STUDIES ON SOME ARYL ISOINDOLES

THESIS

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STUDIES ON SOME ARYL ISOINDOLES

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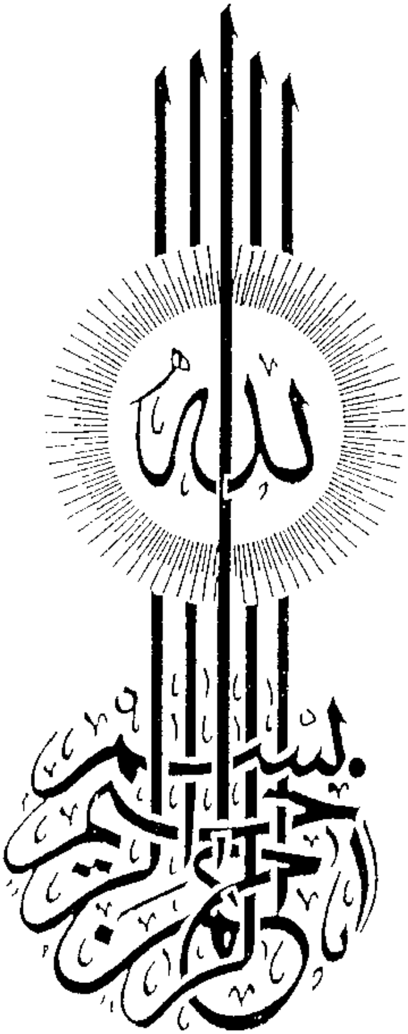
بسم الله الرحمن الرحيم

NOTE

Beside 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 Mechanism.

2 - Electronic, Infrared, Raman, Mass and N.M.R. spectroscopy of organic molecules.

3 - Organic Reactions.

4 - Natural Products

5 - Polymers.

The applicant Abo-El Fetouh El-Sayed Murad has passed successfully all the above mentioned courses in the academic year 1972-1973

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ACKNOWLEDGEMENT

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VITAE

Abo El-Fetouh El-Sayed Murad was born in February 7, 1947 in Ezbet El Gondy, Faraskour, Demiatta, Egypt. He attended Faraskour Secondary School from 1963 till 1966 and got the Secondary School Certificate in 1966. He was then enrolled in the Faculty of Science; Ain Shams University, Cairo, Egypt, where he majored in chemistry and received the degree of Bachelor of Science with first class honours in 1970.

In 1970, he was appointed as a demonstrator in the Chemistry Department, Faculty of Science; Ain Shams University, and was registered for the degree of M.Sc. in organic chemistry in 1971 under the supervision of Dr. G.E.M. Moussa; Professor of Organic Chemistry and co-supervision of Dr. M.N. Basyouni; Assistant Professor of Organic Chemistry.

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SYNOPSIS

The hitherto unknown 2-phthalimidomethyl benzophenones (CXXXIX a-l) (Fig. I) were prepared, by the Friedel-Craft's ketone synthesis, from the acid chloride (XLV) and eight alkyl benzenes, one alkoxy benzene and three disubstituted (alkoxy alkyl and alkoxy bromo) benzenes, in presence of anhydrous aluminium chloride. The acid chloride, namely α-phthalimido-o-toluyl chloride (XLV), was prepared from α-phthalimido-o-toluic acid (XLVI, R=OH), obtained by opening the ring of phthalide with N-potassium phthalimide, by reaction with thionyl chloride.

The structures of the 2-phthalimidomethyl benzophenones (CXXXIX a-l) were established by analytical data, infra-red and ultraviolet spectroscopy (cf. Table VII, Fig. I). Treatment of the 2-phthalimido-methyl benzophenones (CXXXIX a-l) with hydrazine hydrate (4 moles) in refluxing ethanol gave the corresponding 1-aryl isoindoles (CXLII a-l) (Fig. X). The same products were also obtained by using only two moles of hydrazine hydrate. The action of other nucleophilic reagents such as phenyl hydrazine also was investigated.

The structures of the 1-aryl isoindoles (CXLII a-l) were established largely from their electronic and infra red spectra (Table VIII, Fig.X), and further confirmed by formation of a blue (or green) solution with p-dimethylamino-benzaldehyde in an acid solution (Ehrlich test); a test which is characteristic of the isoindole ring. However, a correct elemental analysis was obtained in the case of 1-p-methyl phenyl isoindole (CXLII a); the other 1-aryl-isoindoles have analogous electronic spectra to that of (CXLII a). The electronic spectra of the 1-aryl isoindoles may indicate that they are an equilibrium mixture of isoindoles-isoindolenines with the latter predominating.

An attempt was made for the synthesis of α-benzyl-α-phthalimido-o-toluic acid(CXLIa)from benzyl phthalide and N-potassium phthalimide. However a neutral product was obtained and proved to be α-benzyl-α-phthalimido-toluene.

Ethyl α-phthalimido-o-toluate (CXLIII), obtainable from the acid chloride (XLV) and absolute alcohol, was treated with benzyl amine to give phthalimidine which was identical with an authentic specimen. Hydrazine hydrate failed to effect the same conversion.

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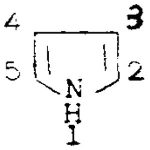
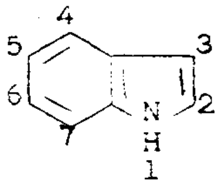
INTRODUCTION

CHEMISTRY OF ISOINDOLES,
DIHYDROISOINDOLES AND PHTHALIMIDINES

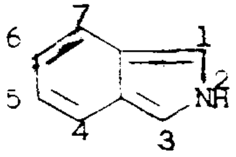
ISOINDOLES

Fusion of a benzene ring on to a pyrrole ring can occur in two ways to give two isomeric heterocyclic rings. Thus fusion with the 2,3-(or 4,5-) carbon atoms of pyrrole produces the heterocyclic ring indole (I), while fusion with the 3,4-carbon atoms gives its isomeric compound isoindole(II). Although indole was first prepared in 1866 (1), isoindole was not prepared until 1966 (2) when its presence in solution was inferred from the formation of Diels - Alder adducts with maleic anhydride and N-phenyl maleimide. This may indicate that isoindole (II) is too unstable to be isolated.





(I)



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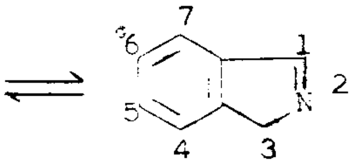
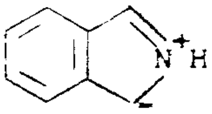


(III)

By analogy to indole there is no evidence which suggests that isoindole (II) tautomerises to a detectable extent to isoindolenine (III) or 1-H isoindole and according to a molecular orbital calculation of Veber and Lwowski (3), isoindole should be favoured over its tautomer isoindolenine by about 8 K.cal/mole.

Many resonance structures can be written for isoindole but of the uncharged structures, (II) would contribute largely to the resonance of the isoindole molecule, Of the ionic structures possible (IV, V, VI, VII, VIII and IX) only those with a negative charge in the nitrogen containing ring would account for a major part of the remainder. The contributions of the less stable quinonoid forms (VIII) and (IX) would in all probability be negligible owing to charge separation (4).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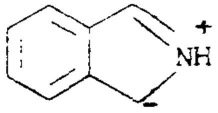
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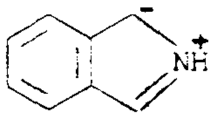
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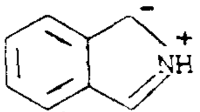
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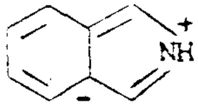
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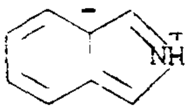
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Since 1893 there have been many reports of unsuccessful synthesis of isoindole and its derivatives (5), (6), and (7). It was not until 1951 that an isoindole substituted at the 2-position (N-atom) was prepared (8). The methods for the synthesis of N-unsubstituted and N-substituted isoindoles will now be outlined.

METHODS FOR THE SYNTHESIS OF ISOINDOLES

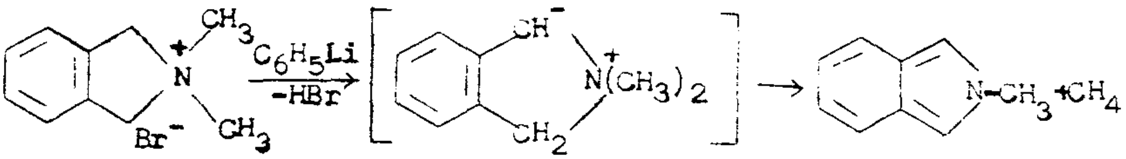
I.- Synthesis from Isoindolines:

Isoindolines comprise a group of well-characterized and easily synthesized substances (4), and being at the next stable reduction state below that of isoindoles, they constitute stable precursors for synthesis of the latter. In principle, either oxidation or elimination from isoindolines should lead to isoindoles, however, in view of the succeptibility of isoindoles to further oxidation, elimination has been preferred, and in all cases reported the leaving group has been placed on nitrogen rather than carbon (9).

1 - Isoindolinium Salts:

This method has only been used for the synthesis of N-substituted isoindoles. Actually, the first clearly authenticated preparation of an isoindole was reported by Wittig *et*. *al*. (8) in 1951 from isoindolinium halides. Thus it was found that elimination from isoindolinium bromides and iodides with bases such as aryl and alkyl lithium afforded 2-substituted isoindoles in variable yields. For instance, 2,2-dimethylisoindolinium bromide (X) on treatment with one equivalent of phenyl lithium in ether under nitrogen, evolved methane and gave 2-methylisoindole (XI) in 74% yield. With methyl lithium as base, a slightly lower yield was obtained. The reaction is considered as proceeding over an intermediate **ylid** in the formation of which a proton is withdrawn from carbon atom at position 1, and subsequent loss of methane (4).

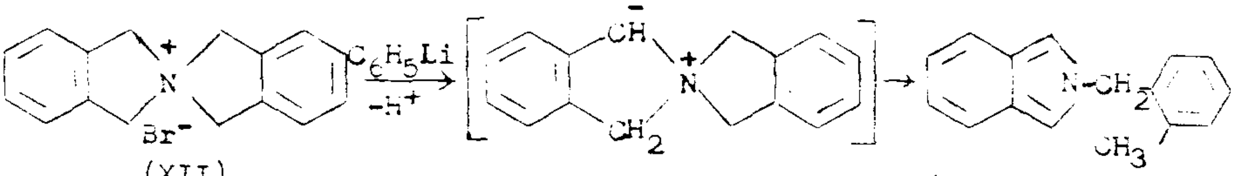
Di-o-xylyleneammonium bromide (XII) gave only an 8% yield of 2-o-xylylisoindole (XIII) with phenyllithium, although the yield was improved slightly when aqueous silver oxide was used



(X)

(XI)

and the resulting hydroxide pyrolyzed at 170°. Again an **ylid** is the postulated intermediate (4).



(XII)

(XIII)

In the case of elimination from (XIV) isoindole formation was found to compete with 1,2-migration of the benzyl group (Stevens rearrangement) (10), which gave 1-benzyl-2-methylisoindoline (XV), and also with migration accompanied by attack at the ortho position of the phenyl ring (Sommelet rearrange-