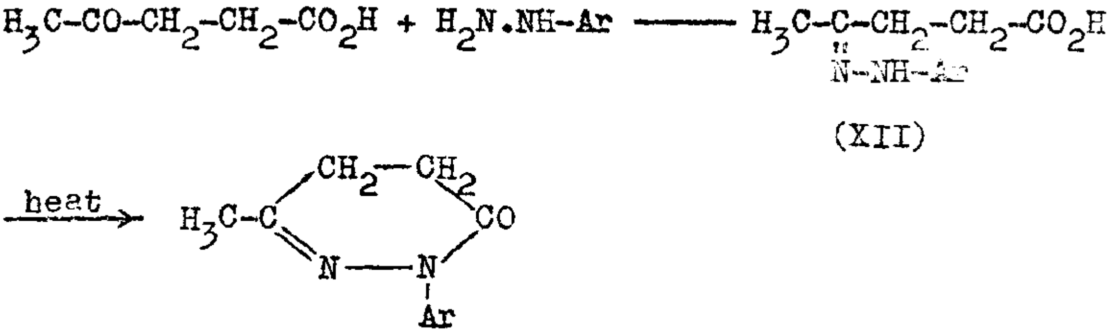


(X) (XI)

	Ref.
a; $R_1 = R_4 = H$, $R_2 = R_3 = Cl$	5
b; $R_1 = R_2 = H$, $R_3 = R_4 = Cl$	
c; $R_1 = R_2 = R_3 = H$, $R_4 = Cl$	
d; $R_1 = R_2 = R_3 = H$, $R_4 = Br$	
e; $R_1 = R_2 = R_3 = H$, $R_4 = I$	
f; $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$	10
g; $R_1 = R_2 = R_3 = R_4 = H$	11

C- By reaction with hydrazine derivatives in glacial acetic acid.

When a mixture of laevulinic acid and aromatically substituted hydrazines in glacial acetic acid was heated, the corresponding hydrazones (XIIa – i) were isolated, which were cyclised by heating for few hours to give the corresponding 3-pyridazinones (XIIIa – f). However, compounds (XIIg, h and i) were unstable and decomposed on standing.



$$H_3C-CO-CH_2-CH_2-CO_2H + H_2N.NH-Ar \longrightarrow \underset{\displaystyle N-NH-Ar}{H_3C-\overset{}{C}}-CH_2-CH_2-CO_2H$$

(XII)

(XIII)

		Ref.			Ref.
a;	$Ar=C_6H_5$	12,13	e;	$Ar=C_6H_4.OCH_3$-p	15
b;	$Ar=C_6H_4.NO_2$-p	12	f;	$Ar=C_6H_4.OC_2H_5$-p	
c;	$Ar=C_6H_4.CH_3$-m	14	g;	$Ar=C_6H_4.Cl$-o	16
d;	Ar=2-pyridyl		h;	Ar=2,4-dichlorophenyl	
			i;	$Ar=C_6H_4.CH_3$-p	17

2,3,4,5-Tetrahydro-6-ethyl-2-phenylpyridazin-3-one was obtained when β-propionylpropionic acid was heated with phenylhydrazine in the presence of triethanol amine followed by heating under reduced pressure.[18]