THERMAL AND PHOTOCHEMICAL REACTIONS

OF DIHYDRODIAZINES

Promotor : dr.H.C.van der Plas, hoogleraar in de organische scheikunde

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THERMAL AND PHOTOCHEMICAL REACTIONS OF DIHYDRODIAZINES

proefschrift

ter verkrijging van de graad
van doctor in de landbouwwetenschappen
op gezag van de rector magnificus,
dr.H.C.van der Plas,
hoogleraar in de organische scheikunde,
in het openbaar te verdedigen
op woensdag 9 mei 1979
des namiddags te vier uur in de aula
van de Landbouwhogeschool te Wageningen.

NN08201,758

STELLINGEN

1. Om de adducten van nucleofielen met (hetero)aromaten "complexen" te noemen, is niet in overeenstemming met de daarvoor geldende regels.

   R.F.Francis, C.D.Crews and B.S.Scott, J.Org.Chem., 43, 3227 (1978).
   J.P.Geerts and H.C.van der Plas, J.Org.Chem., 43, 2682 (1978).
   G.Briegleb, "Electronen-Donator-Acceptor-Komplexe", Springer-Verlag (1961).
   F.A.Cotton and G.Wilkinson, "Advanced inorganic chemistry", Interscience 3rd ed. (1972).

2. Uit de n.m.r. spectra van de produkten, verkregen door reactie van organolithium reagentia met 5,6-digesubstitueerde (geannelleerde) pyrimidinen gevolgd door reactie met ethyl chloorformiaat of zoutzuur, valt niet te concluderen dat in bovengenoemde reactie 1,4-dihydropyrimidinen worden gevormd.

   G.B.Bennett, J.Heterocyclic Chem., 15, 671 (1978).

3. De opsplitsing van het signaal van H(5) in het n.m.r. spectrum van 4-(4-methoxyfenyl)-1,4-dihydropyrimidine met een koppelconstante van 1,2 Hz wordt niet veroorzaakt door een 1,5-koppeling maar door een 2,5-koppeling.

   W.P.K.Girke, Chem.Ber., 112, 1 (1979).
   Dit proefschrift.

4. Bij de verklaring over de omzetting van 5-carbomethoxy-2,4,7-trichloorpyrido [2,3-*d*]pyrimidine in 4-amino-5-carboxamido-2,7-dichloorpyrido [2,3-*d*]pyrimidine wordt ten onrechte het S_N(ANRORC) mechanisme buiten beschouwing gelaten.

   G.L.Anderson, J.L.Shim and A.D.Broom, J.Org.Chem., 42, 993 (1977).
   H.C.van der Plas, Acc.Chem.Res., 11, 462 (1978).

5. De vorming van 1,6-diaza-3-methoxy-2-methyl-4-oxospiro[4,5]dec-2-een door bestraling van 6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-on in methanol kan verklaard worden door een di-π-methaanomlegging gevolgd door alcoholyse.

T.Yamazaki, M.Nagata, S.Hirokami and S.Miyakoshi, Heterocycles 8, 377 (1977).

6. De methode die Hale en Perham toepassen om te bepalen hoeveel lipoinezuur eenheden lipoaat acetyltransferase in het pyruvaat dehydrogenase multienzym complex van *Escherichia coli* bevat is specifiek noch kwantitatief voor lipoinezuur.

   G.Hale and R.N.Perham, Biochem.J., 177, 129 (1979).

7. Horeca exploitanten houden te weinig rekening met de toegenomen voorkeur van de Nederlandse konsument voor bruin- en volkorenbrood boven witbrood.

8. Gezien het veelvuldig optreden van lichamelijke gebreken als gevolg van sportbeoefening, dient de uitspraak "sport is gezond" met een zekere terughoudendheid te worden gebezigd.

9. Het valt te betreuren dat rijwielen die gemaakt zijn om er het snelst mee te rijden, worden uitgerust met het minst betrouwbare remsysteem.

R.E.van der Stoel — Wageningen, 9 mei 1979

Thermal and photochemical reactions of dihydrodiazines

Aan mijn ouders,
aan Anke en Mariëlle

VOORWOORD

Op deze plaats wil ik allen bedanken, die hebben bijgedragen aan de voltooiing van dit proefschrift. In de eerste plaats wil ik Prof.Dr.H.C.van der Plas danken voor zijn enthousiaste begeleiding en voor de vrijheid die hij mij gelaten heeft bij het onderzoek. Veel dank ben ik hem ook verschuldigd voor de snelle en kritische beoordeling van het manuscript.
Verder dank ik Cees Landheer, Willem Combé en Maarten Posthumus voor de massaspectroscopische gegevens, Beb van Veldhuizen voor de opname en interpretatie van vele n.m.r. spectra en Pim Melger voor adviezen op chromatografisch gebied.
Voorts ben ik dank verschuldigd aan een aantal mensen zonder wie de uitvoering van dit onderzoek onmogelijk geweest zou zijn, te weten Gerrit Lelyveld, Eef Vleeming, Wim Nieuwboer, Willem van Barneveld en wijlen Job Jansen.
In het bijzonder wil ik Hugo Jongejan en Bert Hoeve bedanken voor hun bijdrage aan het onderzoek, beschreven in hoofdstuk 3 en de eerstgenoemde tevens voor alle microanalyses. Ook Bart Geurtsen en André Stork voor de plezierige samenwerking. Discussies met Dick de Bie werkten zeer verhelderend. Het illustratieve gedeelte komt op naam van Sander Schuchhard, terwijl Mies Snell zo vriendelijk was in record tijd het proefschrift te typen. Bert van Amersfoort heeft het typewerk voor de publicaties verricht. Tenslotte wil ik alle niet genoemde leden van de vakgroep Organische Chemie bedanken voor de bijzonder prettige samenwerking.

CONTENTS

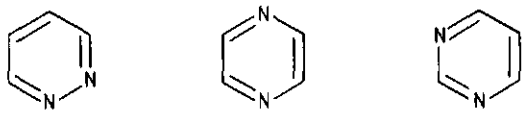
Chapter 2 has been published in the literature : Rec.Trav.Chim., 97, 116 (1978).

Chapters 4 and 5 have been accepted for publication by the Journal of the Chemical Society, Perkin Transactions I.

1 INTRODUCTION

1.1 GENERAL

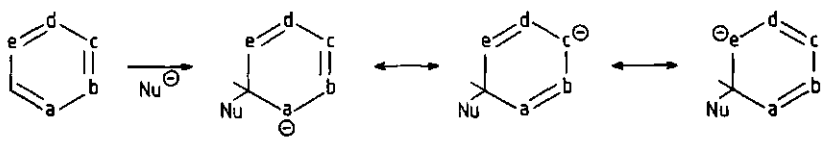
Due to their great biochemical importance, heteroaromatic compounds containing one or more nitrogen atoms have been studied for many years at the Laboratory of Organic Chemistry of the Agricultural University in Wageningen[1]. The behaviour of derivatives of pyridazine (1), pyrazine (2) and especially pyrimidine (3) towards nucleophiles has attracted much attention during the past decade[2].



1 2 3

Scheme 1.1

The reactions of these substrates with nucleophiles have in common that they proceed *via* an initial addition of the nucleophile at the carbon centre of the highly polarized azomethine bond[3]. During the formation of this σ-adduct the aromatic character is lost; the carbon atom that is attacked undergoes a change in hybridization ($sp^2 \rightarrow sp^3$) and the excess of negative charge is delocalized over the remaining atoms of the ring, the larger part being located at the electronegative nitrogen(s). This is depicted below with valence bond structures 4a-c for the adduct.



1-3 4a 4b 4c

Scheme 1.2

Table 1.1

-N-	-CH-	diazine	pos.of attack
a,b	c,d,e	pyridazine	3
a,c	b,d,e	pyrimidine	4
a,d	b,c,e	pyrazine	2
a,e	b,c,d	pyrimidine	2
b,c	a,d,e	pyridazine	4

Of the structures 4a-c the *para* quinoid structure 4b is lowest in energy[4], especially in the structures in which atom c is nitrogen. It explains why pyrimidine is attacked by preference at the carbon atom of the N(3)-C(4) azomethine bond and why it is possible that pyridazine can be attacked at carbon atom 4, although not forming part of an azomethine bond (in both adducts atom c represents nitrogen).

1.2 PURPOSE AND SCOPE OF THE INVESTIGATION

Adduct formation is accompanied by loss of the aromatic character; the adducts formed from the diazines with nucleophiles contain the structural features of imines, enamines, amidines and cyclohexadienes. The adducts may show azadienamine and diazacyclohexadiene reactivity and this induced us to study the reactivity of these adducts on this behaviour. For our purpose we chose as substrates the adducts obtained from the diazines with some carbon nucleophiles (organolithium compounds) as well as the corresponding conjugate acids *i.e.* the dihydrodiazines. We subjected both substrates to electrophilic reactions - typical for enamines[5] - and moreover the dihydropyrimidines to ultraviolet irradiation, known to cause isomerization reactions[6] with cyclohexadienes. In the following paragraph a literature survey is presented of the formation and reactivity of organolithium-(di)azine adducts and dihydro(di)azines. Since in our photochemical experiments the dihydropyrimidines were found to give di-π-methane rearrangements, important literature data on this subject will also be discussed (paragraph 1.3.3).

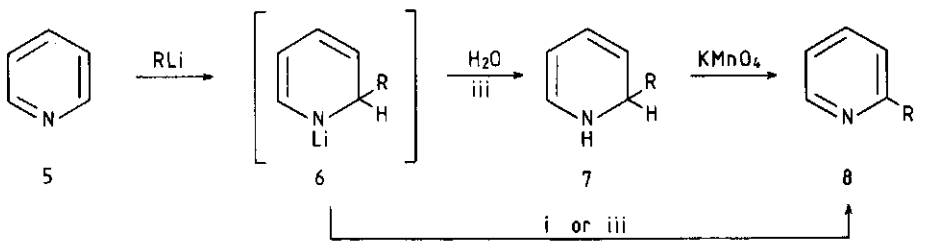
1.3 LITERATURE SURVEY

1.3.1 Reactions of organolithium-(di)azine adducts and dihydro(di)azines with electrophilic reagents

Most research on this subject has been dedicated to pyridine and its derivatives. Since there is structural similarity between pyridine and the diazines a survey of the reactions involving pyridine is presented first.

1.3.1.1 Pyridine

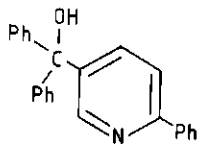
The reaction of organolithium compounds with pyridine (5) was investigated for the first time in 1930 with the aim of developing a method for introduction of substituents into the pyridine nucleus in 2(6)-position[7,8].



Scheme 1.3

Conversion of 5 into 2-R-pyridine (8) proceeded *via* the postulated intermediate 1-lithio-2-R-1,2-dihydropyridine (6). Compound 8 was obtained by heating the reaction mixture of 5 with RLi in toluene (method i). In 1960 the addition of phenyllithium to substituted pyridines was taken up in order to investigate the effect of substituents on regioselectivity[9]. Alternative methods for obtaining the phenylated pyridines from the adduct solutions were developed *i.e.* direct oxidation with (air)oxygen (method ii) and hydrolysis followed by oxidation of the reaction mixture with potassium permanganate (method iii)[10]. Among other facts it was found that bulky substituents in 3-position (*t*-Bu, Ph) of the pyridine ring induced phenyllithium to attack the 6-position[9,11].
In 1968 the ^{1}H-n.m.r. spectrum of the reaction mixture obtained by treating pyridine with *n*-butyllithium was recorded, providing evidence for the intermediacy of 6 (R= *n*-Bu)[12]. Careful hydrolysis of the reaction mixture gave the corresponding 1,2-dihydropyridine 7 (R= *n*-Bu) which was fairly stable making it possible to measure the n.m.r. spectrum.A great similarity of the spectra

of adduct 6 and 1,2-dihydropyridine 7 was found. One year later the lithium salt 6 (R=Ph) and several derivatives were actually isolated and could be purified by recrystallization[13].
In 1963 Abramovitch *et al.*[14] used the intermediate 6 as reducing agent for carbonyl compounds. The reaction of 6 (R=Ph) with benzophenone gave benzhydrol 8 (R=Ph) and a by-product, which turned out to have structure 9[15,16].



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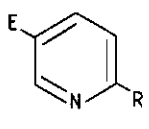
Scheme 1.4

The formation of compound 9 suggested that C(5) in adduct 6 had nucleophilic properties. This interesting facet probably induced Giam in 1970, soon followed by others, to start an investigation of reactions of 6 with several electrophiles[17-27]. From these reactions several kinds of products were obtained in very divergent yields. Selected examples are summarized in scheme 1.5 and table 1.2.



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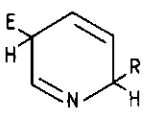

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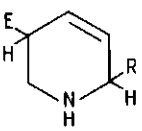

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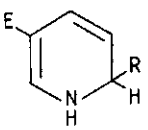

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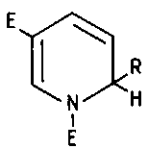

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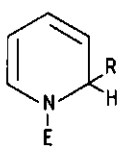

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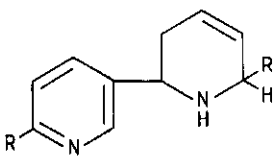

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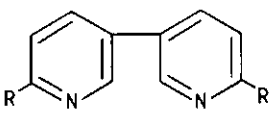

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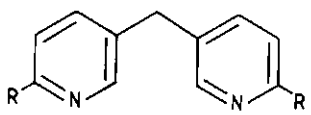

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Scheme 1.5

Table 1.2 Reactions of adduct 6(R) with electrophilic reagents (E-X)

R	E	X	products (yields, %)	ref.
Ph	MeCO	Cl	8(7), 15(34)	19
Ph	$pNO_2C_6H_4CO$	Cl	8(37), 15(6)	19
Ph	CF_3CO	Cl	8(17), 10(5), 13(13), 15(1)	19
Ph	$pEtOC_6H_4CO$	Cl	8(16), 14(30), 15(15)	19
Ph	CH_3CO	OEt	8(12). 15(56)	19
Ph	Me	I	10(45)	17
Ph	PhS	SPh	10(8)	25
n-Bu	Br	CN	8(22), 17(26)	21
n-Bu	CF_3	Br	8(38), 18(41)	21
n-Bu	(2-pyridyl)CO	OEt	8(15), 10(4), 13(48)	24
t-Bu	Me	I	10, 11, 12	27
Me	BuS	SBu	10(27)	25

As can be seen from table 1.2 the reagents with the softer electrophilic centra yielded mainly 2-R-5-E-pyridines 10. In one case (R=*t*-Bu, E=CH_3) the 2,5-dihydropyridine 11 could be isolated, but in most cases compound 11 was either oxidized during work up into 10, disproportionated into 10 and tetrahydropyridine 12 or was isomerized into the more stable 1,2-dihydropyridine 13.Compound 13 was susceptible to a second electrophilic attack resulting in 14. The harder electrophilic reagents (acid chlorides, esters,isocyanates) gave considerable amounts of N-substitution products 15. In all reactions the oxidation product 8 was formed. The reaction of 6 with this compound yielded the 2,3' coupling product 16. The 3,3' coupling product 17 was formed in those cases where E=Br. When E=CF_3 the intermediate 11 (or 10,13) was attacked by another molecule of 6 eventually leading to 18.

Like the lithium salts 6 (R=*n*-Bu, Ph), the 1,2-dihydropyridines 7 (R=*n*-Bu, Ph) were used as substrates for reactions with electrophilic reagents[21,22,24].

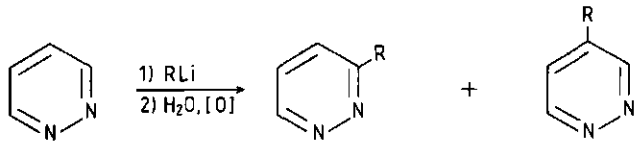
In some cases the products and yields obtained from the reactions of the dihydropyridine 7 (R=*n*-Bu) were of the same order as those from the reactions of the lithium salt 6 (R=*n*-Bu) with the same reagent (see cases A and B in table 1.3) In other cases (C and D) a completely different reaction mixture was obtained.

Table 1.3 Reactions of 6 (R=n-Bu) and 7 (R=n-Bu)

	Starting material	Reagent	Products (yields, %)
A	6	PhSeCl	10(16) ; 8(12)
	7		10(16) ; 8(15)
B	6	CNBr	8(22) ; 17(26)
	7		8(27) ; 17(7)
C	6	EtN=C=O	10(15) ; 14(12) ; 15(52)
	7		16(35)
D	6	PhN=C=O	10(30) ; 13(43) ; 14(15) ; 15(9)
	7		10(15) ; 15(30)

1.3.1.2 Diazines

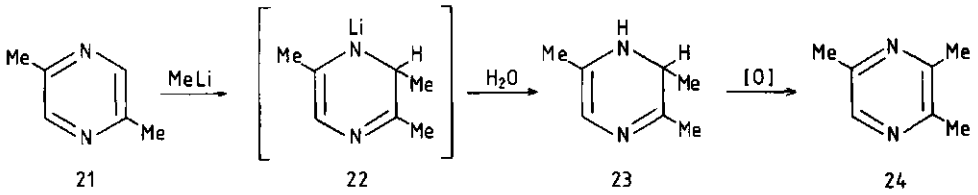
The reaction of phenyl- or *n*-butyllithium with *pyridazine* (1) in ether yielded after work up with water 3-R-pyridazine (19)(R=Ph, *n*-Bu)[28]. The solvent appeared to be a factor in determining the substitution pattern; when reacting *n*-butyllithium with pyridazine in a mixed ether-tetrahydrofuran solvent a mixture of 3- and 4-*n*-butylpyridazine was obtained. No systematic investigation of a solvent effect on the substitution pattern has ever been performed. To our knowledge there are no reports of reactions of the organolithium-pyridazine adducts with reagents other than water.



1 19 20

Scheme 1.6

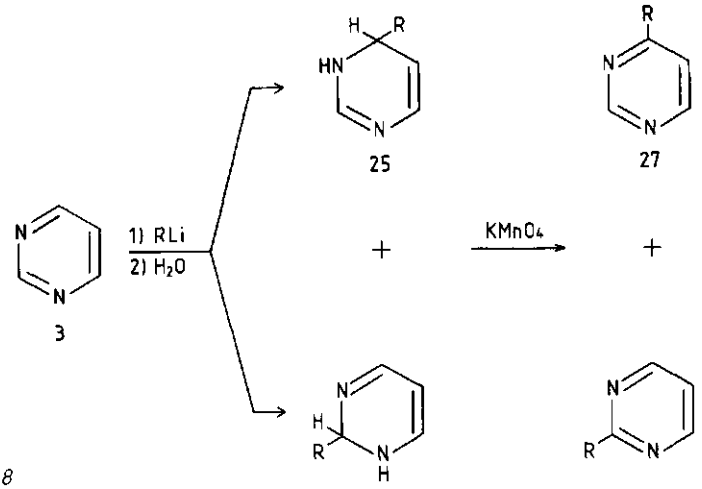
Only tar was obtained when reacting phenyllithium with *pyrazine* (2)[29]. However, organolithium reagents were reported to react with methyl substituted pyrazines yielding products resulting from ring alkylation (or arylation) and side-chain metalation[29-31]. Infrared analysis of a crude reaction mixture obtained by addition of methyllithium to compound 21 and subsequent hydrolysis showed absorptions that were attributed to the 1,2-dihydropyrazine (23). Work up of the mixture yielded trimethylpyrazine (24). Attempts to trap the intermediate adduct 22 with dimethyl sulfate or methyl benzoate were not successful[31].



21 22 23 24

Scheme 1.7

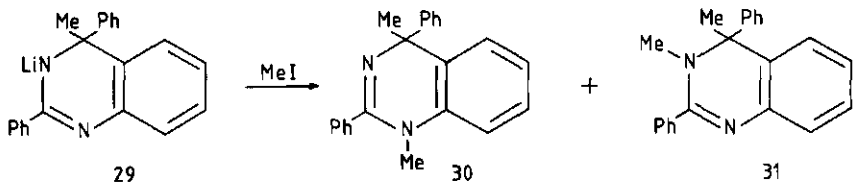
Reactions of organolithium compounds with *pyrimidine* (3) and derivatives have been reported to give after work up a mixture of 4- and 2-substituted pyrimidines 27 and 28 respectively[34-43]. Most of these studies were directed towards the preparation of the substituted pyrimidines and therefore the proposed dihydropyrimidines[44] 25 and 26 were never identified or isolated.



3 25 26 27 28

Scheme 1.8

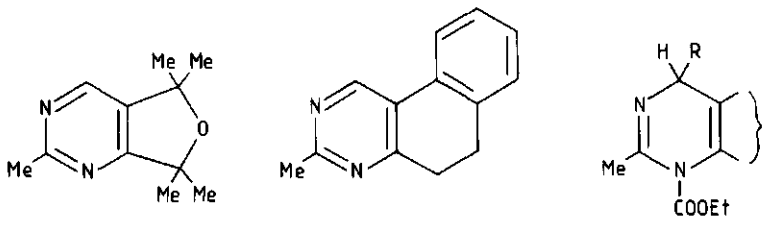
Reactions of the adducts formed from organolithium compounds and fused pyrimidines with electrophilic reagents, have also been reported. The adduct 29, obtained on reacting methyllithium with 2,4-diphenylquinazoline, was treated with methyliodide and gave both the 1-methyl-1,4-dihydroquinazoline (30) and 3-methyl-3,4-dihydroquinazoline (31)[45].



29 30 31

Scheme 1.9

Recently adducts of RLi with fused pyrimidine derivatives 32 and 33 have been reacted with ethyl chloroformate to yield products, which were assigned - based on ^{1}H-n.m.r. data - to have the 1,4-dihydropyrimidine structure 34[46].

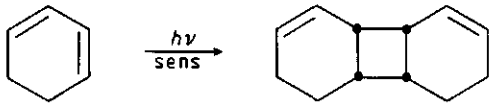


32 33 34

Scheme 1.10

1.3.2 Photochemistry of cyclohexadienes and their aza-analogues

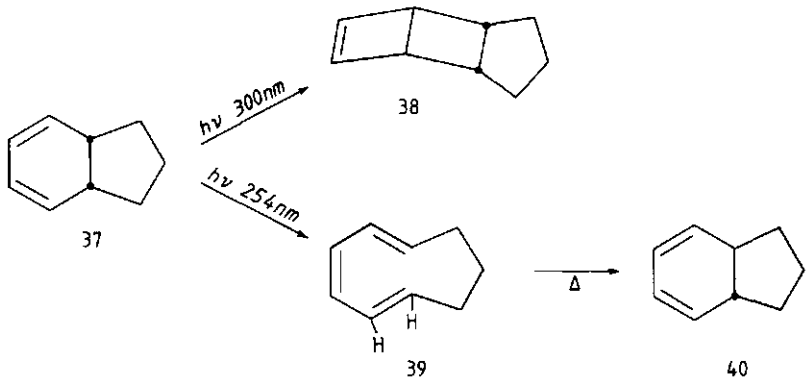
Molecules containing the cyclohexadiene chromophore showed several different types of reaction upon irradiation. *Dimerization* occurred when 1,3-cyclohexadiene (35) was irradiated in the presence of a sensitizer. Dimer 36 as well as other dimers were formed[47,48].



35 36

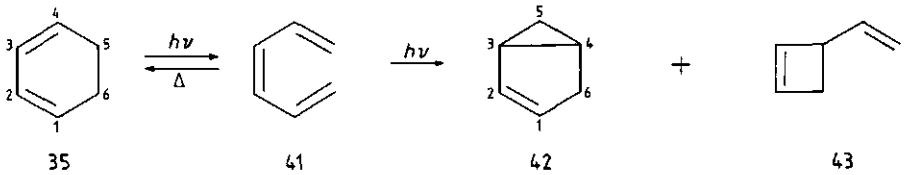
Scheme 1.11

On the other hand bicyclo [4.3.0]nona-2,4-diene (37) gave upon direct irradiation with light of 300 nm an intramolecular *2+2 cycloaddition* into tricyclononene 38 [49]. Irradiation with 254 nm light however, induced a *4+2 cycloreversion*



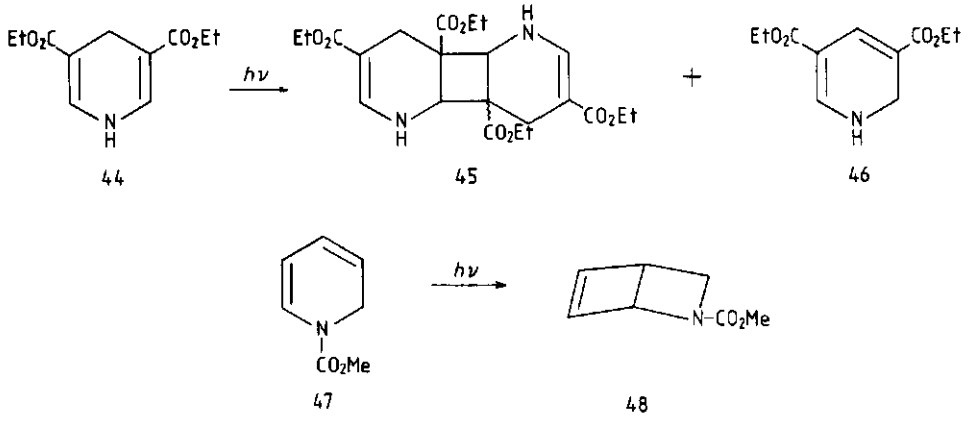
Scheme 1.12

into 1,3,5-cyclononatriene (39). The molecules resulting from ring opening were usually not stable, in this case 39 underwent a thermally induced ring closure leading to the *trans* isomer of 37, *i.e.* 40. Another example of this behaviour was the photolysis product 41, which thermally reconverted into 35, and photochemically underwent a 4+2 cycloaddition into bicyclo [3.1.0] hexene



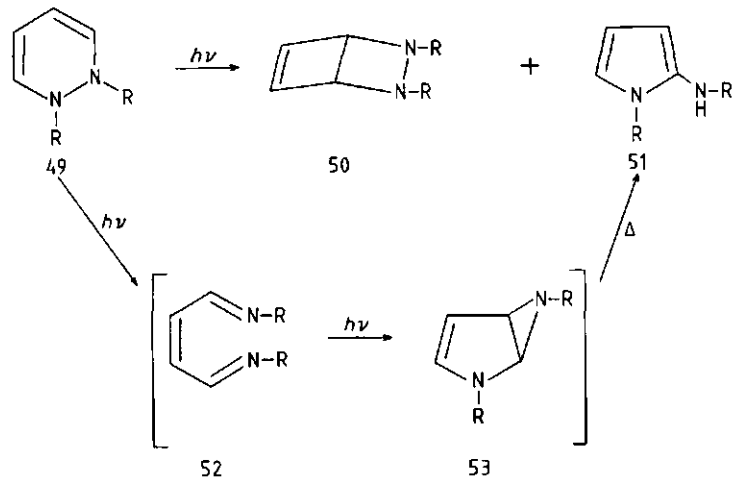
Scheme 1.13

(42) along with photochemical 2+2 cycloaddition into vinylcyclobutene (43)[50,51]. Dimerization, 2+2 cycloaddition and ring opening with subsequent photochemical and thermal transformations have also been reported to occur on irradiation of dihydro(di)azines. However, most studies were not very detailed. Thus, 1,4-dihydropyridine (44) underwent photodimerization into 45 and photoisomerization into 46[52], while intramolecular 2+2 cycloaddition has been observed with 1,2-dihydropyridine (47) yielding an azabicyclo [2.2.0] hexene (48)[53].



Scheme 1.14

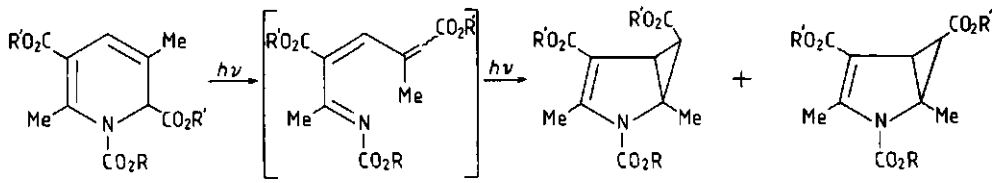
The dihydropyridazine (49)(R=CO_2Me) also showed intramolecular 2+2 cycloaddition leading to 2,3-diazabicyclo [2.2.0] hexene (50). Along with this product the 2-aminopyrrole 51 was formed. This ring contraction was believed to proceed



Scheme 1.15

through 4+2 cycloreversion product 52 and subsequent 4+2 cycloaddition into diazabicyclo [3.1.0] hexene (53). Opening of the three-membered ring and subsequent aromatization of the five-membered ring yielded the final product 51[54].

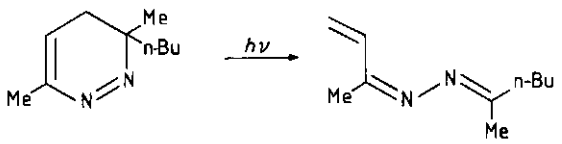
A similar reaction course was assumed to occur during the formation of azabicyclo [3.1.0] hexenes (56 and 57) by irradiation of 1,2-dihydropyridine (54)[55].



54 55 56 57

Scheme 1.16

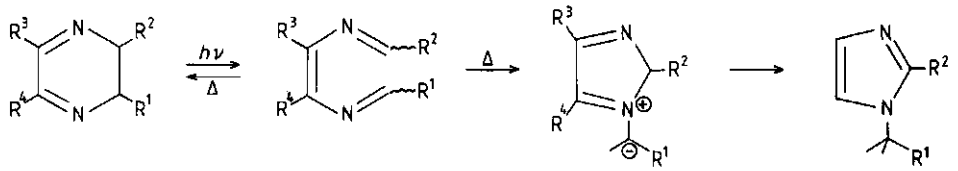
In above-mentioned reactions the (di)azahexatrienes have not been isolated or detected. On irradiation of 3-*n*-butyl-3,6-dimethyl-3,4-dihydropyridazine (58) however, an open-chain product was formed which was identified by n.m.r.spectroscopy as the diazahexatriene (59)[56].



58 59

Scheme 1.17

2,3-Dihydropyrazines (60) also produced diazahexatrienes on irradiation; they were sufficiently stable to be isolated. The products 61 showed thermal reconversion into the starting materials and ring contraction into imidazoles (63), presumably *via* the ylides (62)[57-60].

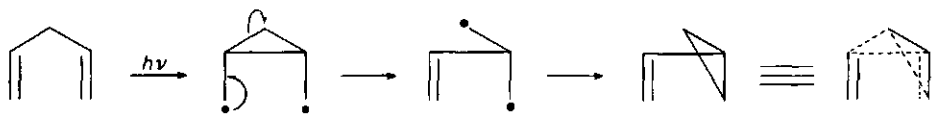


60 61 62 63

Scheme 1.18

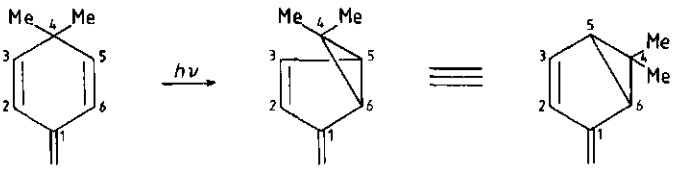
1.3.3 *Di-π-methane rearrangement*[61]

This rearrangement occurs on photolysis of compounds having two π-moieties bonded to a single sp^3-hybridized carbon atom. It formally involves the migration of one π-moiety from the saturated carbon atom to the adjacent sp^2-hybridized carbon atom of the second π-moiety with concomitant formation of a three-membered ring.
The skeletal change can be described by the mechanism which is represented below.



Scheme 1.19

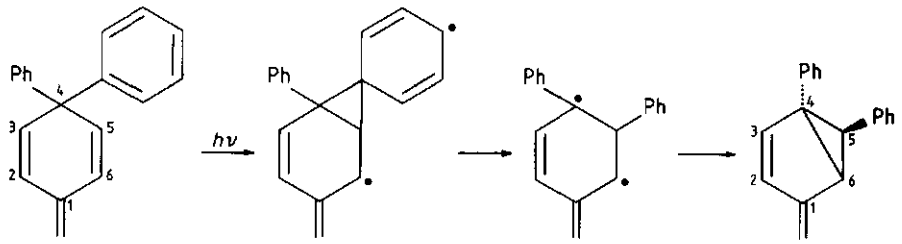
The di-π-methane rearrangement is not restricted to systems that contain two vinyl moieties (vinyl-vinyl bridging), it may be extended to other unsaturated systems (*e.g.* phenyl, ethynyl, carbonyl and others, see chapter 5). In those cases where the di-π-methane system is comprised in a six-membered ring - as in the 1,4-cyclohexadiene (64) - the reaction led to the formation of the bicyclo [3.1.0] hexene derivatives (65) as shown[62].



64 65

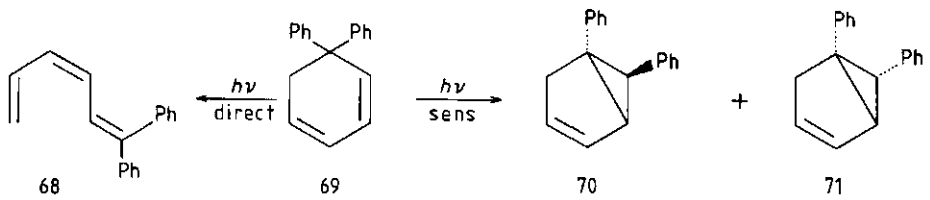
Scheme 1.20

When the sp^3-hybridized carbon bears phenyl groups as in compound 66, product 67 was formed indicating that phenyl-vinyl bridging is favoured over vinyl-vinyl bridging[63,64]. It is of importance to note the reorganization of carbon atoms of the six-membered ring in the former process (and in the process involving ring opening and subsequent 4+2 cycloaddition as discussed in sect.1.3.2) being distinct from the shift of the phenyl substituent from C(4) to C(5), together with C(4) - C(6) bonding. In the latter rearrangement the bicyclic photoproducts with the *trans-endo* relationship of the phenyl groups were either predominant or exclusive[62-66].



Scheme 1.21

For acyclic di-π-methane systems the singlet manifold is the preferred excited state from which rearrangement occurs.The triplet is inert because acyclic 1,4-dienes are able to dissipate their triplet energy by *cis-trans* isomerization pathways ('free rotor effect'). On the other hand the triplet excited states of cyclic systems are incapable of 'free rotor' energy dissipation due to their rigid structures and the di-π-methane rearrangement of these systems can be sensitized by triplet sensitizers. For example the sensitized irradiation of 5,5-diphenyl-1,3-cyclohexadiene (69) yielded a mixture of the stereoisomeric bicyclo [3.1.0] hexenes (70 and 71) whilst direct irradiation resulted in ring opening into 68[67,68].



Scheme 1.22

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2 A ^{13}C-NMR STUDY ON THE PHENYLLITHIUM-DIAZINE ADDUCTS AND THE CORRESPONDING DIHYDRODIAZINES

R.E.van der Stoel and H.C.van der Plas

2.1 INTRODUCTION

In this laboratory there is continuing interest in the reactivity of azines towards nucleophiles. Especially the behaviour of the halogeno derivatives and quaternary salts derived from pyrimidine, pyrazine and pyridazine has attracted our attention[1]. Several n.m.r. studies have been published dealing with the regiospecificity of the addition of the amide ion to pyrimidine and halogenopyrimidines in solutions of liquid ammonia[2-5]. It was found that with pyrimidine the 1:1 σ-adduct 4-amino-1(or 3)pyrimidinide ion is formed[5]. Attempts to isolate the conjugate acid of this pyrimidinide *i.e.* 4-amino-1,4(3,4)-dihydropyrimidine failed, as it rearomatizes easily to the starting material. In the case of the presence of a leaving group - like a halogeno atom - the σ-adducts can react further yielding either open-chain compounds or ring transformation products[1].
Reaction of organolithium compounds with the three parent diazines and subsequent hydrolysis yield dihydrodiazines[6-14]. Due to their instability, they were, however, not properly characterized. In this paper the results of an n.m.r. study are presented, being undertaken to establish in more detail the structure of the adducts formed between the three diazines and phenyllithium, especially in the light of recent results on the reactivity of phenyllithium-pyridine adducts towards electrophilic reagents[15-19].

2.2 RESULTS AND DISCUSSION

2.2.1 Pyrimidine

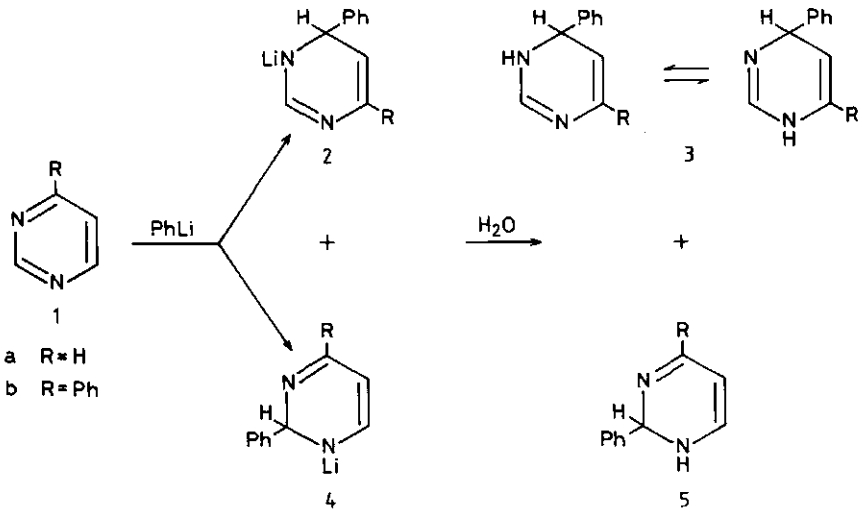
Treatment of pyrimidine (1a) with phenyllithium in ether gave a solution of which the ^{1}H- and ^{13}C-n.m.r. spectra showed only the presence of a stable adduct (2a) (Scheme 2.1); no pyrimidine could be detected. Owing to the distinct splitting pattern all peaks in the ^{1}H-n.m.r. spectrum of 2a could easily be assigned (Table 2.1). This also made an unambiguous assignment of the peaks in the ^{13}C-n.m.r. spectrum possible (Table 2.2) by recording the spectrum in the proton-

Table 2.1 ^{1}*H-n.m.r. data of the phenyllithium-diazine adducts and dihydrodiazines*

	H(2)	H(3)	H(4)	H(5)	H(6)	NH	H(arom)	coupling constants (Hz)
2a[a,b]	7.74	-	5.21	4.32	6.07	-	7.06-7.30	$J_{4,5}$= 2.3; $J_{5,6}$= 7.5
2b[b,c]	7.69	-	5.19	4.66	-	-	7.00-7.55	$J_{4,5}$= 3.8; $J_{2,5}$= 1.0
3a	6.70	-	5.02	4.58	5.96	6.70	7.35	$J_{2,5}$= 1.1[d]; $J_{4,5}$= 3.5; $J_{5,6}$= 7.5
3b	6.95	-	5.19	5.19	-	5.84	7.30	
4b[b,c]	4.89	-	-	5.62	7.36[e]	f	f	$J_{5,6}$= 4.5
10a[a]	-	4.23	4.74	5.73	6.83	-	7.10-7.60	$J_{3,4}$= 3.7; $J_{4,5}$= 8.0; $J_{4,6}$= 1.9; $J_{5,6}$= 5.3
10b[c]	-	4.43	4.93	6.35	-	-	7.10-7.70	$J_{3,4}$= 3.8; $J_{4,5}$= 8.0
11a	-	4.82	5.75	5.75	6.73	6.18	7.24	$J_{4,6}+J_{5,6}$= 5.0; $J_{3,4}+J_{3,5}$= 2.8[g]
11b	-	4.91	6.01	6.50	-	6.35	7.2-7.8	$J_{3,4}$= 4.3; $J_{3,5}$= 1.5; $J_{4,5}$= 9.8
12a[h]	-	6.5	f	4.36	6.5	-	7.2-7.5	
13a	-	6.45	3.91	4.52	6.23	f	7.25-7.30	$J_{3,4}$= 3.0; $J_{3,5}$= 2.3; $J_{4,5}$= 3.8; $J_{5,6}$= 7.5
15[b,i]	4.08	5.25	-	5.84	6.60	-	7.06-7.33	

[a] In ether
[b] Rather broad signals
[c] In benzene-d_6/ether
[d] Was measured in pyridine-d_5 at 70°
[e] Due to overlap of H(6) with the phenyl protons, chemical shift was measured after reaction of 4-(pentadeuteriophenyl)pyrimidine with pentadeuteriophenyllithium
[f] Could not be measured because of overlap of signals
[g] A case of deceptive simplicity (ref.34)
[h] In THF/ether
[i] In TMEDA/ether at -20°

decoupled mode and selective decoupling experiments. The chemical shifts were not much different from the shifts found for the 4-amino-1(or 3)-pyrimidinide ion (7)[4,5]. From these data it is evident that positions 4 and 6 in 2a are unequal, indicating the presence of the phenyl group on position 4(6) in the adduct. The structure of the phenyllithium adduct was confirmed by the high field absorption of C(4) and the magnitude of the one-bond carbon to hydrogen coupling constant of C(4)(^1J(CH) = 140 Hz)[4].



Scheme 2.1

After hydrolysis of the ethereal solution containing 2a and careful working up of the reaction mixture, crystals of 4-phenyldihydropyrimidine (3a) could be isolated. On prolonged exposure to air the crystals became sticky, presumably due to polymerization; in addition a slow oxidation into 4-phenylpyrimidine was observed. The ^{1}H- and ^{13}C-n.m.r. spectra of 3a resembled the spectra of 2a (Tables 2.1 and 2.2). From these data it could not be decided whether 3a was a 1,4- or a 3,4-dihydropyrimidine or a tautomeric mixture of both. The infrared spectrum ($CHCl_3$) distinctly showed two sharp free-NH stretching vibration absorptions at 3490 and 3465 cm^{-1}. This clearly indicates the presence of two different dihydropyrimidines being in rapid (on n.m.r. time scale) equilibrium 20
Attempts to obtain n.m.r. spectra of each of the tautomers by lowering the temperature (-88°) of an ^{1}H-n.m.r. sample failed; it resulted only in considerable line broadening of the signals.

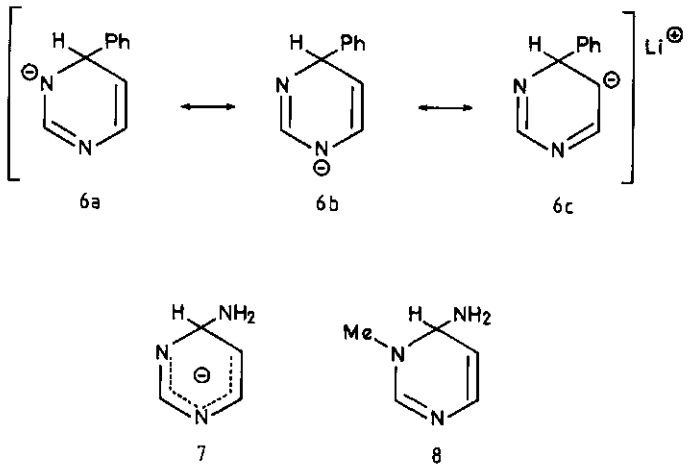


Fig. 2.1

It can be questioned whether contributions of polar structures 6a ↔ 6b ↔ 6c are of any importance in describing the structure of the phenyllithium-pyrimidine adduct. In order to evaluate this, the charge density on the *ortho* and *para* positions (with respect to the sp^3-carbon atom) is of crucial importance. Despite criticism[21] ^{13}C chemical shifts in many instances gave reasonable indications about charge densities on carbon atoms[23-26]. A 1-electron density is considered to induce an upfield shift of about 160 ppm[27,28].

Table 2.2 ^{13}C-n.m.r. data of the diazines, the σ-adducts and the dihydrodiazines

	C(2)	C(3)	C(4)	C(5)	C(6)
1a[a]	159.5	-	157.5	122.1	157.5
2a	161.7	-	58.4	103.4	135.5
3a	145.9	-	55.9	104.6	128.8
7	156.7	-	62.5	98.0	140.5
8	150.3	-	62.9	108.2	134.8
9a	-	151.9	126.6	126.6	151.9
10a	-	61.1	105.8	118.4	131.7
11a	-	55.0	128.1	118.2	134.6
11b	-	55.2	128.3	117.7	142.2
12a	-	133.2	40.9	89.2	140.0
13a	-	136.9	38.7	97.2	128.0[b]
14a	-	146.1	146.1	146.1	146.1
15	-	61.7	116.0[b]	110.8[b]	144.6

[a] Ref.30
[b] uncertain assignment

In a recent paper[22] Olah *et al.* compared the chemical shifts of Meisenheimer complexes formed between potassium methoxide and dinitroanisoles with those of their *aromatic* precursors in order to be informed about charge distribution. They stated, however, that the more obvious method of comparing the ^{13}C data of these adducts with those of the *cyclohexadiene* derivatives would lead to the same results because the chemical shifts of the sp^2carbons in cyclohexadiene are not different from those of benzene.

Table 2.3 Differences (Δ) between chemical shifts of the adducts 2a, 10, 12a and 15 and the diazines 1a, 9a and 14

	C(2)	C(3)	C(4)	C(5)	C(6)
Δ(2a-1a)	+ 2.2	-	-99.1	-18.7	-22.0
Δ(10a-9a)	-	-90.8	-20.8	- 8.2	-20.2
Δ(12a-9a)	-	-18.7	-85.7	-37.4	-11.9
Δ(15-14)	-84.4	-30.1	-	-35.3	- 1.5

Table 2.4 Differences (Δ) between chemical shifts of the adducts 2a, 7, 10a and 12a and the dihydrodiazines 3a, 8, 11a and 13a

	C(2)	C(3)	C(4)	C(5)	C(6)
Δ(2a-3a)	+ 15.8	-	+ 2.5	- 1.2	+ 6.7
Δ(7-8)	+ 6.4	-	- 0.4	-10.2	+ 5.7
Δ(10a-11a)	-	+ 6.1	-22.3	+ 0.2	- 2.9
Δ(12a-13a)	-	- 3.7	+ 2.2	- 8.0	+12.0

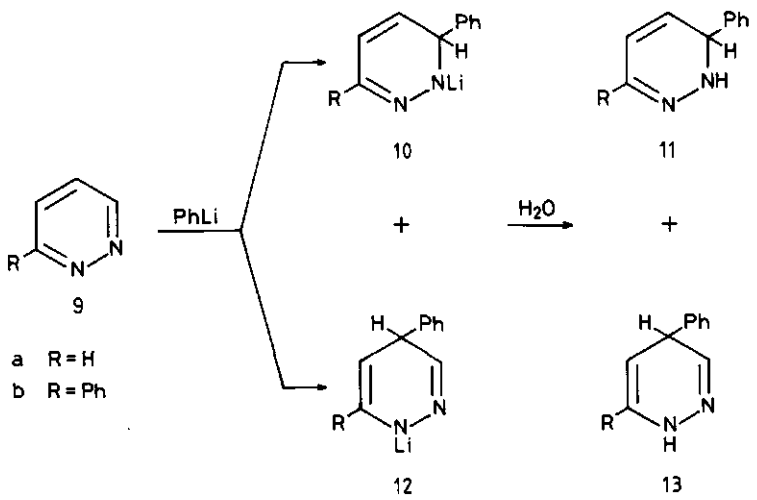
Comparison of the chemical shift of C(5)(δ = 103.4 ppm) in the phenyllithium-pyrimidine adduct 2a with the shift of C(5) in the precursor pyrimidine (1a) (δ = 122.1 ppm) leads to an upfield shift of 18.7 ppm upon adduct formation (Table 2.3). From this it may be concluded that a considerable amount of charge is located on C(5) in 2a. This conclusion, however, is erroneous since comparison of the chemical shift of C(5) in 2a with that of the corresponding dihydropyrimidine 3a only gives an upfield shift of 1.2 ppm (Table 2.4) . Apparently the 18.7 ppm upfield shift of C(5) in 2a upon adduct formation is caused mainly (17.5 ppm) by the change of the heteroaromatic structure in 1a into the dihydropyrimidine structure in 2a.

From these data the conclusion can be drawn that structure 6c does not contribute significantly in describing the structure of the phenyllithium adduct. However, these data do not allow of any conclusion about the contribution of the polar structures 6a and 6b. In this respect it is instructive to compare the ^{13}C-n.m.r. data of the completely ionic σ-adduct 7 with the neutral σ-adduct 8[4] (see Table 2.2). C(5) in 7 is shifted 10.2 ppm to higher field with respect to C(5) in 8. This upfield shift is only in part attributable to the γ-effect of the methyl group (in general not exceeding 1-3 ppm[29]). Thus in 7 the negative charge is delocalized over C(5). This seems to implicate that the phenyllithium-pyrimidine adduct 2a has less ionic character than the amide-pyrimidine adduct 7.
Although attack by organolithium compounds on position 2 of the parent pyrimidine has already been reported[8,11]; in our investigations by n.m.r.spectroscopy no 4a could be detected in the solution containing the phenyllithium-pyrimidine adduct. However, after hydrolysis and oxidation with potassium permanganate, a small amount of 2-phenylpyrimidine was detected by g.l.c. (ratio 4-phenylpyrimidine/2-phenylpyrimidine = 25).
Addition at position 2 was observed to a somewhat greater extent in the reaction of 4-phenylpyrimidine (1b) with phenyllithium; along with 2b a small amount of 4b was formed. The ratio 2b/4b was 7.2, as determined directly by ^{1}H-n.m.r. spectroscopy of the adduct solution and indirectly by g.l.c. analysis of the reaction mixture obtained after hydrolysis and oxidation, showing 4,6- and 2,4-diphenylpyrimidine to be present in the same ratio. In contrast to 3a the 6-phenyl derivative 3b, obtained from hydrolysis of 2b, is more stable and could be obtained in an analytically pure state. It is generally known that the reactivity of organolithium compounds may be altered by the addition of complexing agents[7]. We observed a change in ratio C(4)-attack/C(2)-attack from 7.2 to 1.8 when the phenylation of 1b was carried out at -45° in the presence of *N,N,N',N'*-tetramethyl-1,2-diaminoethane (TMEDA). The reaction of pyrimidine with phenyllithium in the presence of TMEDA only caused a minor change in ratio of the products.
The 1,2-dihydropyrimidines (5) were even more sensitive to oxygen than the 1,4(3,4)-dihydropyrimidines (3) and could not be isolated.

2.2.2 *Pyridazine*

Similar to pyrimidine, pyridazine (9a) underwent quantitative conversion with phenyllithium into an adduct which was stable for several hours at room temperature. The ^{1}H-n.m.r. spectrum of this adduct in ether showed a set of

mutually coupled signals (see Table 2.1),based on chemical shifts and splitting pattern, structure 10a was assigned to this phenyllithium-pyridazine adduct (Scheme 2.2).



Scheme 2.2

The correctness of peak assignment was proved by measuring the phenyllithium adduct of pyridazine-4,5-d_2. Apart from the signals caused by the aromatic protons the spectrum showed only two singlets at δ = 6.8 and δ = 4.2 ppm. In the ^{13}C-n.m.r. spectrum of 10a (Table 2.2) unambiguous peak assignment was made by using the selective decoupling technique. Hydrolysis of 10a yielded the corresponding 3-phenyl-2,3-dihydropyridazine (11a). The infrared spectrum of 11a showed an NH-stretching vibration absorption at 3415 cm^{-1}; oxidation of 11a with potassium permanganate gave 3-phenylpyridazine. Assignment of the peaks in the ^{13}C-n.m.r. spectrum of 11a by using the selective decoupling technique was hampered by overlap of the H(4)- and H(5) signals in the ^{1}H-n.m.r. spectrum of 11a. The ^{13}C-resonances at δ = 128.1 and δ = 118.2 ppm were tentatively assigned to C(4) and C(5) respectively[32]. In order to establish this assignment more firmly the ^{1}H- and ^{13}C-n.m.r. spectra of 3,6-diphenyl-2,3-dihydropyridazine (11b), obtained by treatment of 3-phenylpyridazine with phenyllithium and subsequent hydrolysis, were taken. In 11b the signals of H(4) and H(5) are separated by 0.5 ppm. Irradiation at the H(5) frequency caused a collapse of the doublet arising from C(5) in 11b at 117.7 ppm into a singlet.

The consequence of the assignments made is that C(4) and C(6) in the phenyllithium-pyridazine adduct 10a are shifted upfield 22.3 ppm and 2.9 ppm,respectively, compared with the dihydropyridazine 11a (see Table 2.4). Thus C(4) in 10a carries considerably more negative charge than C(6) in 10a and C(5) in 3a. The 20.8 ppm upfield shift observed for C(4) upon formation of the adduct 10a from 9a (Table 2.3) must be caused completely by charge density, induced by the lithium atom; the change of the aromatic structure in 9a into the diene structure in 10a causes a *downfield* shift of 1.5 ppm. On the other hand, the 20.2 ppm upfield shift of C(6) is caused mainly by the change of the aromatic structure into the dihydropyridazine structure (17.3 ppm) and only to a minor extent by charge density (2.9 ppm).

The addition of phenyllithium across the azomethine bond yielding an adduct at position 3 is distinct from the addition of the amide ion at C(4) in pyridazine[5]. Although by n.m.r. spectroscopy no C(4) adduct of pyridazine and phenyllithium could be detected after reaction in ether, g.l.c. analysis of the product after hydrolysis and oxidation revealed the presence of a small amount of 4-phenylpyridazine (ratio of 3-phenylpyridazine/4-phenylpyridazine = 18). By using the complexing agent TMEDA or tetrahydrofuran (THF) and carrying out the reaction at lowered temperatures this ratio was altered significantly. For instance at -75^{0} with THF as co-solvent a reaction mixture was obtained, which by n.m.r. spectroscopy was proved to contain both the C(3) adduct 10a and the C(4) adduct 12a in a ratio of 1:4. Chemical shifts of the peaks in the ^{1}H-n.m.r. spectrum of this solution attributed to the C(4) adduct agreed well with those of the 4-amino-1,4-dihydropyridazinide ion described in the literature[5].

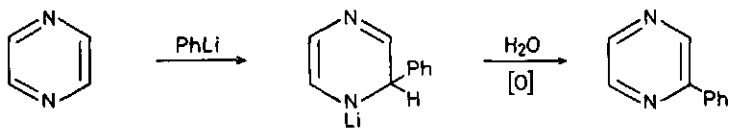
Hydrolysis of the above-mentioned solution containing the adducts 10a and 12a gave a mixture of the corresponding dihydropyridazines in the same ratio. Based on chemical shifts, intensities and splitting pattern the peaks attributed to 4-phenyl-1,4-dihydropyridazine (13a) could be assigned (Table 2.1).

In order to study the electronic structure of the C(4) adduct 12a, the ^{13}C-n.m.r. spectra of 12a and 13a were analysed. Peak assignment was made as already described. With 12a no selective decoupling experiments were performed, because several proton resonances overlap. It could be established, however, that in 12a the carbons *ortho* to the sp^3 carbon atom [C(3) and C(5)] are shielded with respect to the corresponding carbon atoms in the neutral dihydropyridazine 13a, $\Delta\delta$ C(3) = -3.7 ppm and $\Delta\delta$ C(5) = -8.0 ppm (Table 2.4). So C(3) in 12a carries about the same amount of charge as C(6) in 10a, but C(5) in 12a considerably less than C(4) in 10a.

The dihydropyridazines 11a, 11b and 13a appeared to be sensitive to oxidation and polymerization and could not be purified by recrystallization or by chromatography. Samples of these compounds when stored for longer than a few days decomposed seriously.

2.2.3 Pyrazine

Upon treatment with phenyllithium at -45° a solution of pyrazine in THF or TMEDA immediately turned orange. The ^{1}H-n.m.r. spectrum of this solution showed that pyrazine had been converted completely into an adduct *i.e.* 15 (Scheme 2.3). The ^{1}H-n.m.r. spectrum showed, apart from the signals caused by the phenyl protons, four broad unresolved signals of equal intensity (Table 1.1). Due to the broadness of the signals no coupling constants could be measured but



Scheme 2.3 14 15 16

comparison of the spectrum of 15 with the spectrum of the corresponding potassium amide adduct allowed the assignment made. The phenyllithium-pyrazine adduct 15 proved to be stable upon heating up to 0° but at room temperature rapid decomposition occurred. Also the ^{13}C-n.m.r. spectrum of 15 was recorded. In the proton-decoupled spectrum four broad resonances were attributed to the ring carbons. No comparison with the spectrum of the corresponding dihydropyrazine could be made as careful addition of water or methanol to 15 resulted in the formation of a considerable amount of tarry products along with some phenylpyrazine (9% isolated yield). No phenyldihydropyrazine could be obtained. Yet the signal in the aliphatic region was assigned to C(2) and the other high-field signals (δ = 116.0 and δ = 110.8 ppm) were attributed to C(3) and C(5), *ortho* and *para* to the sp^3-carbon. The high-field position of these signals (pyrazine resonates at δ = 146.1 ppm) seems to indicate a considerable amount of charge density on these carbon atoms. Since comparison with a dihydropyrazine was not possible an estimation of that part of these shifts that is caused by the change from the aromatic system in 14 to the dihydro system in 15 could not

be made. As noted above the yield of phenylpyrazine after hydrolysis of 15 is poor. However, this yield was improved considerably by direct oxidation of 15 with dry (air) oxygen (60% isolated yield).

2.3. EXPERIMENTAL

Melting points are uncorrected. Infrared spectra of solutions in chloroform were taken on a Perkin Elmer model 237 apparatus. The ^{1}H-n.m.r. spectra were obtained from a JEOL JNM C-60 spectrometer using $CDCl_3$ as solvent (unless otherwise stated) and TMS as the internal standard. ^{13}C spectra were recorded with a Varian XL-100 spectrometer in the pulse FT mode using $CDCl_3$ as solvent (unless otherwise stated) and TMS as the internal standard. Reactions involving organometallic compounds were carried out in an atmosphere of predried nitrogen. The solvents diethyl ether, THF and TMEDA were dried by adding an ethereal solution of phenyllithium and distilling these solvents directly into the reaction vessel; pentane, benzene and benzene-d_6 were dried over sodium wire.
Pyrimidine[33] and 4-phenylpyrimidine[6] were prepared as described in the literature, pyridazine was obtained from Aldrich and pyrazine from Merck. Pyrimidine and pyridazine were dried over molecular sieve type 4A (Merck). A solution of phenyllithium in ether was prepared by reacting bromobenzene in ether with lithium chips. The concentration of phenyllithium in the ethereal solution was determined by hydrolysis and titration of the hydrolysate with acid.

2.3.1 General procedure for the formation of the dihydrodiazines 3a, 3b, 11a, 11b and 13a

The phenylation reactions were carried out with 1.4 eq. of 1.0-1.4 *M* solutions of phenyllithium in ether and 1.0 eq. of 0.2 *M* solutions of the starting material in a solvent and at a temperature as specified in Table 2.5. After addition, the reaction mixture was cooled to -75^{o} and with vigorous stirring methanol was added. The solution was then allowed to warm up to room temperature and water was added (in the case of the reactions of 1b and 9b only water was added). After separation, the aqueous layer was extracted three times with chloroform. The combined organic layers were dried over $MgSO_4$, filtered and the solvents evaporated *in vacuo*. The resulting crude dihydrodiazines 11a and 13a were yellow oils and all attempts to obtain crystalline products failed. The crude dihydrodiazines 3a, 3b or 11b crystallized either spontaneously or after being held at -20^{o} for several days. The crystals were washed three times with cold ether

yielding a pale yellow sample of the dihydrodiazine. 11a could not be purified any further, 3a was separated from neutral impurities by a careful acid-base separation procedure (isolated yield 59%). No analytically pure sample could be prepared, however. Compound 3b was purified by column chromatography (silica gel, acetone) and several recrystallizations from acetone without heating. Yield 59%; m.r. 96-112°. Despite the broad melting range due to decomposition during melting, it had a correct microanalysis. $C_{16}H_{14}N_2$(234.29); calcd. C, 82.02; H, 6.02; found C. 82.0; H, 6.0%.

Table 2.5 Reaction conditions for the formation of the dihydrodiazines

Starting material	Solvent	Temperature °C	Product(s)
1a	pentane*	0	3a
1b	benzene**	0	3b
9a	ether*	0	11a
9a	THF**	-75	11a + 13a
9b	benzene**	0	11b

* The solution of the starting material was added to the phenyllithium solution.

** The phenyllithium solution was added to the solution of the starting material.

Preparation of 3-phenylpyridazine (9b)

11a was oxidized with potassium permanganate in acetone[6] directly after its preparation. The crude 9b was subjected to column chromatography (silica gel, chloroform/ethyl acetate 4:1); yield 60% m.p. 101-102°(lit. 102-103°).

Preparation of phenylpyrazine (16)

To a stirred solution of 0.50 g of pyrazine (6.25 mmol) in 20 ml THF at -75° 1.4 eq. of a 1.0 *M* solution of phenyllithium in ether was added slowly. After the addition, dry air was passed through the reaction mixture for 30 min at -75° and an additional 30 min at room temperature. Water was added and the mixture was extracted with chloroform. The combined extracts were dried over $MgSO_4$, filtered and the solvents were evaporated *in vacuo*.

Crude 16 was subjected to column chromatography (silica gel, chloroform/ethyl acetate 4:1), yielding 0.58 g of 16 (60%). An analytical sample was prepared by several recrystallizations from petroleum ether (b.r. 40-60°), m.p. 70-70.5°. $C_{10}H_8N_2$(156.18); calcd. C, 76.90; H, 5.16; found C, 77.0; H, 5.3%. ^{1}H-n.m.r.: δ 8.98 (1H,d), δ 8.55 (1H, 2 x d), δ 8.42 (1H,d), δ 7.98 (2H,m), δ 7.45 (3H,m); $J_{3,6}$ = 1.5; $J_{5,6}$= 3.0 Hz.

2.3.2 Preparation of n.m.r. samples for measurements of the adduct spectra

The ^{1}H-n.m.r. samples of 2b and 10b were prepared by injection of a solution of 1.0 eq. of phenyllithium in ether into a cooled (0°) n.m.r. sample tube, containing 80 mg of substrate in 0.5 ml of ether or benzene-d_6. Samples of 2a and 10a were prepared by injection of solutions of 80 mg of substrate in 0.5 ml of ether into a cooled (0°) n.m.r. sample tube, containing a solution of 1.0 eq. of phenyllithium. The sample containing 12a was made by addition of a solution of 1.0 eq. of phenyllithium in ether to a stirred solution of 9a in THF at -75°. The resulting reaction mixture was warmed to room temperature and put into the n.m.r. sample tube. A solution of 15 was made by injection of 1.0 eq. of phenyllithium in ether into a cooled (-40°) n.m.r. sample tube containing 80 mg of 14 in 0.5 ml of TMEDA. After addition of TMS all spectra were taken at ambient temperature except that of 15, which was recorded at -20°. The ^{13}C-n.m.r. samples were prepared in the same way, but on a larger scale (200 mg substrate in 2-3 ml solvent in a 12 mm (o.d.) n.m.r.sample tube).

2.3.3 Isomer ratio determination

The ratio of the adducts present in the adduct solution was determined indirectly by hydrolysis, oxidation with potassium permanganate and subsequent g.l.c. analysis of the phenyldiazines thus obtained, using a Hewlett-Packard apparatus model 5700 A and a glass column (length 200 cm, o.d. 1/8 inch) filled with 9.2% OV-275 on Chromosorb W-HP 100-200 mesh, operating at various temperatures (170-230°).

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31. These ^{13}C-n.m.r. data should be interpreted cautiously because a comparison is made between a compound which in reality is a mixture of two tautomeric compounds in a rather inert solvent and a compound which is probably strongly associated with the solvent and perhaps exists as an oligomer which is common for organolithium compounds (ref.3).
32. The reverse assignment was considered less probable since in that case C(5) in 10a, without carrying charge, would have been shifted 9.7 ppm *upfield* in contrast to the trend observed in 2a and enolates (ref.23).
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3 REACTIONS OF ORGANOLITHIUM-DIAZINE ADDUCTS AND DIHYDRODIAZINES WITH ELECTROPHILIC REAGENTS

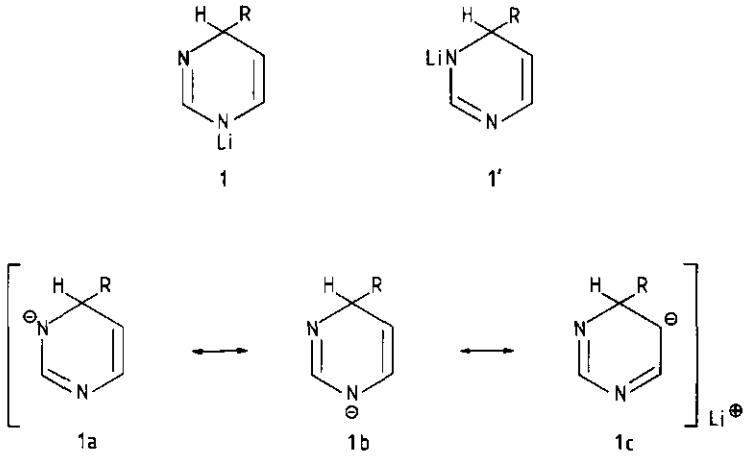
3.1 INTRODUCTION

The reactions of organolithium reagents with pyridine have been studied for many years; adducts were formed initially which could be converted subsequently into substituted pyridines[1]. However, since 1-lithio-2-phenyl-1,2-dihydropyridine (the adduct of phenyllithium and pyridine) was found to be a stable and isolable compound[2] several reports have been published concerning reactions of organolithium-pyridine adducts with electrophilic reagents. The products of these reactions resulted from attack of the electrophile either at carbon or at nitrogen. The electrophiles with the softer centre, *e.g.* methyliodide, attacked the carbon in *para* position with respect to the sp^3 carbon yielding 2,5-disubstituted dihydropyridines (which could not be isolated in most cases, but were oxidized to give the corresponding pyridines). The harder electrophiles, *e.g.* carbonyl compounds, gave mainly reaction at nitrogen leading to *N*-substituted 1,2-dihydropyridines (see sect.1.3.1).
Some of these reactions have been performed with the conjugate acids of the 1-lithio-2-R-1,2-dihydropyridines, *i.e.* 2-R-1,2-dihydropyridines, and from these reactions too, products resulting from attack at carbon and nitrogen in the ring have been obtained. Apparently the enhanced negative charge at nitrogen and at carbon that is induced by the presence of lithium is neither necessary for the reactions to occur nor decisive in determining the orientation of the electrophilic attack[3].
The diazines are related to pyridine in structure and resemble pyridine in many of its properties. The diazines also react with organolithium compounds to yield organolithium-diazine adducts. These adducts could not be isolated, however, and their characterization was based on n.m.r. spectra of the reaction mixtures, obtained by addition of a solution of the organolithium compound to the diazines (see chapter 2). The n.m.r. spectra thus obtained revealed that the structure of these organolithium-diazine adducts were very similar to the structure of the organolithium-pyridine adducts. Therefore a similar reactivity of the organolithium-diazine adducts towards electrophilic reagents was anticipated.

3.2 RESULTS AND DISCUSSION

3.2.1 Pyrimidine

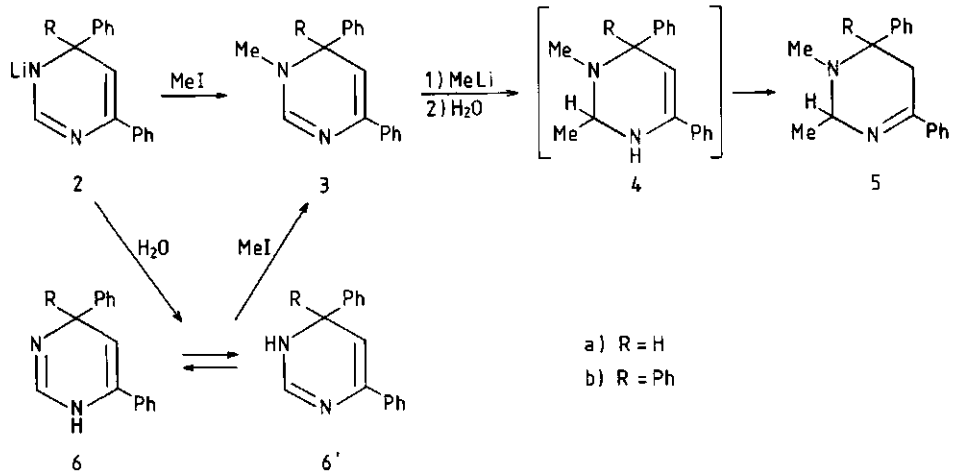
The organolithium-pyrimidine adducts are frequently represented for the sake of simplicity by their 1,4-dihydro- (1) or their 3,4-dihydro structure (1'). The mesomeric structures 1a-c suggest that electrophilic attack may occur at N(1), N(3) and C(5) leading to 1,4-disubstituted 1,4-dihydropyrimidines, 3,4-disubstituted 3,4-dihydropyrimidines and/or 4,5-disubstituted 4,5-dihydropyrimidines respectively.



Scheme 3.1

When the solution obtained from the reaction of phenyllithium with 4-phenylpyrimidine in ether was treated with methyliodide a product A was isolated by column chromatography. Compound A had a molecular weight of 248 and the n.m.r. spectrum showed along with the phenyl protons two mutually coupled signals at δ 5.39 and 5.10 of equal intensity and a singlet at δ 2.69 having thrice the intensity of the former signals. These data justified the conclusion that in the above-mentioned reaction *N*-methyl-4,6-diphenyldihydropyrimidine had been formed. In order to decide which of the two possible *N*-methyldihydropyrimidine structures (3a or 7a) can be attributed to this compound A,the n.m.r. and u.v. spectral data of related compounds were compared with the spectral data of compound A. As pointed out in chapter 2[4] the dihydropyrimidine obtained by hydrolysis of 2a exists as a mixture

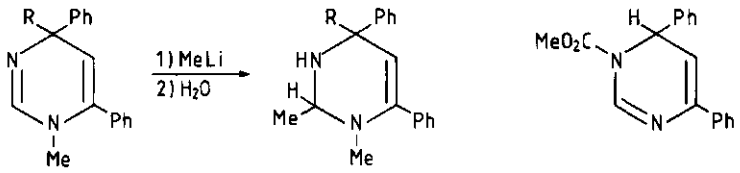
of both tautomeric dihydropyrimidines 6a and 6'a. In the n.m.r. spectrum of this mixture of tautomers H(5) resonates at δ 5.19 and due to a rapid (on n.m.r. time scale) equilibrium between both tautomers this signal will be positioned between the H(5) signal of 1,4-dihydropyrimidine 6a and the H(5) signal of 3,4-dihydropyrimidine 6'a. In the conjugate diene system of 6'a the H(5) signal will be at lower field (δ > 5.19) than the H(5) signal in the



Scheme 3.2

isolated alkene group of 1,4-dihydropyrimidine 6a (δ < 5.19)(compare 1-phenyl-1,2-dihydropyridine: H(5) at δ 5.21 vs. 1-phenyl-1,4-dihydropyridine: H(5) at δ 4.53)[5]. Since the chemical shift of H(5) in the *N*-methyl-4,6-diphenyldihydropyrimidine lies at a *lower* field (δ 5.39) than the H(5) in 6a ⇌ 6'a (δ 5.19) the structure of the 3-methyl-3,4-dihydro derivative (3a) was ascribed to compound A. This structure assignment was confirmed by the u.v. spectrum of A. It shows the longest wavelength absorption at λ_{max} 320 nm, while the tautomeric mixture of 6a ⇌ 6'a showed a broad, flat absorption around 295 nm. Thus the absorption of A is at the longer wavelength end of the combined absorption of the dihydropyrimidines 6a and 6'a. The assignment of the more conjugated structure 3a to compound A is compatible with this observation (cf. 1-trimethylsilyl-1,2-dihydropyridine λ_{max} 320 nm and the corresponding 1,4-dihydropyridine λ_{max} 288 nm)[5]. This result is opposite to the reported exclusive formation of 1,4-dihydropyrimidines from adducts of 5,6-disubstituted (fused) pyrimidines and ethyl chloroformate[6]. Therefore we also tried to prove the structure of A by chemical means.

Compound A was treated with methyllithium and subsequently hydrolysed. Since the i.r. spectrum of the product of this reaction missed an NH absorption and the n.m.r. spectrum missed an olefinic proton it is evident that this product did not have structure 4a. Its molecular weight, however, was 16 higher than that of compound A and the n.m.r. spectrum showed in addition to the *N*-methyl singlet at δ 2.14 a doublet at δ 1.42 (3H). Based on these and further spectroscopic data (see table 3.2) structure 5a was assigned to this product. The formation of this compound can only be explained if product A has the 3,4-dihydropyrimidine structure 3a instead of the 1,4-dihydropyrimidine structure 7a.



7 8 9

a) R = H
b) R = Ph

Scheme 3.3

Methyllithium addition to 3a and subsequent hydrolysis gives 1,2,3,4-tetrahydropyrimidine 4a in which the enamine moiety can undergo a rearrangement into the corresponding imino form 5a. When 7a had been the structure of product A the reaction with methyllithium would have led to 1,2,3,4-tetrahydropyrimidine (8a) *not* capable of an enamine-imine tautomerization. The absence of a signal of an olefinic proton in the n.m.r. spectrum as well as the absence of an NH absorption in the i.r. spectrum exclude structure 8a. Compounds 3a and 5a, although fairly stable could not be obtained in an analytically pure state. The usual purification procedures, recrystallization, distillation and preparative g.l.c. caused decomposition.

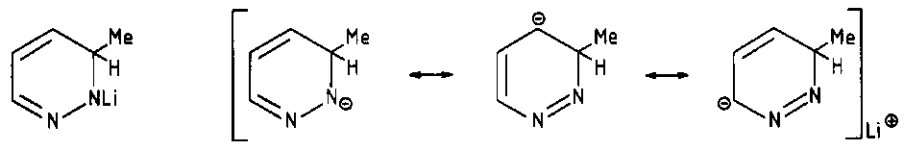
Reaction of adduct 2a with methyl chloroformate yielded the 3,4-dihydropyrimidine 9. Structure 9 was assigned to this product based on similarity of its n.m.r and u.v. spectral data with those of compound 3a. H(5) of the product appeared at δ 5.80 and in the u.v. spectrum the longest wavelength absorption had λ_{max} at 302 nm. The observed hypsochromic shift with respect to 3a is caused by the electron withdrawing methoxycarbonyl group (a similar effect has been observed with dihydropyridines)[5].

The reaction of the conjugate acid of 2a, *i.e.* 4,6-diphenyl-1,4(3,4)-dihydropyrimidine(6a ⇌ 6'a) with methyliodide was also investigated and found to give

the same 3,4-dihydropyrimidine 3a as 2a did. The overall yield (49%) was the same as the yield of the direct reaction of 2a with methyliodide. The reaction of phenyllithium with 4,6-diphenylpyrimidine has been reported to yield 4,4,6-triphenyl-1,4(3,4)-dihydropyrimidine[7] (6b ⇄ 6'b). Treatment of this compound with methyliodide gave two isomeric *N*-methyldihydropyrimidines. The main product (87% yield) had H(5) at δ 5.47 and the longest wavelength absorption maximum at 319 nm (6b ⇄ 6'b has H(5) at δ 5.39 and λ_{max} at 295 nm, a broad, flat peak). Based on these spectral data the 3-methyl-3,4-dihydro structure (3b) was assigned to the main product of the reaction of 6b ⇄ 6'b with methyliodide. Compound 3b is a stable compound from which correct microanalytical data have been obtained. The by-product in this reaction (∿ 1%) has molecular weight of 324, no u.v. maximum at longer wavelength than 298 nm and in the n.m.r. spectrum singlets at δ 4.97 (1H) and δ 2.87 (3H). Based on these data 1,4-dihydro structure (7b) was assigned to this by-product.

3.2.2 Pyridazine

The reaction of methyllithium with pyridazine in ether yielded the adduct 2-lithio-3-methyl-2,3-dihydropyridazine (10). Mesomeric structures 10a-c suggest

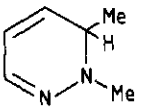


10 10a 10b 10c

Scheme 3.4

that attack by an electrophilic reagent might occur at N(2), C(4) and C(6). Of the three possible products resulting from reaction of 10 with methyliodide, *i.e.* 2,3-dimethyl-2,3-dihydropyridazine, 3,4-dimethyl-3,4-dihydropyridazine and 3,6-dimethyl-3,6-dihydropyridazine only one isomer was formed. The n.m.r. spectrum of this product showed one *singlet* at δ 2.96 (3H) indicating the presence of an N-CH_3 group and a *doublet* at δ 1.08 (3H) ascribed to the methyl group on position 3, in addition to signals at lower field caused by the ring protons. These spectral data only permit structure 11 for this dimethyldihydropyridazine. In the n.m.r. spectrum of the crude reaction product no signals in the aromatic region were observed, excluding the presence of dimethylpyridazines resulting from oxidation of possible intermediate C-substituted dihydropyridazines.

The reactions of 10 with methyl chloroformate and tosylchloride were found to follow the same reaction pattern. Reaction of adduct 10 with methyl chloroformate yielded a single dihydropyridazine. The n.m.r. spectrum of this isomer resembled the spectrum of 11, except that all signals had undergone a downfield shift; the 2,3-dihydropyridazine structure (12) was assigned to this product.



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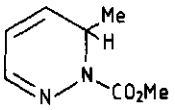

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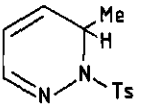


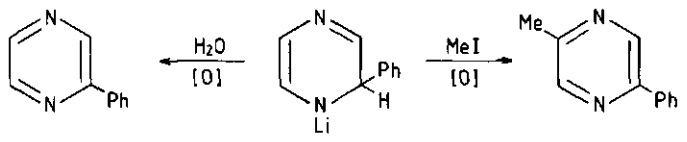
13

Scheme 3.5

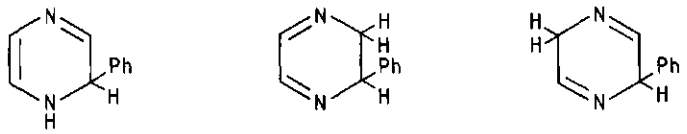
The reaction of the adduct 10 with tosylchloride yielded a white crystalline product, which by n.m.r. spectroscopy was established to be 3-methyl-2-tosyl-2,3-dihydropyridazine (13).

3.2.3 Pyrazine

Hydrolysis of the thermally labile adduct 14, obtained from phenyllithium and pyrazine, produced a considerable amount of tar and some 2-phenylpyrazine (18)[4]. N.m.r. analysis of the crude hydrolysis mixture did not reveal the presence of intermediate 2-phenyldihydropyrazine, but it may have had the 1,2-dihydro- (15), the 2,3-dihydro- (16) or the 2,5-dihydropyrazine structure (17). Structure 16 for this intermediate can be ruled out since 2,3-dihydropyrazines have been described as stable compounds[8] and if 16 had been formed it would have been isolated or at least observed by n.m.r. spectroscopy.
Treatment of 14 with D_2O and analysis of the resulting phenylpyrazine showed that this compound contained 40-50% deuterium. In the n.m.r. spectrum of this product the δ 8.42 doublet attributed to H(5)[4,9] was reduced by the same order. This means that 2-phenyl-2,5-dihydropyrazine (17) exists as an intermediate in the hydrolysis reaction, either formed directly from 14 or *via* 2-phenyl-1,2-dihydropyrazine (15). This observation suggests that in adduct 14 C(5) has nucleophilic properties. This was demonstrated further by the result of the reaction of a solution of 14 with an excess of methyliodide. It gave 5-methyl-2-phenylpyrazine (19) along with 2-phenylpyrazine (18). The intermediate 5-methyl-2-phenyl-2,5-dihydropyrazine could not be detected. Compound 19 was synthesized independently from 2-phenylpyrazine and methyllithium[10].



18 14 19



15 16 17

Scheme 3.6

The reactions of 14 with carbonyl compounds were not successful. With methyl chloroformate, acetylchloride, benzoylchloride or ethyl trifluoroacetate only high molecular weight products were obtained. Bromine when added to 14 did not act as electrophilic reagent[11], but instead oxidized 14 and an increased amount of 18 was obtained after the usual work-up procedure.

3.3 EXPERIMENTAL

Melting points are uncorrected. N.m.r. spectra were determined for solutions of $CDCl_3$ with TMS as the internal standard with a Perkin Elmer R24 B spectrometer. I.r.spectra of solutions in $CHCl_3$ were taken on a Perkin Elmer 257 spectrometer. U.v. spectra were recorded on a Beckman Acta CIII spectrometer of solutions in 96% ethanol. Mass spectra were measured with an AEI-MS-902 mass spectrometer and exact mass measurements are given in lieu of elemental analyses in those cases where the di- and tetrahydrodiazines decomposed during purification. The reactions involving organometallic reagents were performed in an atmosphere of predried nitrogen. Ether and benzene were dried over sodium wire. For column chromatography Merck silica gel 60 (70-230 mesh ASTM) was used as the stationary phase.

Reactions of 1(3)-lithio-4,6-diphenyl-1,4(3,4)-dihydropyrimidine (2a) with electrophilic reagents, general procedure

A solution of 3.2 mmol of 2a in ether was prepared as described earlier[4]. To this solution a solution of the electrophile in 10 ml of ether was added at 0^{o} and the

Table 3.2 N.m.r. data of the products obtained (δ in ppm relative to TMS)

	H(2)	H(3)	H(4)	H(5)	H(6)	H(aromatic)	H(methyl)	coupling constants (Hz)
3a	a	-	5.10	5.39	-	7.70;7.50-7.10	2.69	$J_{2,5}$=1.3;$J_{4,5}$=4.0
3b	a	-	-	5.47	-	7.70;7.46-7.18	2.71	$J_{2,5}$=1.0
5a	4.63	-	4.00	b	-	7.70;7.35-7.20	2.14(s);1.42(d)	$J_{2,5}$=1.6;$J_{4,5A}$=7.3;$J_{4,5B}$=6.3; $J_{H\text{-}CH_3}$=6.5
7b	a	-	-	4.97	-	7.33-7.25	2.87	
9	8.04	-	5.68	5.80	-	7.70;7.40-7.15	3.75	$J_{2,5}$=1.3;$J_{4,5}$=5.0
11	-	3.72	5.68	5.68	6.22		2.96(s);1.08(d)	$J_{4,6}+J_{5,6}$=5.1[c];$J_{H\text{-}CH_3}$=6.0
12	-	4.94	6.14	5.78	7.04		3.84(s);1.19(d)	$J_{3,4}$=5.7;$J_{4,5}$=9.9;$J_{4,6}$=1.9;$J_{5,6}$=3.1;$J_{H\text{-}CH_3}$=5.7
13	-	4.94	6.00	5.72	a	7.80;7.27-7.02	2.39(s);1.08(d)	$J_{3,4}$=5.8;$J_{4,5}$=9.1;$J_{4,6}$=1.8;$J_{5,6}$=3.0; $J_{H\text{-}CH_3}$=5.8;$J_{o,m}$= 6.4

a) Due to overlap with H(aromatic) no data can be given

b) CH_AH_B-group, δ_A: 2.89; δ_B: 2.92

c) deceptive simplicity (ref.12)

reaction mixture stirred for the time given in table 3.1. Water was added and after separation, the aqueous phase was extracted with chloroform (3 times). The combined organic layers were dried over magnesium sulfate, filtered and the solvents evaporated *in vacuo* while the heating bath was kept below 40°. The residue was subjected to column chromatography. The conditions of the reactions with the electrophilic reagents, the eluents used for column chromatography and the yields of products are specified in table 3.1.

Table 3.1 Experimental conditions in the reactions of the adducts 2a and 10 with electrophilic reagents

starting material	reagent (eq)	reaction time (h)	product (yield,%)	eluent for column chromatography
2a	MeI(10)	3.0	3a(49)	P.A.D.[a]
2a	ClCOOMe(1)	1.5	9(35)	$CHCl_3$
10	MeI(10)	3.0	11(20)	$CHCl_3$/ethyl acetate 1:1
10	ClCOOMe(1)	1.0	12(26)	$CHCl_3$/ethyl acetate 1:1
10	TsCl(1)	2.5	13(21)	$CHCl_3$/ethyl acetate 1:1

[a] petroleum ether b.r. 40-60°/acetone/diethyl amine 13:6:1

Reactions of the 1,4(3,4)-dihydropyrimidines 6a and 6b with methyliodide

To a suspension of 3.2 mmol of the substrate in 10 ml of acetonitrile 10 ml of methyliodide were added and the mixture stirred for 1.5 h. The reaction mixture was evaporated to dryness *in vacuo* and dissolved in a mixture of diethyl amine (2 ml) and chloroform (10 ml). The solution was concentrated *in vacuo* and subjected to column chromatography with a mixture of petroleum ether (b.r. 40-60°)/acetone and diethyl amine 13:6:1 as the eluent. Yield 3a: 83%. Yield 3b: 87%. In addition to 3b ∿ 1% of 7b was obtained that had a slightly larger R_f value than 3b.

Reaction of 3a with methyllithium

To a solution of 0.86 g (3.5 mmol) of 3a in 10 ml of benzene 2 ml of a 1.77 M solution of methyllithium in ether were added at ambient temperature. After the addition of water and separation, the aqueous phase was extracted with chloroform (3 times). The combined organic layers were dried over magnesium sulfate, filtered and the solvents evaporated *in vacuo*. Column chromatography with a mixture of petroleum ether (b.r. 40-60°)/acetone/diethyl amine 18:1:1 gave 0.46 g (50%) of 5a. For spectral data see tables 3.2 and 3.3.

Reactions of 2-lithio-3-methyl-2,3-dihydropyridazine (10) with electrophilic reagents, general procedure

A solution of 0.50 g (6.3 mmol) of pyridazine in 10 ml of ether was added to a stirred solution of 1 eq. of methyllithium in ether (1.77 M) at -70°. The solution was warmed to 0°, a solution of the electrophile in 10 ml of ether was added and the reaction mixture stirred for a period of time as specified in table 3.1. The reaction mixture was worked up as described above.

Preparation of 5-methyl-2-phenylpyrazine (19)

A solution of 6.3 mmol of 14 in THF/ether was prepared at -20° as described earlier[4]. This solution was added to a solution of 2.13 g (15 mmol) of methyliodide in 10 ml of ether at -20°. The reaction mixture was worked up as described above yielding a 1:1 mixture of phenylpyrazine (18) and 5-methyl-2-phenylpyrazine (19) that could not be separated by column chromatography with chloroform/

Table 3.3 M.p., elemental or exact mass analysis and partial i.r. data of the products obtained

	m.p.(°C)	elemental analysis				i.r.ν_{max}(cm^{-1})
		calcd		found		
		C	H	C	H	
3b	189[a]	85.15	6.21	85.2	6.5	1642;1635;1607;1590;1575
12	b	54.53	6.54	54.3	6.4	1710;1525;1450
13	94[c]	57.58	5.64	57.6	5.6	1600;1520;1448

		exact mass		
		calcd	found	
3a	d	248.1313	248.1318	1640;1605;1587
5a	e	264.1626	264.1615	1650;1640;1610;1580
9	f	292.1212	292.1218	1735;1643;1606;1580
11	g	110.0844	110.0847	1523;1444

a) from ethanol
b) colourless oil, isolated by g.l.c. using a stainless steel column, 100 cm x 3 mm filled with 2.6 g ABS 70-80 + 20% OV-17 at 170°
c) from atecone/petroleum ether (b.r. 40-60°)
d) yellow solid m.r. 80-85°. The amount of yellow impurity increased by attempts to purify the sample. Compound 3a decomposed at elevated temp.
e) yellow oil
f) yellow oil, showed the same behaviour as compound 3a
g) colourless oil, isolated by g.l.c. using the column as described under b at 110°. The sample turned brown immediately in air (ref.13)

ethyl acetate (4:1) as the eluent. Compound 19 was isolated by preparative g.l.c. using a stainless steel column length 200 cm 3/8 inch o.d. filled with 30.8 g Kieselguhr 40-60 + 27.5% OV-17 at 230° yielding white crystals, m.p. 84°. (Anal. Found: C, 77.7; H, 6.1. $C_{11}H_{10}N_2$(170.21) requires C, 77.62; H, 5.92%). δ 8.75,d (H3); 8.36,d (H6); 7.85,m (*ortho*-C_6H_5); 7.37,m (*meta,para*-C_6H_5) and 2.56,s (CH_3). $J_{3,6}$= 1.3 Hz. The yield determined by g.l.c.analysis was 20%.

3.4 REFERENCES AND NOTES

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9. $J_{3,5}$= 0.0; $J_{5,6}$= 1.3 Hz (ref.12).
10. In the reaction of methyllithium with pyrazine also two isomers of compound 19 were formed (as was determined by GC-MS analysis of the reaction mixture), presumably 3-methyl-2-phenylpyrazine and 6-methyl-2-phenylpyrazine. It was established (g.l.c.) that these compounds were not formed in the reaction of 14 with methyliodide.
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4 A DI-π-METHANE PHOTOREARRANGEMENT OF 4-SUBSTITUTED 1,4(3,4)-DIHYDROPYRIMIDINES LEADING TO 5-SUBSTITUTED 1,2(2,3)-DIHYDROPYRIMIDINES

R.E.van der Stoel and H.C.van der Plas

4.1 INTRODUCTION

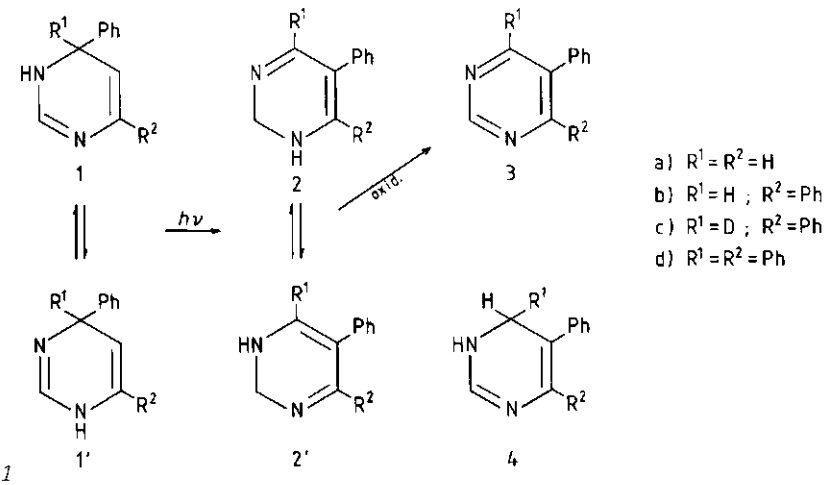
Six-membered heterocyclic compounds have been shown to undergo many types of photochemical reactions[1]. Much research has been done on the photochemistry of the aza-heteroaromatics, their N-oxides[1-3] and N-benzoylimino derivatives[4]. In more recent years the photochemistry of several dihydropyridines, - pyridazines and -pyrazines has attracted attention, in many cases giving rise to isomerization reactions[1]. Many of these isomerizations involve an initial ring opening reaction and a subsequent thermal or photochemical rearrangement. No data, however, are available on the behaviour of dihydropyrimidines on irradiation. In this paper we wish to report on a new photochemical rearrangement reaction of 4-substituted 1,4(3,4)-dihydropyrimidines.

4.2 RESULTS AND DISCUSSION

4.2.1 Irradiation of 4-phenyl-1,4(3,4)-dihydropyrimidines

When a 6.3 x 10^{-3} M solution of 4-phenyl-1,4(3,4)-dihydropyrimidine (1a)[5] in acetone was photolysed until all starting material had disappeared (2 h), a reaction mixture was obtained which according to the spectral data contained as the main product 5-phenyl-1,2(2,3)-dihydropyrimidine (2a)(Scheme 4.1) along with 4-phenylpyrimidine. Because of its instability, isolation of 2a by chromatography or crystallization failed. Evidence for the structure of 2a was based on the following chemical and spectral data. Heating of the crude irradiation mixture in air or oxidation of it with potassium permanganate gave 5-phenylpyrimidine as proved by comparison with an authentic specimen[6]. The infrared spectrum of the crude irradiation mixture of 1a showed one NH stretching vibration absorption at 3465 cm^{-1} (starting material 1a has *two* absorptions[5] at 3465 and 3490 cm^{-1}). The ^{1}H-n.m.r. spectrum featured in addition to the signals

of the phenyl protons at δ 7.1-7.4 three broad absorptions at δ 5.8 (this signal shifted upon addition of D_2O, confirming the presence of an NH-group), 4.5 and 7.4. This latter signal was partially masked by the phenyl proton signals. Using 4-(pentadeuteriophenyl)-1,4(3,4)-dihydropyrimidine (prepared from pyrimidine and pentadeuteriophenyllithium) the intensity ratio of the signals at δ 4.5 and 7.4 was found to be 1 : 1. The proton coupled ^{13}C-n.m.r. spectrum of the photolysis mixture of 1a showed in addition to the phenyl carbon atoms a triplet at δ 58.7, a singlet at δ 111.5 and a doublet at δ 148.5, assigned to the C(2), C(5) and C(4,6) carbon atoms of the heterocyclic ring. Irradiation at the resonance frequencies of the δ 4,5 and 7.4 protons caused the triplet at δ 58.7 and the doublet at 148.5 respectively, to collapse into singlets.



Scheme 4.1

These spectral data favour the 1,2-dihydro structure (2a) rather than the isomeric 3,4-dihydro structure (4a); the 1,2-dihydropyrimidine (2a) is in rapid (on n.m.r. time scale) equilibrium with its tautomer 2,3-dihydropyrimidine (2'a) causing H(4) and H(6) [and C(4) and C(6)] to appear as one signal in the n.m.r. spectra. The tautomerism also leads to one NH-absorption in the infrared spectrum. Supporting evidence of structure 2a $\rightleftarrows$ 2'a as the photolysis product of 1a was found in the chemical and spectral data of the product formed from photolysis of 4,6-diphenyl-1,4(3,4)-dihydropyrimidine (1b). Oxidation of this irradiation product gave 4,5-diphenylpyrimidine. The ^{1}H-n.m.r. spectrum of the irradiation mixture showed in addition to the phenyl protons two broad singlets at δ 7.8 and δ 4.6 (ratio 1 : 2) and a very broad singlet at δ 5.2 which shifted upon the addition of D_2O(NH).

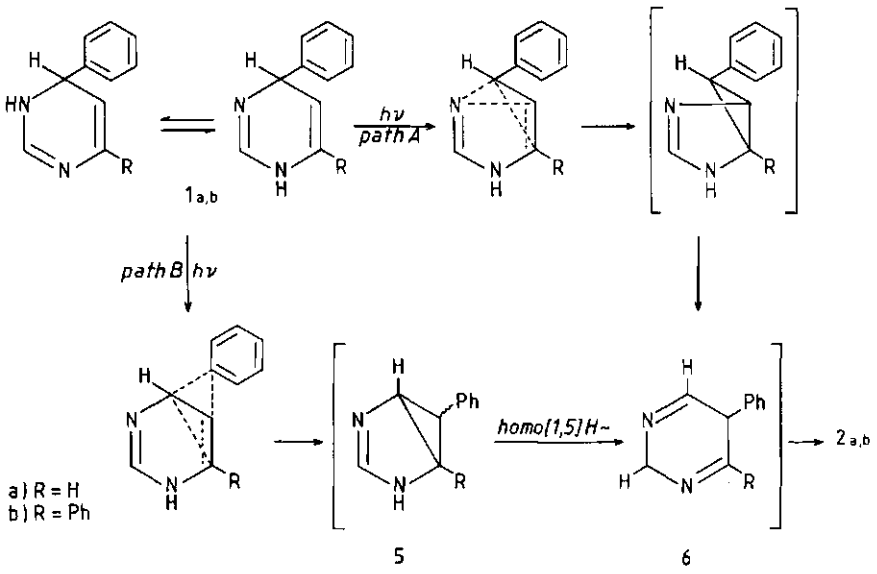
The infrared spectrum showed *two* NH-absorptions at 3440 and 3475 cm^{-1} as can be expected since the tautomeric 1,2-dihydro- (2b) and 2,3-dihydropyrimidine (2'b) are *not* identical. In the ^{13}C-n.m.r. spectrum a triplet was observed at δ 60.2 supporting structure 2 and excluding 4,5-diphenyl-1,4(3,4)-dihydropyrimidine (4, R^1=Ph, R^2=H)[7]. A possible alternative structure for the irradiation product of 1b *i.e.* 5,6-diphenyl-1,4(3,4)-dihydropyrimidine (4b) was also ruled out; photolysis of 4,6-diphenyl-1,4(3,4)-dihydropyrimidine-4-*d* (1c) gave a reaction mixture that did not show the δ 7.8 signal in the ^1H-n.m.r. spectrum and which upon oxidation gave 4,5-diphenylpyrimidine containing the *same* percentage of deuterium as the starting material. If 4c had been an intermediate it would certainly have led to considerable loss of deuterium upon oxidation. Irradiation of a solution of 4,4,6-triphenyl-1,4(3,4)-dihydropyrimidine (1d) in acetone or methanol and subsequent oxidation gave 4,5,6-triphenylpyrimidine (3d). This hitherto unknown compound was also synthesized independently from 4,5-diphenylpyrimidine and phenyllithium.

The quantum yield for the photochemical isomerization of 1a to 2a was found to be 0.06 when the irradiation was carried out in methanol with light of 254 nm and nitrogen was bubbled through the solution. The amount of 2a was determined indirectly by oxidation of 2a to 5-phenylpyrimidine and g.l.c. analysis of the reaction product thus obtained. The photochemical reaction was sensitized by acetone. The quantum yield for the isomerization in acetone solution using light of wavelength 300 nm was 0.02. These results indicate that the isomerization reaction can occur from the triplet excited state of 1a.

4.2.2 *Mechanism of the photochemical rearrangement of 4-phenyl-1,4(3,4)-dihydropyrimidines*

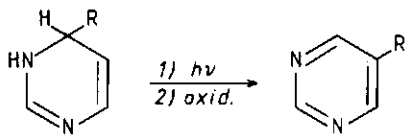
Several mechanisms for photochemical rearrangement of substituents in cycloalkenes and cycloalkadienes have appeared in the literature[8]. Photolysis of diaryl cyclohexadienes[9] and γ-pyrans[10] caused migration of an aryl group to an adjacent carbon atom accompanied by the synchronous formation of a three-membered ring thus leading to a bicyclo [3.1.0] hexene derivative *via* the di-π-methane rearrangement mechanism. Photolysis of cyclohexadienones and cyclohexenones on the other hand may lead to migration of a ring carbon *together* with the substituents or - in the case of arylcyclohexenones - migration of the aryl group in a di-π-methane manner[8]. The photochemical rearrangement of 4-phenyl-1,4(3,4)-dihydropyrimidines into 5-phenyl-1,2(2,3)-dihydropyrimidines can be described similarly either *with* or *without* ring carbon migration.

(scheme 4,2, paths A and B respectively).



Scheme 4.2

The mechanism *via* path A was proved to be unlikely, based on the facts that (i) in the product 3c, obtained by oxidation of the dihydro-intermediate (2c) the deuterium content is the same as in the starting material 1c and (ii) on irradiation of 1d 4,5,6-triphenylpyrimidine (3d) is obtained and not a compound containing two phenyl groups on one carbon atom. Both results exclude the occurrence of path A. Path B seems a more attractive way to describe the rearrangement. A necessary structural requirement is that the substituent at position 4 should contain a π-bond in the correct position. This means that 4-R-1,4(3,4)-dihydropyrimidines lacking the π-bond in the group R may not isomerize under these photochemical conditions. Thus 4-methyl-1,4(3,4)-dihydropyrimidine (7a) (being synthesized from methyllithium and pyrimidine) when irradiated for several hours gave a reaction mixture which after oxidation did not show the presence of 5-methylpyrimidine (Scheme 4.3). On the other hand 4-(2-methyl-1-propenyl)-1,4(3,4)-dihydropyrimidine (7b) and 4-(phenylethynyl)-1,4(3,4)-dihydropyrimidine (7c)[11] did give rearrangement. Irradiation of 7b in acetone for 2 h and subsequent heating of the photolysis mixture in air gave 5-(2-methyl-1-propenyl)pyrimidine (8b) in 14% yield. Irradiation of 7c in acetone for 4 h and subsequent oxidation gave 5-(phenylethynyl)pyrimidine (8c) in 22% yield.



7 8

a) R = Me
b) R = $-CH=C(Me)_2$
c) R = $-C\equiv C-Ph$

Scheme 4.3

As noted above, the isomerization reaction can occur from the triplet excited state although most di-π-methane rearrangements were shown to be singlet reactions and could not be sensitized by triplet sensitizers[12]. The triplet state was considered to be deactivated by rotation about the excited π-bond (free rotor effect). That some compounds with the π-bond in a cyclic system, as in the dihydropyrimidines, underwent rearrangement from the triplet state was attributed to the absence of the free rotor effect in these rigid structures.

As indicated in Scheme 4.2 the postulated mechanism for the rearrangement of 1a should give the intermediate 6-phenyl-2,4-diazabicyclo [3.1.0] hex-2(3)-ene (5a). However, since 2a was obtained from photolysis of 1a, obviously a subsequent rearrangement of 5a into 2a had occurred. This rearrangement is best understood by a two-step reaction involving an opening of the three-membered ring with a concomitant hydrogen shift from nitrogen to carbon C(2)(a thermally allowed homo [1,5] sigmatropic hydrogen shift)[13] into 5-phenyl-2,5-dihydropyrimidine (6a) which then tautomerizes to the more conjugated 1,2(2,3)-dihydropyrimidine (2a). In order to establish more firmly whether the hydrogen on nitrogen in 5 migrates to the adjacent carbon atom C(2) in 6, the compound 4,6-diphenyl-1,4(3,4)-dihydropyrimidine (1b) was dissolved in acetone-D_2O (25:1) and irradiated. In this medium 1b has been completely deuterated on nitrogen. Oxidation of the photolysis mixture gave 4,5-diphenylpyrimidine containing 56.5% deuterium at C(2). It is nearly the amount expected for the homo [1,5] deuterium shift from nitrogen to C(2). 1b and 2b were shown not to incorporate deuterium on carbon significantly under thermal conditions, neither did 2b under photochemical conditions.

The 2,5-dihydropyrimidine (6) could neither be isolated, nor detected by spectroscopic means. Attempts to trap such an intermediate by irradiating 5-substituted 4-phenyl-1,4(3,4)-dihydropyrimidines (9) in order to obtain the stable (with respect to tautomerization) 5,5-disubstituted 2,5-dihydropyrimidines (10) failed. Surprisingly the 5-substituted dihydropyrimidines (9a-c) were rather stable under photochemical conditions. 4,5-Diphenyl-1,4(3,4)-dihydropyrimidine (9a) and

dine (7b) and 4-(3-thienyl)pyrimidine (6b)(6% and 28% respectively, as determined by g.l.c. analysis). The rate of conversion of 3b was slower than that of 3a as was inferred from the longer irradiation time needed to convert 3b completely. This may be one of the reasons why the unwanted photo-oxidation of the substrate became the main reaction course. These results, combined with those obtained from irradiation of 3a indicate that no photo-induced rearrangement in the thienyl group occurs. This is in full agreement with the observation made that irradiation of 2-(2-pyridyl)thiophene gives no rearrangement either[9].

Irradiation of 4-(2-furyl)-1,4(3,4)-dihydropyrimidine (3c) in acetone solution and subsequent treatment with potassium permanganate gave a mixture of 5-(2-furyl)-[(7c), 20%] and 4-(2-furyl)pyrimidine [(6c), 6%]. The rate of disappearance of 3c was not much different from that of 3a. 4-(1-Methyl-2-pyrrolyl)-1,4(3,4)-dihydropyrimidine (3d) under the same conditions was found to be converted much slower; only 2% yield of 5-(1-methyl-2-pyrrolyl)pyrimidine (7d) along with 27% of the 4-isomer (6d) was formed after subsequent treatment of the irradiation mixture with potassium permanganate, as determined by g.l.c. analysis. Of the six-membered heteroaromatic substituents in this study only the 3-pyridyl group was investigated. Upon irradiation in acetone and subsequent treatment with potassium permanganate 4-(3-pyridyl)-1,4(3,4)-dihydropyrimidine (3e) gave the corresponding 5-pyridylpyrimidine [(7e), 26%] along with the pyridyl isomer [(6e), 2%].

Above-mentioned results show that pyrimidines, containing the heteroaryl groups 2- or 3-thienyl, 2-furyl, 1-methyl-2-pyrrolyl and 3-pyridyl at position 5 can be obtained from pyrimidine by a procedure involving heteroarylation at position 4 and subsequent photo-rearrangement. This method is in the cases of 7a and 7c competitive to the one recently reported[10] in which on irradiation of 5-iodopyrimidine in the presence of a large excess of heteroaromatic substance the 5-heteroaryl substituted pyrimidines were obtained. Moreover, by our method the 3-pyridyl compound (7e) could be prepared which is otherwise not available, because we found that this compound could not be prepared by irradiation of 5-iodopyrimidine in the presence of pyridine[11].

5.3 EXPERIMENTAL

General experimental conditions were as described in a previous paper[3]. G.l.c. analyses were performed using a Hewlett-Packard apparatus model 5700A and a glass column (length 200 cm o.d. 1/8 inch) filled with 9.2% of O.V.-275 on

Chromosorb W-HP 100-200 mesh, operating at various temperatures (150-230°). 2-Thienyl-[1], 2-furyl-[1] and 1-methyl-2-pyrrolyl-lithium[12] were prepared by lithium-hydrogen exchange, 3-thienyl-[13] and 3-pyridyl-lithium[1] by lithium-bromine exchange reactions with a solution of *n*-butyl-lithium (1.6M) in hexane as reported in the literature or by a slightly modified procedure.

5.3.1 Preparation of the 4-R-1,4(3,4)-dihydropyrimidines

4-(2-thienyl)-1,4(3,4)-dihydropyrimidine (3a): 2.10 g (25 mmol) of thiophene in 25 ml of ether were added to 15 ml of a cooled butyl-lithium solution (0°). The resulting mixture was stirred for 4 h at room temperature and then cooled to 0°. A solution of 1.44 g (18 mmol) of pyrimidine in 20 ml of ether was added and the resulting reaction product was poured into a mixture of 20 ml of conc. hydrochloric acid and 20 g of crushed ice. The organic layer was separated and extracted with 20 ml of cold 6N hydrochloric acid. The combined acidic layers were made alkaline with an aqueous sodium hydroxide solution (the temperature was kept at 0°) and thereupon extracted three times with chloroform. The combined organic layers were dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo*. The residue was subjected to column chromatography, using silica gel as the stationary phase and a mixture of petroleum ether (b.r. 40-60°), acetone and diethylamine (10:10:1) as the eluent. As the dihydropyrimidine started to leave the column the eluent was gradually replaced by a mixture of 5% diethylamine in acetone. Yield 1.92 g of light brown oil (65%). For n.m.r. data see Table 5.1. $\nu_{max}(CHCl_3)$: 3460; 3435; 3180; 1683; 1640; 1635 and 1588 cm^{-1}. $\lambda_{max}(\log \varepsilon)(EtOH)$: 240 (3.97) and 281 nm (3.36). Oxidation as reported in the literature[1] gave 4-(2-thienyl)pyrimidine (7a), m.p. 67°(lit. 66-67°).

4-(3-thienyl)-1,4(3,4)-dihydropyrimidine (3b) : to a stirred solution of 17.5 mmol of 3-thienyl-lithium at -40° a solution of 1.00 g (12.5 mmol) of pyrimidine in 15 ml of ether was added. After addition the reaction mixture was allowed to come to room temperature and worked up as described above. Yield 1.38 g of pale yellow oil (67%). For n.m.r. data see Table 5.1. $\nu_{max}(CHCl_3)$: 3430; 3420; 3190; 1682; 1648 and 1585 cm^{-1}. $\lambda_{max}(\log \varepsilon)(EtOH)$: 240 (3.70) and 285 nm (3.11). Oxidation with $KMnO_4$ in acetone gave 4-(3-thienyl)pyrimidine (6b), m.p. 88-89.5° (lit.[14] 88.3-89.7°).

4-(2-furyl)-1,4(3,4)-dihydropyrimidine (3c), 500 mg was irradiated for 1¾ h. After oxidation the residue was subjected to column chromatography (silica gel, chloroform/ethyl acetate 4:1), yielding 100 mg of 5-(2-furyl) pyrimidine [(7c), 20%], m.p. 55-57°(lit.[10] 57°) and 28 mg of 4-(2-furyl) pyrimidine [(6c), 6%].

4-(1-methyl-2-pyrrolyl)-1,4(3,4)-dihydropyrimidine (3d), 250 mg was irradiated for 3½ h. After oxidation the residue was subjected two times to column chromatography (silica gel, chloroform/ethyl acetate 1:1), yielding 64 mg of 4-(1-methyl-2-pyrrolyl) pyrimidine (6d) and 11 mg of a 1:1 mixture of 6d and 5-(1-methyl-2-pyrrolyl) pyrimidine (7d). The identity of the latter compound was confirmed by comparison with an authentic sample, prepared as described in the literature[10] (n.m.r. spectrum, t.l.c. and g.l.c. performance).

4-(3-pyridyl)-1,4(3,4)-dihydropyrimidine (3e), 250 mg was irradiated for 2 h. After oxidation the residue was subjected to column chromatography (silica gel, acetone), yielding 64 mg of 5-(3-pyridyl) pyrimidine [(7e), 26%], m.p. 107-108° (from petroleum ether b.r. 60-80°). (Found: C, 68.9; H, 4.2. $C_9H_7N_3$ (157.17) requires C, 68.77; H, 4.49%); δ ($CDCl_3$) : 9.22 (1H,s); 8.95 (2H,s), 8.84 (1H,d, J = 2.3 Hz), 8.70 (1H, dd, J = 2.0 and 4.7 Hz), 7.93 (1H, *m*) and 7.44 ppm (1H, dd, J = 4.7 and 8.0 Hz). In addition 6 mg (2%) of 4-(3-pyridyl) pyrimidine (6e) were obtained.

5.4 REFERENCES AND NOTES

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6. Runs were also made with samples, cooled (77 K), evacuated (0.1 mm) and brought to atmospheric pressure and room temperature under nitrogen three times, but with similar results. Perhaps a disproportionation reaction of the dihydropyrimidine takes place into the aromatic and further reduced species. In fact the n.m.r. spectrum of the irradiation product shows several unidentified peaks with $\delta < 2.5$ ppm. No products were isolated, however. On the other hand

a very rapid photo-oxidation (ref.7 and 8) - as reported for various dihydro-heteroaromatic compounds - by traces of oxygen or by acetone cannot be excluded.

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6 SPECTROSCOPIC EVIDENCE FOR THE INTERMEDIACY OF A 6-R-2,4-DIAZABICYCLO [3.1.0] HEX-2(3)-ENE IN THE PHOTOISOMERIZATION OF 4-R-1,4(3,4)-DIHYDROPYRIMIDINES

6.1 INTRODUCTION

As mentioned in chapter 4 the suggested intermediacy of the 2,4-diazabicyclo [3.1.0] hex-2(3)-ene (2a) in the photoisomerization of 4,6-diphenyl-1,4(3,4)-dihydropyrimidine (1a) could not be confirmed by n.m.r. spectroscopy[1]. Its existence, however, was substantiated by the 57% of deuterium incorporation in position 2 of the product 4,5-diphenylpyrimidine (4a), obtained when 1a was irradiated in an acetone/D_2O mixture and the reaction product subsequently oxidized[2]. It was also observed than when the irradiation of 1a was carried out in acetone and D_2O was added to the acetone mixture after photolysis, still 11% of deuterium was found in 4a. Evaporation of the solvent after irradiation of 1a in acetone, and then addition of D_2O did *not* lead to incorporation of deuterium.

Based on these observations it was concluded that 2a lasted for some time in the photolysis mixture after irradiation and did not rearrange immediately after its formation. Apparently the gentle heating necessary for evaporation of acetone caused 2a to be converted completely into the 1,2(2,3)-dihydropyrimidine (3a). By an immediate recording of spectra after a very careful evaporation of the acetone we tried to obtain spectroscopic evidence for the intermediacy of the bicyclic compound 2. We wish to present in this paragraph the results of a spectroscopic study on the structure of an intermediate in the photolysis of 4-(*p*-trifluoromethylphenyl)-1,4(3,4)-dihydropyrimidine (1b).

6.2 RESULTS AND DISCUSSION

When a solution of 1b in acetone was irradiated and the ^1H-n.m.r. spectrum of the reaction mixture was immediately taken, a doublet at δ 3.75 was observed with a small coupling constant (J=1.7 Hz) and a triplet at δ 0.90, intensity ratio doublet/triplet 2 : 1. The high field position of the latter signal was considered as indicative for the presence of a compound with a three-membered ring[3,4], and was tentatively ascribed to H(6) of 2b. Tautomerism in the -N=C-NH-moiety

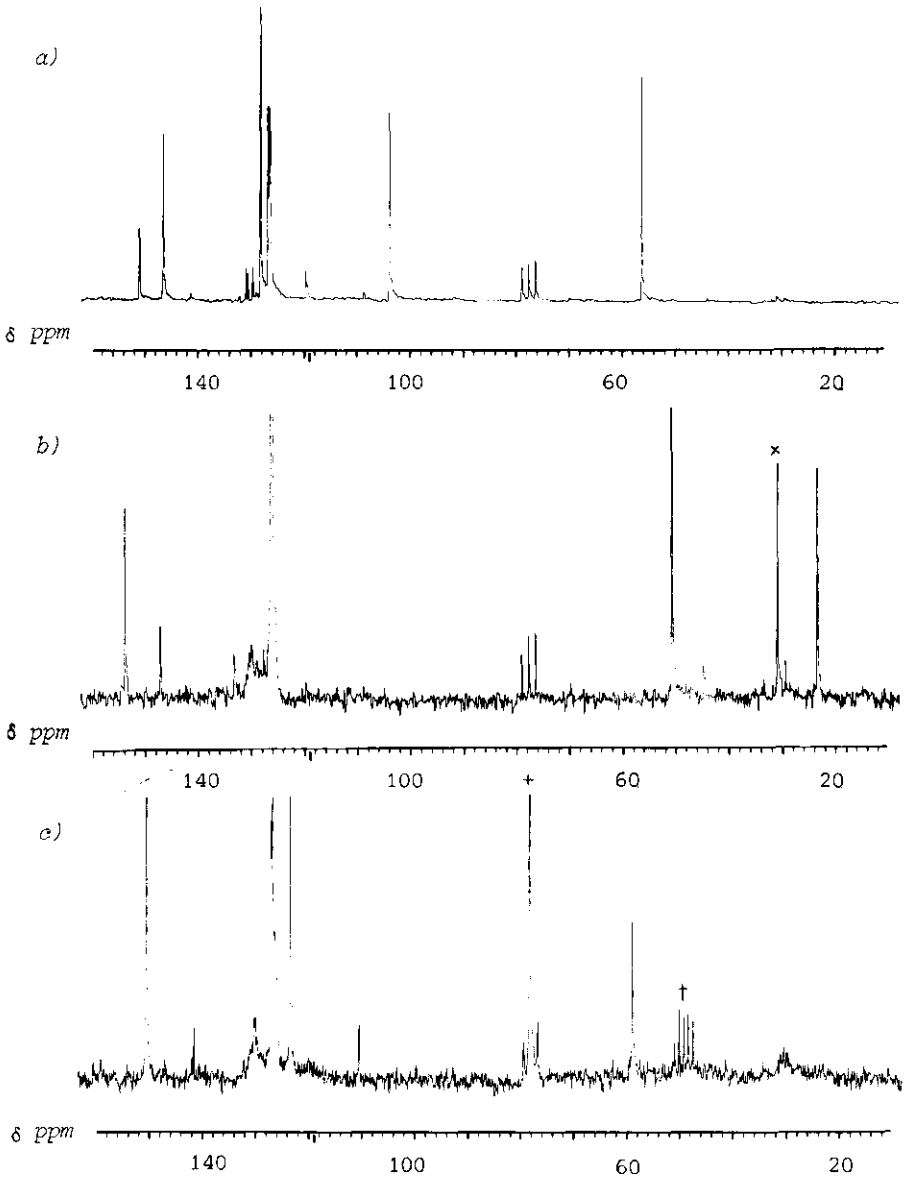

Fig.6.1 *proton decoupled ^{13}C-n.m.r. spectra of*
a) compound 1b; + = $CDCl_3$
b) irradiation mixture (2b); + = $CDCl_3$, x = acetone
c) after addition of KOH/CD_3OD (3b); + = $CDCl_3$/$CHCl_3$, † = CD_3OD

7.3 EXPERIMENTAL

General experimental conditions were as described in previous chapters. U.v. spectra were taken of solutions in 96% ethanol, i.r. spectra of solutions in $CHCl_3$ and n.m.r. spectra of solutions in $CDCl_3$ with TMS as the internal standard. Column chromatography was performed with Merck silica gel 60 (70-230 mesh ASTM) as the stationary phase.

7.3.1 Preparation of the 4-R-1,4(3,4)-dihydropyrimidines

4-(2-thiazolyl)-1,4(3,4)-dihydropyrimidine (1a). To a stirred solution of 23 mmol of 2-thiazolyllithium[25] at -70° a solution of 1.20 g (15 mmol) of pyrimidine in 20 ml of ether was added. The reaction mixture was warmed up to 0° and poured into a mixture of methanol and crushed ice. After separation the aqueous phase was extracted with chloroform (3 times). The combined organic layers were dried over magnesium sulfate, filtered and the solvents evaporated. The residual oil was subjected to column chromatography with a mixture of petroleum ether (b.r. 40-60°)/acetone/diethylamine 10:10:1 as the eluent. The eluent was gradually replaced by 5% diethylamine in acetone. Yield 1.35 g of brown oil[26](55%). ν_{max}: 3470, 3445 (sh), 3270, 1690 (sh), 1685, 1627 and 1585 cm^{-1}. λ_{max}: 240 and 294 nm (log ε 3.74 and 3.31). δ 7.64,d (H4'); 7.21,d (H5'); 7.11,s (H2); 6.08,d (H6); 5.50,d (H4) and 4.87,dd (H5). $J_{4',5'}$= 3.0, $J_{4,5}$= 3.0 and $J_{5,6}$= 7.5 Hz. Oxidation of 1a as reported in literature[25] gave 4-(2-thiazolyl)pyrimidine, m.p. 112°(lit.110°).

4-(2-pyridyl)-1,4(3,4)-dihydropyrimidine (1b). To a stirred solution of 23 mmol of 2-pyridyllithium[27] at -40° a solution of 1.00 g (12.5 mmol) of pyrimidine in 15 ml of ether was added. The resulting reaction mixture was stirred for 15 min and worked up as described above. The eluent for column chromatography was 5% of diethylamine in acetone and was gradually replaced by 5% of diethylamine in methanol. Yield 1.17 g of brown oil[26](60%). ν_{max}: 3470, 3445, 3220, 1685 (sh), 1680, 1638 and 1590 cm^{-1}. λ_{max}: 261 and 290 nm (sh)(log ε 3.70 and 3.23). δ 8.53,m (H6'); 7.83-7.05,m (H3',4',5'); 7.12,s (H2); 6.15,d (H6); 5.80,broad s (NH); 5.28,d (H4) and 4.83,dd (H5). $J_{4,5}$= 3.0, $J_{5.6}$= 7.5, $J_{3',6'}$= 1.0, $J_{4',6'}$= 1.3 and $J_{5',6'}$= 4.7 Hz. Oxidation of 1b with a solution of potassium permanganate in acetone gave 4-(2-pyridyl)pyrimidine[28], m.p. 76-78° (from petroleum ether, b.r. 60-80°. Found: C, 68,7; H, 4.4. $C_9H_7N_3$(157.17) requires C, 68.77; H, 4.49%). δ 9.23,d (H2); 8.81,d (H6); 8.67,m (H6'); 8.50,m (H3'); 8.33,dd (H5); 7.80,m (H4')

and 7.33,m (H5'). $J_{2,5}$= 1.4; $J_{5,6}$= 5.2; $J_{3',4'}$= 7.7; $J_{3',5'}$= 1.5; $J_{3',6'}$= 0.7; $J_{4',5'}$= 7.5; $J_{4',6'}$= 2.0 and $J_{5',6'}$= 4.5 Hz.

4-(4-pyridyl)-1,4(3,4)-dihydropyrimidine (1c). To a stirred solution of 14 mmol of 4-pyridyllithium[29] at -70° 1.12 g (14.0 mmol) of pyrimidine in 15 ml of ether was added. The resulting mixture was stirred for 15 min and worked up as described for compound 1b. Yield 0.52 g of yellow oil[26](23%). ν_{max}: 3470, 3450 (sh), 3200, 1690 (sh), 1685, 1640, 1605 and 1580 cm^{-1}. λ_{max} : 255 and 303 nm (log ε 3.57 and 3.19). δ 8.44,d (H2',6'); 7.22,d (H3',5'); 7.09,s (H2); 6.70,broad s (NH); 6.08, d (H6); 5.11,d (H4) and 4.57,dd (H5). $J_{4,5}$= 3.0; $J_{5,6}$= 7.5; $J_{2',3'}$= 5.5 Hz. Oxidation of 1c with a solution of potassium permanganate in acetone gave 4-(4-pyridyl)pyrimidine, m.p. 135-137° (from petroleum ether b.r. 60-80°. Found: C, 68.9; H, 4.4. $C_9H_7N_3$(157.17) requires C, 68.77; H, 4.49%). δ 9.33,s (H2); 8.86,d (H6); 8.77,d (H2',6'); 7.96,d (H3',5') and 7.80,dd (H5). $J_{2,5}$= 1.2, $J_{5,6}$= 5.0; $J_{2',3'}$= 5.5 Hz..

6-phenyl-4-(2-pyridyl)-1,4(3,4)-dihydropyrimidine (1d). To a stirred solution of 23 mmol of 2-pyridyllithium at -40° a solution of 1.56 g (10 mmol) of 4-phenyl-pyrimidine in 15 ml of ether was added. The resulting mixture was stirred for 15 min and worked up as described above. The eluent for column chromatography was a mixture of petroleum ether (b.r. 40-60°)/acetone/diethylamine 10:10:1 and was gradually replaced by a mixture of 5% of diethylamine in acetone. Yield 1.25 g of yellow oil[26](53%). ν_{max}: 3430; 3275; 1683; 1628; 1597 and 1583 cm^{-1}. λ_{max}: 239, 286 and 330 nm (sh)(log ε 4.21, 3.49 and 2.94). δ 8.45, broad d, (H6'); 7.70-7.20,m (H2,3',4',5',C_6H_5); 5.62,broad s (NH); 5.42,d (H4) and 5.26,d (H5). $J_{5',6'}$= 4.8; $J_{4,5}$= 3.5 Hz. Oxidation of 1d with a solution of potassium permanganate in acetone gave 6-phenyl-4-(2-pyridyl)pyrimidine, m.p. 107-109°(from petroleum ether b.r. 80-100°; lit.[30]102-3°. Found: C, 77.4; H, 5.0. $C_{15}H_{11}N_3$ (233.26) requires C, 77.23; H, 4.75%).δ 9.25,d (H2); 8.72,d (H5); 8.63,m (H6'); 8.44,m (H3'); 8.25,m (*ortho*-C_6H_5); 7.69,m (H4'); 7.40,m (*meta,para*-C_6H_5) and 7.23,m (H5'). $J_{2,5}$= 1.5; $J_{3',4'}$= 7.8; $J_{3',5'}$= 1.5; $J_{3',6'}$= 0.7; $J_{4',5'}$= 7.0; $J_{4',6'}$= 1.8; $J_{5',6'}$= 4.8 Hz.

6-phenyl-4-(2-pyridyl)-1,4(3,4)-dihydropyrimidine-5-d. 1.17 g (5.0 mmol) of 5-bromo-4-phenyl-1,4(3,4)-dihydropyrimidine[16,31] in chloroform was treated with D_2O. After separation of both layers the chloroform layer was dried over magnesium sulfate, filtered and then the solvent evaporated. The residue was dis-

solved in 6 ml of CH_3OD, 0.5 g of NaOH was added and the mixture was refluxed for 1 h. After cooling and addition of water the mixture was extracted with ether (2 times). The extracts were dried over magnesium sulfate, filtered and then the solvents evaporated. Column chromatography with a mixture of chloroform and ethyl acetate (4:1) gave 0.35 g (45%) of 4-phenylpyrimidine, which by mass spectroscopy was found to be monodeuterated for 69% and dideuterated for 5%. By ^{1}H-n.m.r. analysis it was established that position 5 was deuterated for 65-70%. This sample was treated with 2-pyridyllithium as described for the unlabelled compound.

7.3.2 Irradiations

Irradiations were performed in a Rayonet RPR-208 preparative photoreactor equipped with eight RUL 300 lamps at ambient temperature. Nitrogen was bubbled through solutions of 0.50 g of the appropriate 4-R-1,4(3,4)-dihydropyrimidine in 500 ml of acetone in a quartz vessel for 1 h before and during irradiation. Irradiations were carried out until all starting material had disappeared. The 4-substituted pyrimidines, obtained in the photolysis were identified by comparison of spectral data with those of reference samples. Oxidations were carried out with a solution of potassium permanganate in acetone.

Irradiation of 4-(2-thiazolyl)-1,4(3,4)-dihydropyrimidine (1a). The solution of 1a was irradiated for 80 min and after evaporation of the solvent the residue was subjected to column chromatography with ethyl acetate/methanol 9:1 as the eluent yielding 0.07 g (15%) of 4-(2-thiazolyl)pyrimidine and 0.24 g (48%) of 4(5)-(2-thiazolylmethyl)imidazole (2a), yellow oil. δ 9.77, broad s (NH); 7.61,d (H4'); 7.51,s (H2); 7.15,d (H5'); 6.88,s (H4 or 5) and 4.30,s (CH_2). $J_{4',5'}$ = 3.3 Hz. Dipicrate m.p. 192-195°(dec.)(from aqueous ethanol. Found: C, 36.7; H, 1.8. $C_{19}H_{13}N_9O_{14}S$ (623.43) requires C, 36.60; H, 2.10%). No 5-(2-thiazolyl)pyrimidine could be isolated.

Irradiation of 4-(2-pyridyl-1,4(3,4)-dihydropyrimidine (1b). The solution of 1b was irradiated for 1.5 h and after evaporation of the solvent the residue was subjected to column chromatography with ethyl acetate/methanol (9:1) as the eluent yielding 0.03 g (6%) of 4-(2-pyridyl)pyrimidine and 0.28 g (57%) of 4(5)-(2-pyridylmethyl)imidazole (2b), yellow oil. δ 9.80,broad s (NH); 8.40, broad d (H6'); 7.70-6.90,m (H2,3',4',5'); 6.76,s (H4 or 5) and 4.10, s (CH_2). Dipicrate m.p. 215-218°(dec.)(from aqueous ethanol. Found: C, 40.9; H, 2.2. $C_{21}H_{15}N_9O_{14}$(617.40) requires C, 40.85; H, 2.45%). In order to check the presence

of 5-(2-pyridyl)-1,2(2,3)-dihydropyrimidine the following experiment was carried out. An excess of a solution of potassium permanganate in acetone was added immediately. The resulting mixture was concentrated *in vacuo*, isopropanol was added and the solvents were evaporated. The resulting brown solid was extracted thoroughly with acetone and chloroform. These extracts were filtered and the solvents evaporated *in vacuo*. The residue was subjected to column chromatography. Elution with ethyl acetate gave 4-(2-pyridyl)pyrimidine (0.05 g, 10%) and 5-(2-pyridyl)pyrimidine (0.06 g, 12%), m.p. 135-136° (from petroleum ether b.r. 60-80°.Found: C, 68.7; H, 4.4. $C_9H_7N_3$(157.17) requires C, 68.77; H, 4.49%). δ 9.30,s (H4,6); 9.22,s (H2); 8.73,m (H6'); 7.80,m (H3',4') and 7.32,m (H5'). $J_{3',6'}$= 1.0; $J_{4',6'}$= 2.0; $J_{5',6'}$= 4.7 Hz. Elution with a mixture of ethyl acetate and methanol (9:1) gave 0.05 g (9%) of 2b.

Irradiation of 4-(4-pyridyl)-1,4(3,4)-dihydropyrimidine (1c). The solution of 1c was irradiated for 2 h and after evaporation of the solvent the residue was subjected to column chromatography. Elution with ethyl acetate yielded 0.11 g (22%) of 4-(4-pyridyl)pyrimidine. Elution with a mixture of ethyl acetate and methanol (4:1) gave 0.21 g (43%) of 4(5)-(4-pyridylmethyl)imidazole (2c), m.p. 134-135° (from benzene. Found: C, 68.2; H, 5.6. $C_9H_9N_3$(159.19) requires C, 67.90; H, 5.70%). δ 10,22,broad s (NH); 8.34,d (H2',6'); 7.49,s (H2); 7.10,d (H3',5'); 6.73,s (H4 or 5) and 3.90,s (CH_2). $J_{2',3'}$= 6.0 Hz. No 5-(4-pyridyl)pyrimidine could be isolated.

Irradiation of 6-phenyl-4-(2-pyridyl)-1,4(3,4)-dihydropyrimidine (1d). The solution of 1d was irradiated for 40 min and after evaporation of the solvent the residue was subjected to column chromatography with ethyl acetate/methanol 9:1 as the eluent, yielding 0.09 g (18%) of 6-phenyl-4-(2-pyridyl)pyrimidine and 0.25 g (50%) of 4(5)-phenyl-5(4)-(2-pyridylmethyl)imidazole (2d), yellow oil. δ 9.66,broad s (NH); 8.36,broad d (H6'); 7.60-6.80,m (H3',4',5',C_6H_5) and 4.25,s (CH_2). $J_{5',6'}$= 5.0 Hz. Dipicrate m.p. 223-225°(dec)(from aqueous ethanol. Found: C, 46.6; H, 2.6. $C_{27}H_{19}N_9O_{14}$(693.49) requires C, 46.76; H, 2.76%). No 4-phenyl-5-(2-pyridyl)pyrimidine could be isolated.

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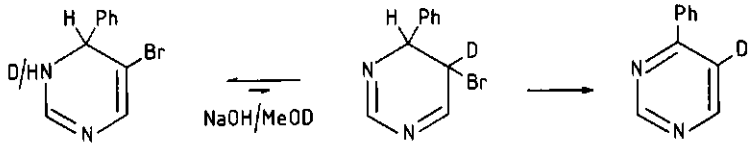
bromine exchange reaction with butyllithium and subsequent treatment with D_2O, since addition across the azomethine bond occurs instead of exchange. However, we observed an elimination of HBr from 5-bromo-4-phenyl-1,4(3,4)-dihydropyrimidine by treatment with NaOH. Presumably this elimination is preceeded by a tautomerization into the 4,5-dihydropyrimidine. In a deuterated solvent a deuterium atom is introduced into the 5-position and subsequent elimination gives 4-phenylpyrimidine-5-*d* as shown.



Scheme 7.3

8 GENERAL DISCUSSION

8.1 THERMAL REACTIONS

As shown in chapter 2 the addition of phenyllithium to pyrimidine (in ether) takes place mainly at C(4). The preference of nucleophiles for position 4 as compared to position 2 has been explained in chapter 1 on the basis of product stability. The regioselectivity in the pyrimidine ring can also be explained in terms of the energy barrier being higher for 2-attack than for 4-attack. The negative charge of the incoming nucleophile will experience in case of attack at C(2) the repulsion of the lone pairs of *two* nitrogen atoms and in case of attack at C(4) the repulsion of the lone pair of only *one* nitrogen atom[1]. Recently the coefficients of the LUMO of pyrimidine (*i.e.* the orbital that has to take up the incoming pair of electrons in case of a nucleophilic attack) have been calculated and found to be zero on position(s) 2 (and 5)[2]. So, if the nucleophilic attack is orbital controlled, position 2 is unfavourable. As mentioned briefly in chapter 2 we observed effects of solvent, temperature and substituents on the ratio 4-attack/2-attack. (See also table 8.1 and 8.2). It is not easy to understand - based on the arguments, given above - how these conditions can determine the ratio of addition on C(4) and C(2).

Table 8.1 Ratio of 4-attack/2-attack obtained in reactions of 2-furyllithium with pyrimidine in various solvent systems and temperatures

	hexane	ether/hexane	THF/hexane
0^{o}	49/51	75/25	97/3
-40^{o}	68/32	-	-
-70^{o}	-	81/19	92/18

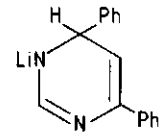
To our knowledge effects of solvent and temperature have not been the subject of a detailed study. Since we were mainly interested in the *preparation* of the 4-substituted 1,4(3,4)-dihydropyrimidines, these effects have not been studied systematically by us either.

Table 8.2 Ratio of 4(6)-attack/2-attack in reactions of RLi with 4(6)-phenylpyrimidine[*]

R	ratio 4/2	solvent	temp.
phenyl	91/9	ether	0^{o}
methyl	74/26	ether	0^{o}
2-thienyl	79/21	hexane/ether	20^{o}
3-thienyl	68/32	hexane/ether	-50^{o}

[*]Reactions of these organolithium compounds with pyrimidine gave no 2-attack (*i.e.* ratio 4/2 > 95/5)

The phenyllithium-diazine adducts 1-3 were characterized by n.m.r. spectroscopy. It was expected that the reactions of electrophilic reagents with these adducts would lead to C- and/or N-substituted products depending on the nature of the electrophile (hard or soft)(as was observed with the organolithium-pyridine adducts)[3,4] and charge density at the various positions. From reactions of 1 and 2 (R=Me) with electrophiles EX, however, only N-substituted dihydrodiazines 4 and 5 respectively were obtained. The phenyllithium-pyrazine adduct (3) upon reaction with methyliodide (soft) gave C-substituted product 6. With methyl chloroformate and other carbonyl compounds only high molecular weight products were obtained. A relation between the position of electrophilic attack and the 'softness' or 'hardness' of the reagent could not be established.



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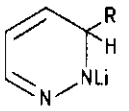

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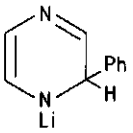

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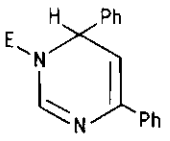

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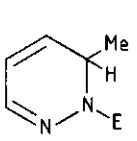

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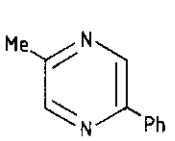


6

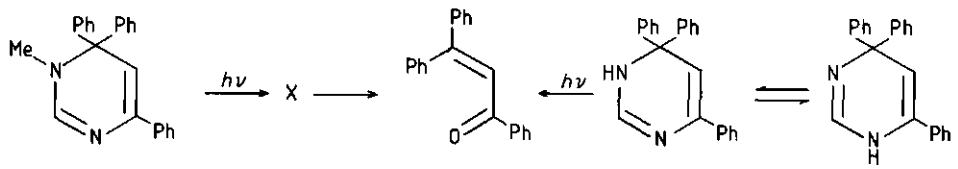
Scheme 8.1

8.2 PHOTOCHEMICAL REACTIONS

As mentioned in the introduction dihydro(di)azines showed several types of reaction under photolytic conditions (dimerization, internal 2+2 cycloaddition, ring opening). When the ring opening was followed by a photochemical 4+2 cycloaddition a (di)azabicyclo [3.1.0] hexene was formed and a reorganization of the atoms of the six-membered ring occurred (sect.1.3.2). In the preceding chapters we have shown that dihydropyrimidines behave differently. 4-R-1,4(3,4)-dihydropyrimidines undergo di-π-methane rearrangement, a reaction type not observed before with dihydrodiazines. A diazabicyclo [3.1.0] hexene is formed *without* reorganization of the atoms of the six-membered ring.

Some questions have remained unanswered. In this section we wish to pay some attention to two important questions i) which dihydropyrimidine (1,4- or 3,4-) is able to undergo di-π-methane rearrangement as described in chapters 4-7 and ii) why do 4-(2-thienyl)- and 4-(2-furyl)-dihydropyrimidine rearrange faster into the 5-substituted 1,2(2,3)-dihydropyrimidine than the 4-(3-thienyl)- and 4-(1-methyl-2-pyrrolyl) derivatives.

We attempted to obtain some insight into the first question by irradiating 3-methyl-4,4,6-triphenyl-3,4-dihydropyrimidine (7). After irradiation and subsequent evaporation of the solvent a product X was obtained. The n.m.r. spectrum of X showed the absence of an N-methyl moiety. Along with the signal of the aromatic protons only a singlet at δ 6.93 was observed. By column chromatography only one product was isolated (45%). The mass spectrum of this compound appeared to be identical to the mass spectrum of an authentic sample of β-phenylchalcone (8)[5]. We have not been able to identify the unstable intermediate X, but from



7 8 9 9

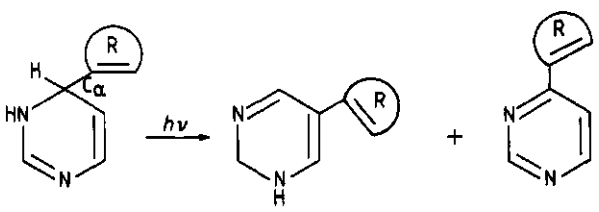
Scheme 8.2

the structure of the final product 8 we could deduce that 7 had not undergone a di-π-methane rearrangement, for this rearrangement would never have led to a product in which two phenyl groups were attached to one carbon atom. It seems likely that of the two tautomeric dihydropyrimidines present in the solutions

of the N-unsubstituted dihydropyrimidines it is only the 1,4-dihydro tautomer that undergoes the di-π-methane rearrangement.
It is evident that the 3,4-dihydro tautomer is photochemically not inert, since photolysis of 4,4,6-triphenyl-1,4(3,4)-dihydropyrimidine (9 ⇌ 9') also yielded compound 8 (chapter 4). Irradiation of the structurally related 4,6-diphenyl-3-methyl-3,4-dihydropyrimidine gave only polymeric material, indicating that 3,4-dihydropyrimidines with only one substituent in position 4, polymerize upon irradiation. This explains the generally low yields and large amounts of tarry products obtained from irradiation of 4-R-1,4(3,4)-dihydropyrimidines.

Regarding the problem of the divergent rates of di-π-methane rearrangement of 4-heteroaryl-1,4(3,4)-dihydropyrimidines (10) we collected irradiation times required to obtain complete conversion of substrates 10a-d in table 8.3.

a R = 2-thienyl
b R = 3-thienyl
c R = 2-furyl
d R = 1-methyl-2-pyrrolyl



10 11 12

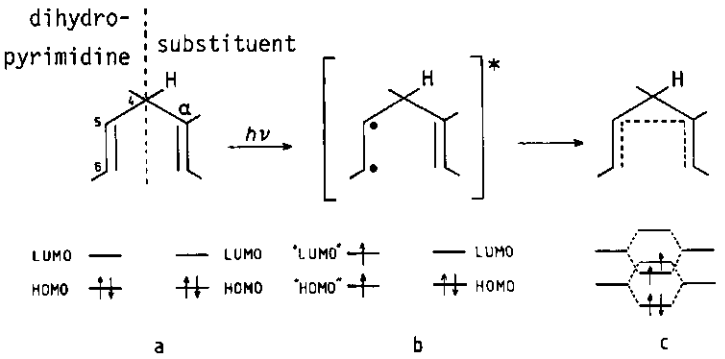
Scheme 8.3

Table 8.3 Irradiation time and yields in photolysis of compounds 10a-d

starting material	irradiation time (h)[a]	yield (%) of compound 11	yield (%) of compound 12
10a	1.3	39	9
10b	6.5	6	28
10c	1.6	20	6
10d	6.9	2	27

a) from sect.5.3.2, concentration corrected

The less efficient di-π-methane rearrangement of the 3-thienyl derivative 10b as compared to its 2-thienyl isomer 10a (in the former case the di-π-methane rearrangement is so slow that the rate of conversion seems to be determined by other processes) may be explained using a very simple model[6], constructed from the molecular orbitals (M.O.'s) of the di-π-methane system in the molecule as shown.



a. ground state
b. non interacting excited state
c. interaction

Fig. 8.1

The 4-R-1,4(3,4)-dihydropyrimidines investigated contain two isolated π-systems connected *via* the sp^3 carbon atom 4[7]. Upon irradiation only the dihydropyrimidine part of the molecule is excited (the triplet energy of acetone, 78-82 kcal/mol.[8] is not sufficient to excite the substituent, *e.g.* benzene E_T= 84.3[8]; thiophene 86.4; furan 92.0 and pyrrole 97.0 kcal/mol [9]).
Thus, by absorption of a photon an electron is promoted from the HOMO into the LUMO of the dihydropyrimidine part of the molecule. On bridging, the HOMO and the LUMO of the substituent in its ground state combine with the 'HOMO' and 'LUMO' respectively of the dihydropyrimidine part[10]. When the coefficients of the interacting orbitals at the bridging centra, *i.e.* C(5) of the dihydropyrimidine part and the carbon atom of the substituent C(α) that is attached to the sp^3 carbon atom, are large, an efficient bridging can occur and a fast rearrangement will be the result[11]. Since the coefficients of the dihydropyrimidine part in the thienyl compounds 10a and 10b are identical it suffices to compare the coefficients of the HOMO and LUMO on the 2-position and the 3-position of the thiophene ring (table 8.4).

Table 8.4 Coefficients of the frontier orbitals of thiophene, furan and pyrrole

		HOMO	LUMO
thiophene[12]	c_2	0.57	-0.66
	c_3	0.36	0.37
furan[13]	c_2	0.57	-0.67
	c_3	0.38	0.40
pyrrole[14]	c_2	0.60	-0.58
	c_3	0.37	0.27

Both in the HOMO and LUMO the coefficient on C(2) is larger than the coefficient on C(3) which might be the explanation for the enhanced rate of conversion of 10a in comparison to 10b.

The coefficients of the frontier orbitals on C(2) in furan are not very different from those on C(2) in thiophene and it can be expected - and in fact is observed - that 10c reacts with a similar conversion rate as 10a.

As can be seen from table 8.3 the 1-methyl-2-pyrrolyl derivative 10d also showed an inefficient di-π-methane rearrangement. The coefficients of the HOMO and LUMO in 2-position of pyrrole are of the same order as those on C(2) in thiophene. Since the N-methyl group will not have this great effect on the coefficients it appears that in this case there is no correlation between the magnitude of these coefficients and the observed low efficiency of the bridging process. We conclude therefore that the model as described above is too simple to account for this behaviour. A recent investigation of the quantum yields of several substituted di-π-methane systems led to the assumption that there exists a balance between diradical and charge transfer[15] character on initial bonding. If the extent of charge transfer is great, efficient non-radiative relaxation of the 'zwitterion' to the ground state molecule takes place, resulting in low quantum yields for the di-π-methane rearrangement. A correlation of rearrangement efficiency and ionization potentials (IP's) of the π-systems,being a measure for the occurrence of charge transfer[15], was found. In our dihydropyrimidines 10a-d such a correlation is found too. The IP's of furan (8.77-9.06 eV) and thiophene

(8.91 eV) are higher than the IP of pyrrole (8.20-8.22 eV). Consequently the contribution of a charge transfer process to the initial bonding in 10d might be larger, leading to a lower quantum yield for rearrangement.

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SUMMARY

This thesis describes the results of an investigation into the thermal and photochemical reactivity of dihydrodiazines.

In order to prepare the title compounds the diazines and some phenyldiazines are treated with phenyllithium in ether, yielding adducts resulting from attack of phenyllithium on the various positions of the heteroaromatic ring. With pyrimidine addition takes place mainly at C(4), with pyridazine at C(3). By using TMEDA, addition at C(2) in 4-phenylpyrimidine and at C(4) in pyridazine is strongly promoted. The structure of the adducts is studied by n.m.r. spectroscopy. The charge distribution pattern in the C(4)-adduct of pyrimidine and in both the C(3)-adduct and the C(4)-adduct of pyridazine is determined by comparing the carbon chemical shifts of these compounds with those of the corresponding dihydrodiazines obtained by hydrolysis of the adducts. C(5) in the phenyllithium-pyrimidine adduct carries little negative charge, C(4) in the phenyllithium-pyridazine adduct has a considerable amount of charge while the charge density at C(6) in the 3-adduct and both C(3) and C(5) in the 4-adduct of pyridazine is moderate.

Some organolithium-diazine adducts and some dihydropyrimidines are treated with electrophilic reagents. Both 4,6-diphenyl-1(3)-lithio-1,4(3,4)-dihydropyrimidine and 4,6-diphenyl-1,4(3,4)-dihydropyrimidine are attacked by the electrophilic reagent (methyliodide, methyl chloroformate) at N(3), yielding 4,6-diphenyl-3-methyl(methoxycarbonyl)-3,4-dihydropyrimidine. 4,4,6-Triphenyl-1,4(3,4)-dihydropyrimidine gives upon treatment with methyliodide mainly 3-methyl-4,4,6-triphenyl-3,4-dihydropyrimidine. The 3,4-dihydro structure of the products is established both spectroscopically and chemically. Reaction of 2-lithio-3-methyl-2,3-dihydropyridazine with methyliodide (methyl chloroformate, tosylchloride) gives the corresponding 2,3-dimethyl-(2-methoxycarbonyl-3-methyl-, 2-tosyl-3-methyl-)2,3-dihydropyridazine. 1-Lithio-2-phenyl-1,2-dihydropyrazine yields upon treatment with methyliodide 5-methyl-2-phenylpyrazine. Reaction with carbonyl compounds only yields high molecular material.

Photolysis of 4-R-1,4(3,4)-dihydropyrimidines causes rearrangement to 5-R-1,2(2,3)-dihydropyrimidines, provided that the substituent R contains a π-bond in α position to the heterocyclic ring (R=phenyl,isobutenyl,phenylethynyl). 4-Methyl-1,4(3,4)-

dihydropyrimidine does not show this rearrangement. Chemical evidence is presented that the rearrangement occurs *via* the di-π-methane mechanism leading to 6-R-2,4-diazabicyclo [3.1.0] hex-2(3)-ene. This latter intermediate undergoes a thermal homo [1,5] hydrogen shift into 5-R-2,5-dihydropyrimidine which on tautomerization gives the final product. The reaction can be sensitized by acetone. 4,5-Diphenyl-, 5-methyl-4-phenyl- and 5-bromo-4-phenyl-1,4(3,4)-dihydropyrimidine do not rearrange under photochemical conditions.

Several 4-R-1,4(3,4)-dihydropyrimidines (R=2- or 3-thienyl,2-furyl, 1-methyl-2-pyrrolyl and 3-pyridyl) containing heteroaryl vinyl methane moieties undergo photochemical rearrangement into 5-R-1,2(2,3)-dihydropyrimidines. Oxidation of these compounds yield 5-heteroarylpyrimidines. The chemical yields are strongly dependent of the nature of the heteroaryl group.

The existence of a 6-R-2,4-diazabicyclo [3.1.0] hex-2(3)-ene as an intermediate in the photoisomerization of 4-R-1,4(3,4)-dihydropyrimidines into 5-R-1,2(2,3)-dihydropyrimidines is confirmed spectroscopically in case R= *p*-trifluoromethylphenyl. It is established that the *p*-trifluoromethylphenyl group is in *exo* position in the bicyclic compound. 6-*Exo*-(*p*-trifluoromethylphenyl)-2,4-diazabicyclo [3.1.0] hex-2(3)-ene immediately gives 5-(*p*-trifluoromethylphenyl)-1,2(2,3)-dihydropyrimidine upon addition of potassium hydroxide in methanol.

Photolysis of 4-R-1,4(3,4)-dihydropyrimidines causes ring contraction into imidazoles, provided that the substituent R is sufficiently capable of stabilizing an anionic centre (R=2-thiazolyl and 2- or 4-pyridyl). Chemical evidence is presented that the ring contraction of 6-phenyl-4-(2-pyridyl)-1,4(3,4)-dihydropyrimidine occurs *via* heterolytic fission of the C(1)-C(6) bond of intermediate 1-phenyl-6-(2-pyridyl)-2,4-diazabicyclo [3.1.0] hex-2(3)-ene. The anion stabilizing effect of R is correlated with the acid strength (pKa) of $R\text{-}CH_3$. A pKa value around 30 determines the border-line between ring contraction into an imidazole and formation of an isomeric 5-R-1,2(2,3)-dihydropyrimidine.

SAMENVATTING

In dit proefschrift worden de resultaten beschreven van een onderzoek naar de thermische en fotochemische reactiviteit van dihydrodiazinen.

Ter bereiding van de titelverbindingen zijn de diazinen en enige fenylgesubstitueerde diazinen behandeld met fenyllithium in ether. Hierbij worden adducten gevormd door aanval van fenyllithium op de verschillende posities in de heterocyclische ring. Bij pyrimidine treedt voornamelijk additie aan C(4) op, bij pyridazine aan C(3). Door TMEDA toe te voegen neemt additie aan C(2) in 4-fenylpyrimidine en aan C(4) in pyridazine sterk toe. De n.m.r. spectra van de adducten en van de overeenkomstige dihydrodiazinen - verkregen door hydrolyse van de adducten- worden beschreven. De vergelijking van de chemische verschuivingen van de koolstofatomen in de adducten met die van de koolstofatomen in de overeenkomstige dihydrodiazinen levert de ladingsverdeling in de adducten. C(5) in het fenyllithium-pyrimidine adduct draagt nauwelijks lading. C(4) in het 3-adduct van pyridazine draagt een aanmerkelijke hoeveelheid lading, terwijl de ladingsdichtheid op C(6) in het 3-adduct en zowel C(3) als C(5) in het 4-adduct van pyridazine er tussenin ligt.

Enige organolithium-diazine adducten, alsmede enige dihydropyrimidinen zijn behandeld met elektrofiele reagentia. Zowel bij 4,6-difenyl-1(3)-lithio-1,4(3,4)-dihydropyrimidine als bij 4,6-difenyl-1,4(3,4)-dihydropyrimidine treedt aanval op van het elektrofiele reagens (methyliodide, methyl chloorformiaat) op N(3), waarbij 4,6-difenyl-3-methyl(methoxycarbonyl)-3,4-dihydropyrimidine ontstaat. 4,4,6-Trifenyl-1,4(3,4)-dihydropyrimidine levert door de behandeling met methyliodide voornamelijk 3-methyl-4,4,6-trifenyl-3,4-dihydropyrimidine. De 3,4-dihydropyrimidine structuur van de produkten wordt zowel spectroscopisch als chemisch bewezen. Reactie van 2-lithio-3-methyl-2,3-dihydropyridazine met methyliodide (methyl chloorformiaat, tosylchloride) levert de overeenkomstige 2,3-dimethyl-(2-methoxycarbonyl-3-methyl-, 2-tosyl-3-methyl-)2,3-dihydropyridazine. 1-Lithio-2-fenyl-1,2-dihydropyrazine levert door reactie met methyliodide 2-fenyl-5-methylpyrazine. Met carbonylverbindingen wordt alleen hoogmoleculair materiaal verkregen.

Fotolyse van 4-R-1,4(3,4)-dihydropyrimidinen veroorzaakt omlegging naar 5-R-

1,2(2,3)-dihydropyrimidinen, vooropgesteld dat de substituent R een π-binding bevat in α-positie ten opzichte van de hetero-ring (R=fenyl, isobutenyl en fenylethynyl). 4-Methyl-1,4(3,4)-dihydropyrimidine vertoont deze omlegging niet. Chemisch bewijs wordt geleverd dat de omlegging verloopt volgens het di-π-methaan mechanisme, waarbij 6-R-2,4-diazabicyclo [3.1.0] hex-2(3)-een als intermediair optreedt. Dit intermediar ondergaat een thermische homo [1.5] waterstofverschuiving tot 5-R-2,5-dihydropyrimidine; tautomerisatie hiervan levert het uiteindelijke waargenomen produkt. De reactie kan gesensibiliseerd worden door aceton. 4,5-Difenyl-, 4-fenyl-5-methyl- en 5-broom-4-fenyl-1,4(3,4)-dihydropyrimidine leggen niet om onder fotochemische condities.

Verscheidene 4-R-1,4(3,4)-dihydropyrimidinen (R=2- of 3-thienyl, 2-furyl, 1-methyl-2-pyrrolyl en 3-pyridyl), met heteroaryl vinyl methaan fragmenten ondergaan fotochemische omlegging naar 5-R-1,4(3,4)-dihydropyrimidine. Oxidatie van deze verbindingen levert 5-heteroarylpyrimidinen. De chemische opbrengsten van de fotoisomerisatie zijn sterk afhankelijk van de aard van de heteroaryl groep.

Het optreden van een 6-R-2,4-diazabicyclo [3.1.0] hex-2(3)-een als intermediair in de fotoisomerisatie van 4-R-1,4(3,4)-dihydropyrimidine naar 5-R-(1,2(2,3)-dihydropyrimidine wordt spectroscopisch aangetoond in het geval R = *p*-trifluormethylfenyl. Tevens wordt vastgesteld dat de *p*-trifluormethylfenylgroep de *exo* positie inneemt in het bicyclische intermediair. 6-*Exo*-(*p*-trifluormethylfenyl)-2,4-diazabicyclo [3.1.0] hex-2(3)-een levert onmiddellijk 5-(*p*-trifluormethylfenyl)-1,2(2,3)-dihydropyrimidine door toevoeging van KOH in methanol.

Fotolyse van 4-R-1,4(3,4)-dihydropyrimidinen veroorzaakt ring contractie tot imidazolen, vooropgesteld dat de substituent voldoende in staat is een anionisch centrum te stabiliseren (R=2-thiazolyl en 2- of 4-pyridyl). Chemisch bewijs wordt geleverd dat de ring contractie van 6-fenyl-4-(2-pyridyl)-1,4(3,4)-dihydropyrimidine verloopt *via* heterolytische breuk van de C(1)-C(6) binding van intermediair 1-fenyl-6-(2-pyridyl)-2,4-diazabicyclo [3.1.0] hex-2(3)-een. Het anion stabiliserende effect van de groep R wordt gecorreleerd met de zuursterkte (pKa) van $R\text{-}CH_3$. Een pKa waarde van omstreeks 30 bepaalt de grens tussen ring contractie tot een imidazool en de vorming van een isomere 5-R-1,2(2,3)-dihydropyrimidine.

CURRICULUM VITAE

Na het behalen van het eindexamen HBS-B aan het Chr. Lyceum te Dordrecht in 1969, begon ik in september van dat jaar met een studie in de scheikunde aan de Technische Hogeschool te Delft.
Het kandidaatsexamen (richting 3) werd in maart 1973 afgelegd. De studie werd voortgezet onder leiding van Prof.Dr.Ir. H.van Bekkum en Prof.Dr.H.C. Beyerman (organische chemie) en Dr.Ir.H.C.A.van Beek (chemische technologie). Het doctoraalexamen werd afgelegd in november 1974.
Sinds december 1974 ben ik als wetenschappelijk medewerker werkzaam op het Laboratorium voor Organische Chemie van de Landbouwhogeschool te Wageningen, alwaar het in dit proefschrift beschreven onderzoek werd verricht. Daarnaast verleende ik assistentie op practica voor studenten in de KA en KB fase.