A THESIS
entitled

STUDIES ON SOME NITROGENOUS HETEROCYCLIC FIVE AND SIX MEMBERED ONES

Presented by

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(B. Sc., M. Sc.)

For the Degree of Ph. D.

UNIVERSITY COLLEGE
FOR WOMEN
AIN SHAMS UNIVERSITY
CAIRO

1974

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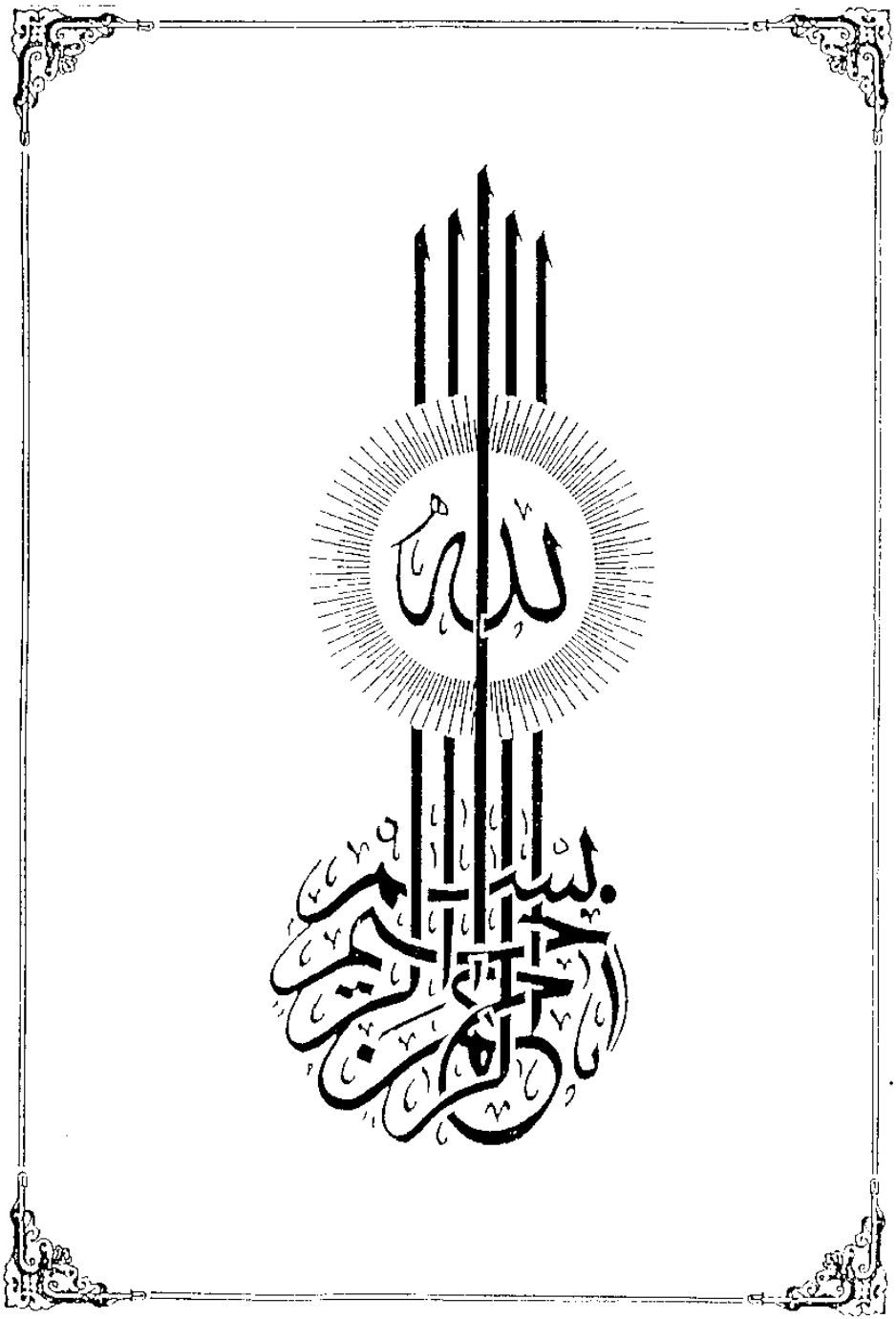

ACKNOWLEDGEMENT

The author wishes to express her appreciation to Professor Dr. S. Abdel Wahab for her kind help and the facilities at her disposal.

The author wishes also to express her thanks and deep gratitude to Professor Dr. W.I. Awad, D.Sc., professor of organic chemistry, University College for Women, and Dr. M.F. Ismail, lecturer of organic chemistry, Chemistry Department, Faculty of Science, Ain Shams University, not only for suggesting the subjects investigated but also for their continuous advice and valuable criticism.

C O N T E N T S

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p-Tolylmagnesium bromide on the other hand did not react with N,N'-bisuccinimide (1 mole) at room temperature. However, when the reaction was carried out under reflux, it yielded bis-(β-p-toluoylpropionyl)hydrazine (CIV).

Benzylmagnesium chloride (4 moles) reacts with N,N'-bisuccinimide (1 mole) at room temperature to give bis-(3,3-dibenzyl-3-hydroxypropionyl)hydrazine (CIII).

c) Action of aryl- or alkylmagnesium halides on N,N'-biphthalimide (CV).

The reaction of N,N'-biphthalimide (CV) with phenyl-, p-tolyl-, and benzylmagnesium halides at room temperature proceeded in most cases through the ring cleavage on the biimide ring to form 3,3-disubstituted phthalides (CVIIa-d). In these cases it was possible to identify hydrazine in the reaction mixture. However, in the case of ethyl-magnesium iodide it was possible to isolate in addition to the 3,3-diethylphthalide (CVIId), 1-ethylphthalan-4-one (CVIIIe).

d) Action of arylmagnesium halides on asymmetric biimides (CIX) and (CX).

N-Phthalimidomaleimide (CIX) and N-phthalimido-succinimide (CX) are prepared by the direct interaction between N-aminophthalimide and maleic or succinic anhydrides, respectively.

Part III

1,3-Dipolar Addition to N,N'-Bimaleimide and N-Phthalimidomaleimide.

Hydrazoic acid reacts with N,N'-bimaleimide (XCIV) or biisomaleimide (XCVI) to give N,N'-bi-α-azidosuccinimide (CXVI). N-phthalimidomaleimide (CIX) undergoes similar reaction with hydrazoic acid to give (CXVII). The reaction involved the addition of the hydrazoic acid to the activated double bond in each case.

Diazomethane reacts with N,N'-bimaleimide or biisomaleimide to give the Δ^1-pyrazoline derivative (CXVIII). Diphenyldiazomethane, on the other hand reacts with the same biimides to give a compound which loses nitrogen spontaneously giving the corresponding cyclopropane derivative (CXIX).

N-Phthalimidomaleimide (CIX) reacts with diazoethane to give Δ^2-pyrazoline derivatives (CXX).

Diphenyldiazomethane or diazofluorene reacts with the above biimide (CIX) to give the cyclopropane derivatives (CXXI) and (CXXII), respectively.

The structures of the above compounds are inferred from analytical data and a study of their infrared, and electronic spectra.

LIST OF NEW COMPOUNDS

1) Bis-(β-benzoyl-α-phenylpropionyl) hydrazine (XCVa).
2) Bis-(β-p-toluoyl-α-tolylpropionyl) hydrazine (XCVb).
3) Bis-(β-p-methoxybenzoyl-α-methoxyphenylpropionyl) hydrazine (XCVc).
4) Bis-(3-benzoyl-1-hydroxy-1-phenylpropionyl) hydrazine (CI).
5) Bis-(β-p-toluoylpropionyl)hydrazine (CIV).
6) Bis-(3,3-dibenzyl-3-hydroxypropionyl)hydrazine (CIII).
7) N-Phthalimidomaleimide (CIX).
8) N-Phthalimidosuccinimide (CX).
9) N-Cyclohexylidene aminophthalimide (CXIe).
10) N-Diphenylmethylamino-(3-hydroxy-3-phenyl)-phthalimidine (CXIIa)
11) N-(1-p-Methoxyphenyl-1-phenyl)-amino-(3-hydroxy-3-phenyl)phthalimidine (CXIIb).
12) Desoxybenzoin-p-carboxylic-1,2-diphenyl-1-ethyl hydrazide (CXIIIc).
13) Desoxybenzoin-p-carboxylic-1-p-methoxyphenyl-2-phenyl-1-ethylhydrazide (CXIIId).

14) Desoxybenzoin-Q-carboxylic-1-cinnamyl-2-phenyl-ethyl hydrazide (CXIIIe).

15) N-(acetyl)-1,2-diphenylethylamino-3-benzalphthalimide (CXIV).

16) N,N'-Bi-α-azidosuccinimide (CXVI).

17) N-Phthalimido-α-azidosuccinimide (CXVII).

18) N,N'-Bi-Δ^1-pyrazoline-4,5-dicarboximide (CXVIII).

19) N-Phthalimido-Δ^2-pyrazoline-4,5-dicarboximide (CXX).

20) N,N'-Bi-1,1-diphenylcyclopropane-2,3-dicarboximide (CXIX).

21) N-Phthalimido-1,1-diphenylcyclopropane-2,3-dicarboximide (CXXI).

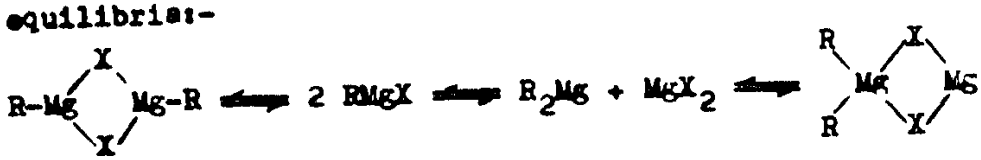
22) N-Phthalimido-1-fluorenylcyclopropane-2,3-di-carboximide (CXXII).

COMPOSITION OF GRIGNARD REAGENT

The composition of Grignard compounds has been the subject of much study and controversy[1,2]. Although many suggestions have been made concerning the composition of Grignard compounds, only two of these received much attention. The first suggestion made by Grignard[3,4] and later supported by Meisenheimer[5], was that the Grignard compounds are best represented by the formula RMgX. The second suggestion was made by Jolibois[6] and involved the representation of Grignard compounds by the formula $R_2Mg.MgX_2$. The first convincing evidence permitting a clear-cut choice between these formulations was presented in 1957 by Dessy and co-workers[7]. They found no exchange between $^{28}MgBr_2$ and $(C_2H_5)_2Mg$ and presented evidence that an equimolecular mixture of $MgBr_2$ and $(C_2H_5)_2Mg$ has the same characteristics as the Grignard reagent prepared from C_2H_5Br and Mg. Thus, it was concluded that alkyl exchange does not take place in diethyl ether and that the RMgX species does not exist in solution and therefore Grignard compounds are best represented by the structure first suggested by Jolibois, namely, $R_2Mg.MgX_2$.

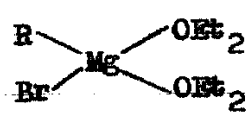
Since the work of Dessy, the representation $R_2Mg.MgX_2$ for Grignard compounds has been widely accepted. Thus,

in tetrahydrofuran and that the composition of Grignard compounds in diethyl ether is best described by the equilibria:-



with the position of equilibria being a function of the nature of R group, the halogen as well as the concentration. Their conclusions were based on molecular association data and reinterpretation of existing data in the literature reported by other authors.

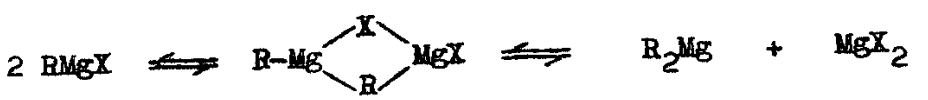
Some other recent reports have contributed importantly to eliminating the confusion in this area. First, Dessy and his co-workers[13] have reported the exchange experiments they initially reported in 1957. In their most recent publication they found exchange with certain, but not all, grades of ^{28}magnesium. Soon thereafter, Cowan, Hsu and Reborts[14] reported similar results using ^{25}magnesium. Moreover, Rundle and his co-workers[15,16] reported the structure (I) for phenyl and ethylmagnesium bromides in the solid state based on X-ray studies.



(I)

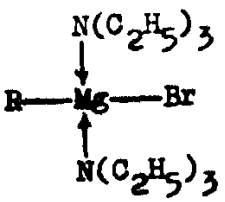
Although whether a single solid state structure can be equated for a species in solution is questionable, this work did add to the evidence supporting the existence of RMgX species in diethyl ether in Grignard compounds.

The first direct observation of RMgX species in diethyl ether other than as an intermediate was provided recently[18]. The same report also claimed that RMgX is the initial species formed when an alkyl halide and magnesium react. It was argued that the difference between the composition of Grignard compounds in tetrahydrofuran and diethyl ether is explained by the difference in basicity of the two solvents. Ebullioscopic measurements show a monomer-dimer equilibrium in diethyl ether, but only monomer, present in tetrahydrofuran. Thus, tetrahydrofuran co-ordinates with magnesium more strongly than diethyl ether, and a stable halogenbridge compound is not formed. The exchange of alkyl groups in either tetrahydrofuran or diethyl ether can be explained by an intermediate mixed alkyl-halogen bridge structure of the type suggested earlier[12].



Grignard compounds co-ordinated to a more basic solvent than diethyl ether or tetrahydrofuran might not form such intermediates if the magnesium orbitals were

strongly bonded to the basic solvent. The disproportionation might be prevented and the initial species formed by the reaction of RX and Mg could be isolated. In order to test this hypothesis, the above author[17] prepared ethylmagnesium bromide from ethyl bromide and magnesium in triethylamine. The reaction product (II) was fractionally crystallised into seven fractions. Each fraction had a Mg:Br:N ratio of



(II)

1.0:1.0:1.0 within experimental error. (Although C_2H_5MgBr crystallises from triethylamine as the bisolvent, the monosolvate was isolated on drying under high vacuum). Molecular association measurements of the crystallised fractions in triethylamine at 35° showed the presence of monomeric species over a wide concentration range. Because of the highly insoluble nature of $MgBr_2$ in triethylamine and the soluble nature of $(C_2H_5)_2Mg$, precipitation of $MgBr_2$ from solution would have occurred if an unassociated mixture of these products was present. These data proved to him that the reaction product is a single species and not a mixture. He also found that the product $C_2H_5MgBrN(C_2H_5)_3$

did not disproportionate in boiling triethylamine during 24 hours, nor was it formed by redistribution of $(C_2H_5)_2Mg$ and $MgBr_2$ in triethylamine. Thus, it was concluded that C_2H_5MgBr is the initial product formed by the reaction of C_2H_5Br and magnesium, and in triethylamine solution the composition can be represented by this single structure.

In a similar way, the existence of RMgX in diethyl ether was established. When a diethyl ether solution of ethylmagnesium bromide, prepared from C_2H_5Br and Mg in diethyl ether, was added slowly to a large, rapidly stirred volume of triethylamine, $C_2H_5MgBr.N(C_2H_5)_3$ was isolated in over 90% yield by fractional crystallisation. The fact that no $MgBr_2.N(C_2H_5)_3$ was isolated although it is the most insoluble of the possible products, led to the conclusion that the rate of the solvation is greater than the rate of equilibration and therefore in diethyl ether solution ethylmagnesium bromide consists mainly, if not entirely, of RMgX species (as a monomer or dimer).

Moreover, Smith and Becker[18] from thermochemical studies indicated that in diethyl ether solution the equilibrium lies predominantly to the right.

$$R_2Mg + MgX_2 \rightleftharpoons 2\ RMgX\ .$$

Similar thermochemical experiments were conducted by Smith and Becker[19,20] in tetrahydrofuran. They found that the above equilibrium is not nearly as far to the right as in diethyl ether. The results are in agreement with earlier work carried out by Salinger and Mosher[21].

Kharasch[22] summarised the determinations made by some authors to the percentages of RMgX, R_2Mg and MgX_2 for some Grignard reagents in the following table.

RX	RMgX %	R_2Mg %	MgX_2 %
CH_3I	87.0	6.5	6.5
C_2H_5I	43.0	28.5	28.5
C_2H_5Br	41.0	29.5	29.5
C_2H_5Cl	15.0	42.5	42.5
$n\text{-}C_3H_7I$	24.0	38.0	38.0
$n\text{-}C_3H_7Br$	24.0	38.0	38.0
$n\text{-}C_3H_7Cl$	17.0	41.5	41.5
C_6H_5I	38.0	31.0	31.0
C_6H_5Br	30.0	35.0	35.0
$2,4\text{-}(CH_3)_2\text{-}C_6H_3Br$	44.0	28.0	28.0
$2,4\text{-}(CH_3)_2C_6H_3I$	55.0	22.5	22.5
$2,4,6\text{-}(CH_3)_3\text{-}C_6H_2Br$	64.0	18.0	18.0