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ENAMINES; Part. 48[1]. 3,4-DIHYDROQUINAZOLINES FROM ENAMINES AND S,S-DIMETHYL-N-(N-ARYLBENZIMIDOYL)SULFIMIDES.

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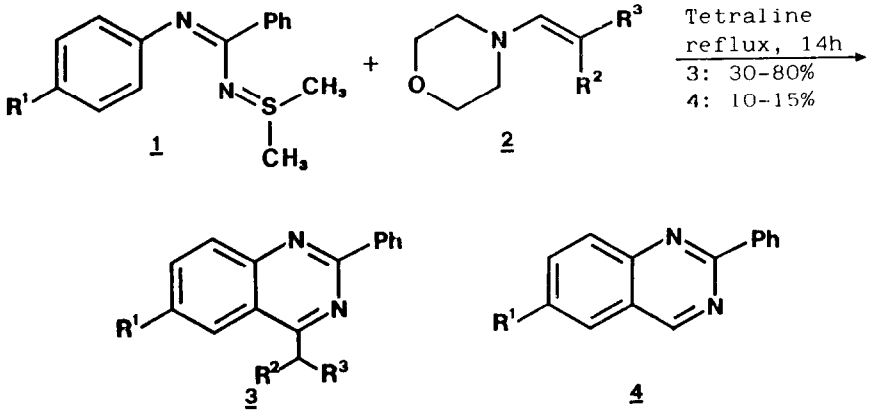
Abstract. Treatment of S,S-dimethyl-N-(N-arylbenzimidoyl)sulfimides with enamines derived from ketones gives 4,4-disubstituted-2-phenyl-3,4-dihydro quinazolines. The reaction involves an 1,3-diaza-1,3-diene intermediate which undergo electrocyclic ring closure to give the final products.

In a recent paper[1] we reported a new synthesis of quinazolines by reaction of S,S-dimethyl-N-(N-arylbenzimidoyl)sulfimides **1** with enamines **2** derived from aldehydes, SCHEME 1.



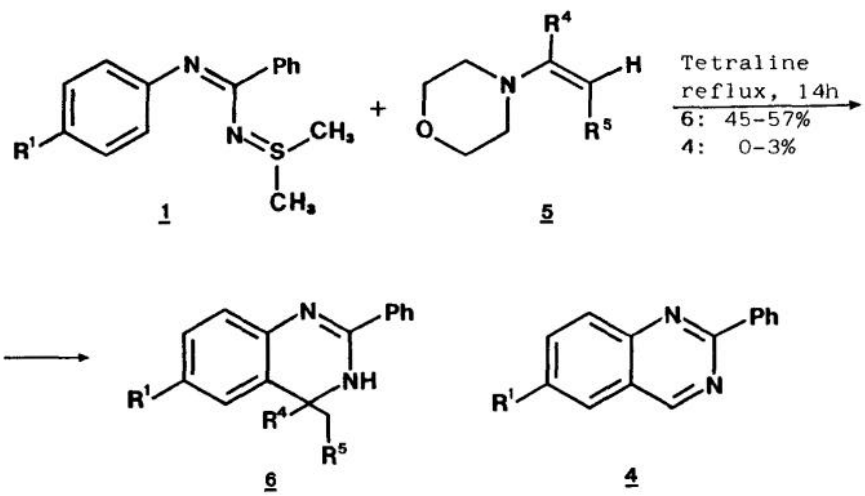
SCHEME 1

The formation of the 4-alkylquinazolines **3** was tentatively explained as involving a thermal cleavage of the imidoylsulfimides **1** into the corresponding imidoylnitrenes and dimethyl sulfide. Nitrene insertion on the enamine double bond and subsequent rearrangement of the aziridine intermediate thus formed would give the final product **3**[1].
The formation of the by-product **4** involves a known intramolecular rearrangement of the benzimidoylsulfimides employed[2].

Since it is well known that the reactivity of the enamines is strongly dependent upon the substituents on the double bond[3,4,5] we wanted to investigate the behaviour of the enamines **5** derived from ketones and bearing at the α-carbon atom a substituent different from hydrogen. The aim of this research was also to explore the synthetic potential of the reaction between sulfimides and enamines and to deepen our knowledge of the mechanism involved.

RESULTS

The reaction of benzimidoylsulfimides **1** with enamines **5** (SCHEME 2) was performed in boiling tetraline using three equivalents of enamines **5**. The crude mixture gave, after chromatographic purification over silica gel, the 4,4- disubstituted-2-phenyl-3,4-dihydro quinazolines **6a-f** as well as small amounts (0-3%) of the 4-unsubstituted quinazolines **4a** ($R'=CH_3$) and **4b** ($R'=OCH_3$).



1a: $R^1=CH_3$
1b: $R^1=OCH_3$

5	R^4	R^5
a	C_6H_5	H
b	C_2H_5	CH_3
c	$-(CH_2)_3-$	
d	$-(CH_2)_4-$	

6	R^1	R^4	R^5
a	CH_3	C_6H_5	H
b	CH_3	C_2H_5	CH_3
c	CH_3	$-(CH_2)_3-$	
d	CH_3	$-(CH_2)_4-$	
e	OCH_3	C_6H_5	H
f	OCH_3	$-(CH_2)_4-$	

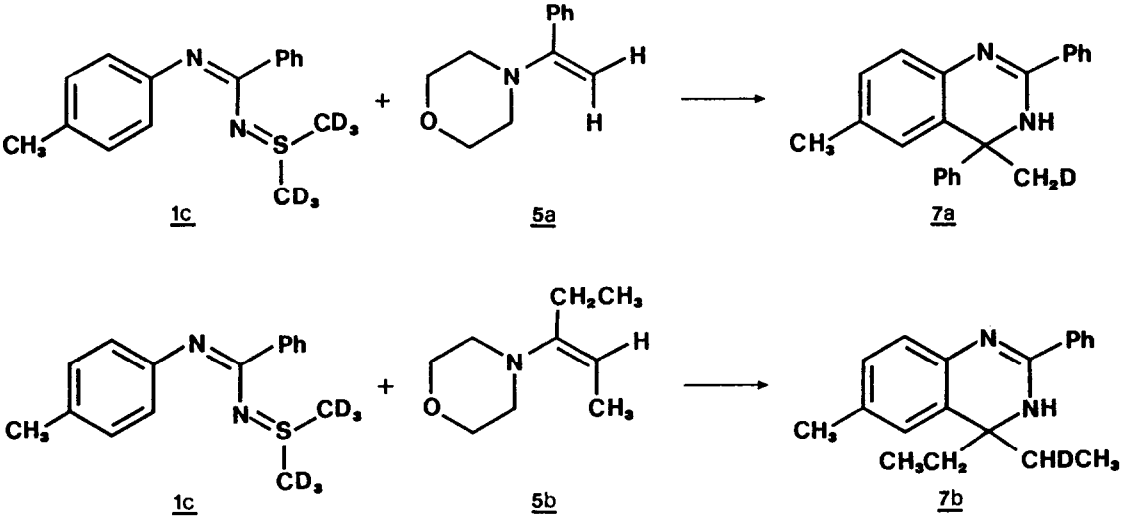
SCHEME 2

Compounds 6 prepared and their relevant physico-chemical properties are listed in Table 1; for data of compounds 4 see Ref. 1.

The stoichiometry of the reaction depicted in SCHEME 2 deserves particular attention. Actually, the reaction products **6a-f** contain an atom of hydrgen in excess compared to the sulfimide **1** and to the enamine 5. The hydrogen in excess is exactly located, in the final products **6a-f**, on the ß-carbon atom of the enamine moiety. This experimental result was not in agreement with the proposed mechanism, but suggested that a donor of hydrogen was present in the reaction mixture. The most likely donor of hydrogen was, in our opinion, the dimethylthio group of the sulfimide **1**.

In order to verify this hypothesis and to achieve a better understanding of the mechanism of the quinazoline ring formation we synthesized the S,S-hexadeuterodimethyl-N-[N-(4-methylphenyl)benzimidoyl] sulfimide **1c**.

The sulfimide **1c** was reacted with morpholinoenamines **5a** and **5b** derived from acetophenone and 3-pentanone respectively. The reaction conditions were the same as those described above and the usual work up of the reaction mixture resulted in the isolation of compounds **7a** and **7b**, respectively, as the sole reaction products, SCHEME 3.



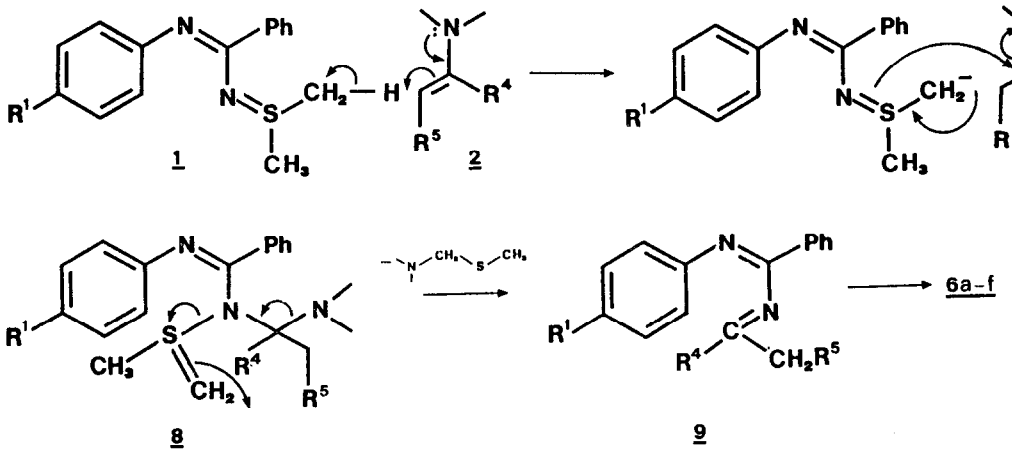
SCHEME 3

The structure of **7a** and **7b** was assigned as 2,4-diphenyl-6-methyl-4-monodeuteromethyl-3,4-dihydroquinazoline and 4-ethyl-4-(1-monodeuteroethyl)-6-methyl-2-phenyl-3,4-dihydroquinazoline, respectively, on the basis of MS and NMR data. EI mass spectra confirmed the presence of one deuterium atom

in each product with molecular ions at 313 m/z for **7a** and at 279 m/z for **7b**. The exact location of the deuterium atom was determined by NMR spectra: the ^{13}C-NMR spectra of compound **7a**, recorded at 200 MHz in total decoupling mode, shows a triplet centered at 29.7 ppm which agrees in multiplicity and chemical shift with the CH_2D carbon atom. The ^{1}H-NMR spectra of compound **7b**, recorded at 200 MHz, shows at 1.64 and 1.94 ppm two multiplets (six broad lines and 1.5 hydrogen each) that can be attributed to the CH_2 / CHD system.

DISCUSSION

The mechanism proposed for the reaction between S,S-dimethyl-N-(N-arylbenzimidoyl)sulfimides **1** and enamines **5** is depicted in SCHEME 4[6].



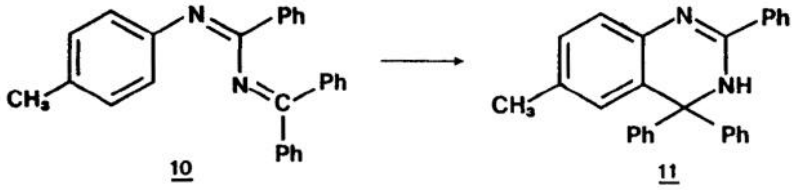
SCHEME 4

In the first step the enamine **5** removes a proton from the methylthio group of the sulfimide **1**. The iminium salt thus formed can undergo a nucleophilic addition reaction that results in the formation of the intermediate **8**. Afterwards the intermediate **8** evolves by intramolecular elimination of morpholino4- [(methylthio)methyl] to give the 1,3-diaza-1,3-diene **9**. Quinazoline **6** may then be formed by electrocyclic ring closure.

The deuterated products **7a** and **7b** obtained when enamines **5a** and **5b** were allowed to react whith the S,S-hexadeutero dimethyl-N-[N-(4-methylphenyl) benzimidoyl]sulfimide **1c** support the proposed mechanism.

Further, the capability of the 1,3-diaza-1,3-diene system **9** to undergo electrocyclic ring closure was proved through an alternative synthesis. We

prepared the N-diphenylmethylene-N'-(4-methylphenyl)-benzamidine **10** as described in Ref. 7; this diene derivative when heated in tetraline at reflux give quantitatively the 6-methyl-2,4,4-triphenyl-3,4-dihydroquinazoline **11**, SCHEME 5.

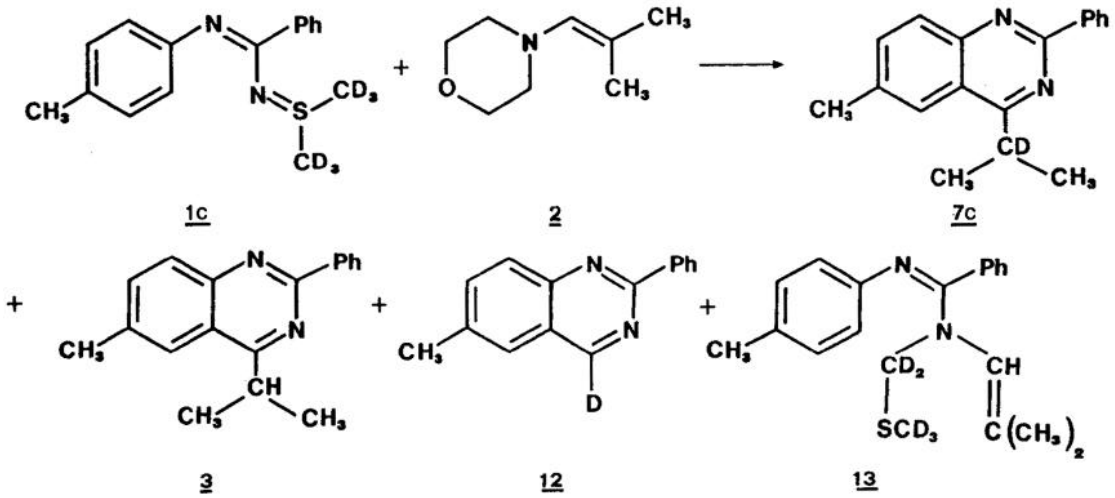


10 **11**

SCHEME 5

Taking into consideration these results we wanted to extend our finding to the reaction between S,S-dimethyl-N-(N-arylbenzimidoyl)sulfimides 1 and enamines 2 derived from aldehydes.

In order to verify if also in this case the reaction pathway was the same of those described in SCHEME 4 for the reaction between sulfimides 1 and enamines 5 derived from ketones, we performed the reaction with the hexadeuterosulfimide 1c using in this case the enamine 2 derived from isopropanal; the results are summarized in SCHEME 6.



1c **2** **7c**

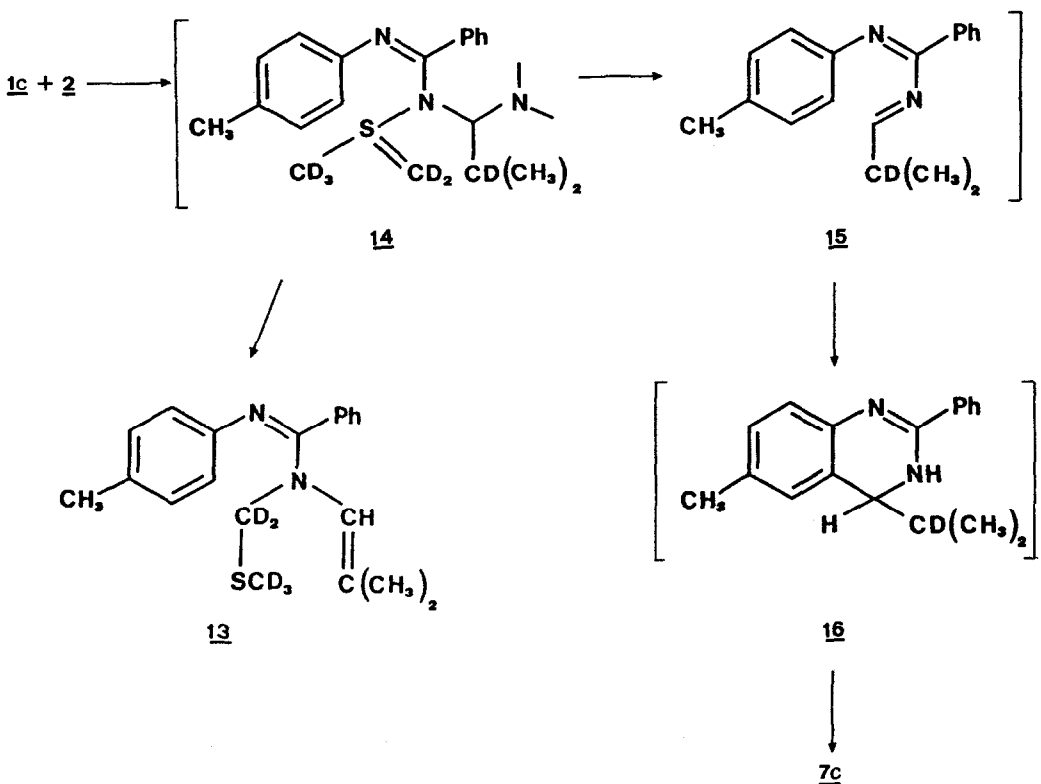
3 **12** **13**

SCHEME 6

The expected 4-alkylquinazoline was deuterated, at the 4-alkyl substituent, only to the extent of 77% , as demonstrated by the analysis of the ^{1}H-NMR spectrum recorded at 200 MHz. Besides this product, it was possible to isolate the 4-deutero-6-methyl-2-phenylquinazoline **12** (4%) and a new

compound (13, 9%). The structure of 13 was assigned as N-isobutenyl-N-(methylthiomethyl-d_5)-N'-(4-methylphenyl)benzamidine on the basis of analytical and spectral properties.

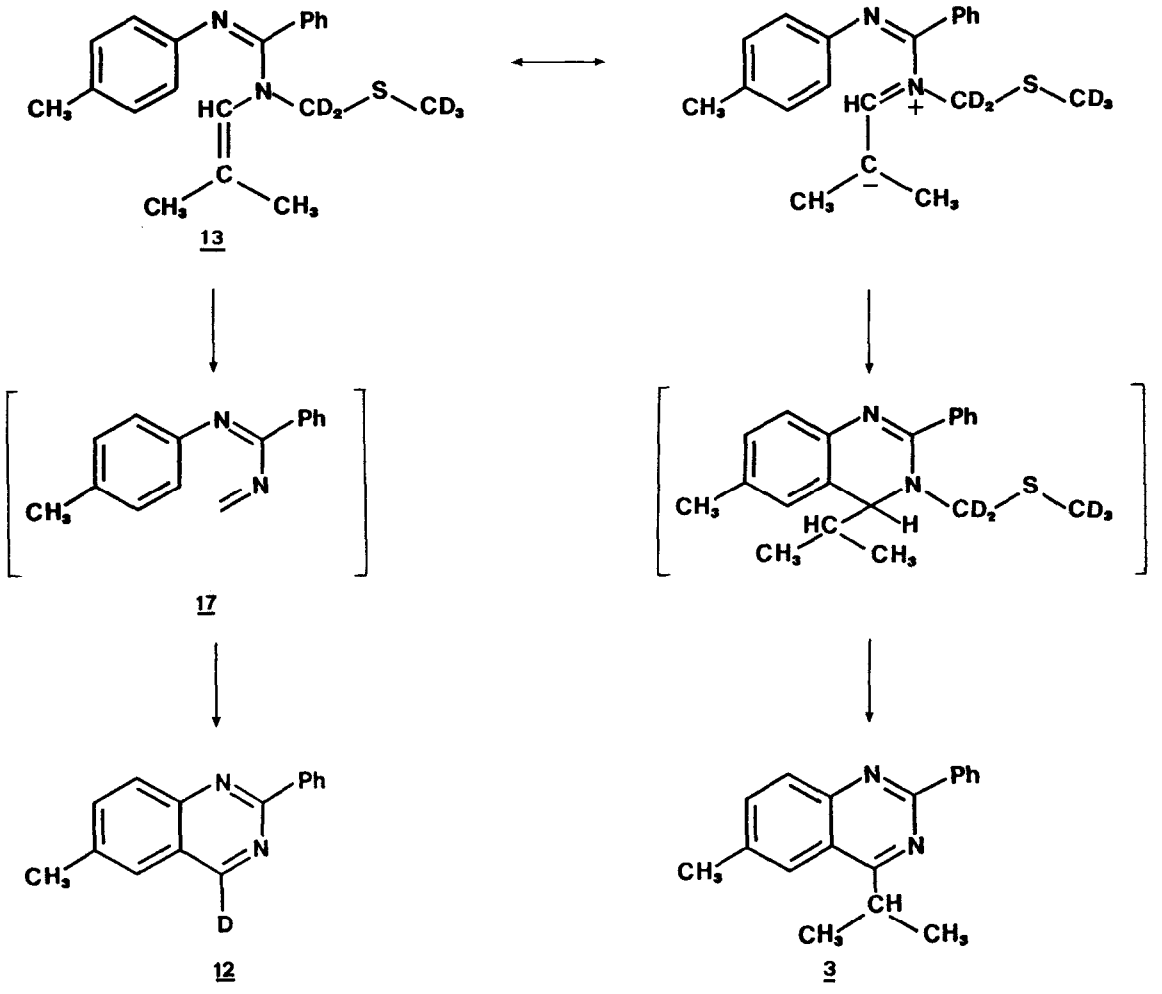
The labelled quinazoline 7c was probably formed following the reaction pathway described in SCHEME 4 for enamines 5. In this case the electrocyclic ring closure of the 1,3-diaza-1,3-diene 15 affords the 3,4-dihydroquinazoline 16 which aromatize under the reaction conditions to give the final product 7c, SCHEME 7. Alternatively, the intermediate 14 can undergo Stevens rearrangment and loss of morpholine to give the benzamidine 13, SCHEME 7[8]. This type of rearrangement has been proposed as a first step in the thermolysis of some N-acylsulfimides [9].



SCHEME 7

Moreover compound 13 was found to be the precursor of the quinazolines 3 and 12. Actually, when 13 was heated at reflux in tetraline, it was possible to isolate, after chromatographic purification over silica gel,

the quinazoline 3 and 12, SCHEME 8.



SCHEME 8

Thus it seems that, in the case of the reaction between S,S-dimethyl-N-(N-arylbenzimidoyl)sulfimides and enamines derived from aldehydes two different mechanisms are involved for the quinazoline ring formation. The first follows the scheme described for enamines 5 and results in the formation of the deuterated quinazoline **7c**. The second involves as intermediate the benzamidine **13** which, by electrocyclic ring closure and loss of dimethylsulfide, give the quinazoline 3 (SCHEME 8).

The reaction mechanism which provides the formation of the 4-unsubstituted quinazoline 12 parallels the mechanism proposed by Gilchrist et al. [2] in the thermolysis of some S,S-dimethyl-N-(N-arylbenzimidoyl)sulfimides.

Actually, the benzamidine **13** can be thermally converted into imine **17** and the quinazoline **12** may then be formed by electrocyclic ring closure and aromatization.

EXPERIMENTAL

M.p.s were taken with a Büchi apparatus and are uncorrected. ^{1}H-NMR were recorded on a Varian A360 spectrometer with Me_4Si as internal standard and mass spectra on a VG70 SE Q mass spectrometer using the electron ionization technique (electron energy 70eV).

Enamines (**5a-d**).

The enamines employed in this work are known compounds and were prepared according to described methods[2].

N-(N-arylbenzimidoyl)sulfimides (**1a-c**).

S,S-Dimethyl-N-[N-(4-methylphenyl)benzimidoyl] sulfimide **1a** and S,S-dimethyl-N-[N-(4-methoxyphenyl)benzimidoyl] sulfimide **1b** are known compounds[1], S,S-hexadeuterodimethyl-N-[N-(4-methylphenyl)benzimidoyl] sulfimide **1c** is new and was prepared according to the procedure described in Ref. 1.Yield: 82%; m.p. 175°C;elem. anal.,found % (calcd for $C_{16}H_{12}D_6N_2S$): C 69.72(69.52) H 6.61(6.51); N 10.08(10.13).

4,4-Disubstituted-2-phenyl-3,4-dihydroquinazolines (**6a-f**);

General Procedure:

A mixture of the S,S-dimethyl-N-(N-arylbenzimidoyl)sulfimide **1** (0.005mol), the enamine **5** (0.015mol), and dry tetraline (40ml) was heated under reflux for 14h. The solvent was removed under reduced pressure, the crude residue was washed with sat. aq. $NaHCO_3$ (30ml), and extracted with CH_2Cl_2 (2x30ml). The organic layer, freed from the solvent by distillation in vacuo, gave the crude product mixture, which was chromatographed on silica gel (70-230 mesh) column (ratio crude product/silica gel, 1:40) yielding 4,4-disubstituted-2-phenyl-3,4-dihydroquinazolines **6a-f**, for data see Table 1.

Reaction of S,S-hexadeuterodimethyl-N-[N-(4-methylphenyl)benzimidoyl]sulfimide **1c** with enamines **5a**, **5b** and **2**.

A mixture of the sulfimide **1c** (0.005mol), the appropiate enamine **5a**, **5b** or **2** (0.015mol), and dry tetralin (40 ml) was heated under reflux for 40h. Then the solvent was removed under reduced pressure, the crude residue was washed with sat. aq. $NaHCO_3$ (30ml), and extracted with CH_2Cl_2 (2x30ml). The organic layer, freed from the solvent by distillation in vacuo, gave the crude product mixture, which was chromatographed on silica gel (70-230 mesh) column (ratio crude product/silica gel, 1:40).

A In the case of the reaction with enamines **5a** and **5b**, elution with cyclo-

hexane/triethylamine 8:2 gave 3,4-dihydroquinazolines **7a** and **7b** respectively, for data see Table 2.

B For enamine **2** elution with CH_2Cl_2 yielded progressively 0.25g of a 2.3:7.7 mixture of quinazoline **3**[1] and **7c** (for data of **7c** see Table 2), 0.045g (4%) of 4-deutero-6-methyl-2-phenylquinazoline **12** and 0.15g (9%) of N-isobutenyl-N-(methy$_1$thiomethyl-d_5)-N'-(4-methylphenyl)benzamidine **13**.

4-Deutero-6-methyl-2-phenylquinazoline **12**: m.p. 131-132°C (petroleum ether, 80-110); elem. anal., found % (calcd for $C_{15}H_{11}DN_2$): C 81.22(81.42); H 5.40(5.46); N 12.75(12.66); ^{1}H-NMR($CDCl_3$/TMS), δ :2.45(s,3H,CH_3);7.10-7.80(m,4H$_{arom}$);7.90-8.15(m,2H$_{arom}$);8.50-8.65(m,2H$_{arom}$); MS, m/z: M^+ 221 (100); 220(84); 194(24); 193(54).

N-Isobutenyl-N-(methylthiomethyl-d_5)-N'-(4-methylphenyl)benzamidine **13**: m.p. 97-99°C (petroleum ether, 80-110); elem. anal., found % (calcd for $C_{20}H_{19}D_5N_2S$): C 72.67(72.90); H 7.33(7.34); N 8.39(8.50); ^{1}H-NMR($CDCl_3$/TMS) δ:1.65(d,3H,=C-CH_3);2.03(d,3H,=C-CH_3);2.15(s,3H,CH_3);6.36(m,1H,=CH);6.98(s,4H$_{arom}$)7.23(m,5H$_{arom}$); MS, m/z: M^+ 329(8); 158(100); 104(48).

N-diphenylmethylene-N'-(4-methylphenyl)benzamidine (**10**).

The benzamidine **10** was prepared from N-(4-methylphenyl)benzimidoyl chloride and N-trimethylsilyl(diphenylmethylene)amine in benzene at reflux as described for analogous compounds in Ref. 7. Yield: 75%; m.p. 163-165°C (ethanol); elem. anal.,found % (calcd for $C_{27}H_{22}N_2$): C 86.18(86.63); H 5.79 (5.88); N 7.38(7.48).

6-Methyl-2,4,4-triphenyl-3,4-dihydroquinazoline (**11**).

A mixture of the benzamidine **10** (0.00165mol) and dry tetralin (8ml) is heated at reflux for 30h. The solvent was then removed by distillation in vacuo and the crude was purified by column chromatography over silica gel (ratio crudeproduct/silica gel 1:40). Elution with cyclohexane/ triethylamine 8:2 give 6-methyl-2,4,4-triphenyl-3,4-dihydro quinazoline **11**. Yield: 52%; m.p. 186°C (diisopropylether); elem. anal., found % (calcd for $C_{27}H_{22}N_2$): C 86.68(86.63); H 5.83(5.88); N 7.24(7.48). ^{1}H-NMR($CDCl_3$/TMS); δ:2.20 (s,3H,CH_3);4.65-4.85(bs,1H,NH);7.00-7.50(m,16H$_{arom}$);7.75-8.00(m,2H$_{arom}$).

Thermolysis of N-isobutenyl-N-(methylthiomethyl-d_5)-N'-(4-methylphenyl)-benzamidine (**13**).

A mixture of benzamidine **13** (0.0003mol) and dry tetraline (2ml) was heated at reflux for 6h. The solvent was then removed by distillation in vacuo and the crude was purified by column chromatography over silica gel (ratio crude product/silica gel 1:40). Elution with CH_2Cl_2 yielded progressively the 4-isopropyl-6-methyl-2-phenylquinazoline **3** (40%, for data see Ref. 1) and 4-deutero-6-methyl-2-phenylquinazoline **12** (30%, for data see above).

TABLE 1. 4,4-Disubstituted-2-phenyl-3,4-dihydroquinazolines, **6a-f**.

No	Eluent for chromatography	Yield[a] %	m.p.[b,c] (°C) (solvent)	Molecular formula	Elemental analysis,%[d] C	H	N	^{1}H-NMR($CDCl_3$)[e] δ from TMS	M^+(%)
6a	cylohexane/ triethylamine 8:2	49	oil	$C_{22}H_{20}N_2$ (312.4)				1.88(s,3H,CH_3);2.13(s,3H,CH_3);5.3-5.7(bs,1H,NH);6.58(m,1H$_{arom}$);6.9-7.6(m,10H$_{arom}$);7.7-7.9(m,2H$_{arom}$).	312[f] (10.4)
			picrate						
			195-197 (EtOH)	$C_{28}H_{23}N_5C_7$ (541.5)	61.77 (62.10)	4.22 (4.28)	12.76 (12.93)		
6b	cyclohexane/ triethylamine 8:2	47	125-128 (PE)[h]	$C_{19}H_{22}N_2$ (278.4)	81.78 (81.96)	8.04 (7.96)	9.94 (10.06)	1.8(t,6H,CH_3);1.2-2.2(m,4H,CH_2);2.25(s,3H,CH_3);4.4-4.8(bs,1H,NH);6.75-7.6(m,6H$_{arom}$);7.7-7.9(m,2H$_{arom}$).	
6c	cyclohexane/ triethylamine 8:2	45	140-145 (PE)[h]	$C_{19}H_{20}N_2$ (276.4)	82.03 (82.55)	7.17 (7.29)	9.86 (10.13)	1.6-2.2(m,8H,CH_2);2.25(s,3H,CH_3);4.8-5.3(bs,1H,NH);6.8-7.55(m,6H$_{arom}$);7.7-7.9(m,2H$_{arom}$).	
6d	ethylacetate/ chloroform 1:1	56	oil	$C_{20}H_{22}N_2$ (290.4)				1.55-2.1(m,10H,CH_2);2.28(s,3H,CH_3);4.5-4.9(bs,1H,NH);6.85-7.6(m,6H$_{arom}$);7.7-7.9(m,2H$_{arom}$).	290[g] (100)
			picrate						
			243-247 (EtOH)	$C_{26}H_{25}N_5O_7$ (519.5)	59.86 (60.11)	5.02 (4.85)	13.38 (13.48)		
6e	benzene/ triethylamine 8:2	57	oil	$C_{22}H_{20}N_2O$ (328.4)				1.73(s,3H,CH_3);3.36(s,3H,OCH_3);3.2-3.5(bs,1H,NH);6.3-6.8(m,3H$_{arom}$);7.0-7.5(m,8H$_{arom}$);7.6-7.8(m,2H$_{arom}$).	328[g] (100)
			picrate						
			205-208 (EtOH)	$C_{28}H_{23}N_5O_8$ (557.5)	60.05 (60.32)	4.09 (4.16)	12.44 (12.56)		
6f	cyclohexane/ triethylamine 8:2	51	oil	$C_{20}H_{22}N_2O$ (306.4)				1.38(s,3H,CH_3);1.5-2.2(m,10H,CH_2);3.73(s,3H,OCH_3);3.5-3.8(bs,1H,NH);6.7-7.6(m,6H$_{arom}$);7.7-8.0(m,2H$_{arom}$).	306[f] (24)
			picrate						
			218-220 (EtOH)	$C_{26}H_{25}N_5O_8$ (535.5)	58.16 (58.31)	4.64 (4.70)	12.78 (13.08)		

a) Isolated analytically pure product, after chromatographic purification.

b) Uncorrected.

c) Oils have been characterized as picrate; m.p. and microanalyses are also given in Table 1.

d) Calculated values in parentheses.

e) Recorded at 60 MHz on a Varian A360 spectrometer.

f) Recorded with a Varian MAT 311-A spectrometer (FD mode).

g) Recorded with a Finnigan mod. 1020 (EI mode,70ev).

h) PE = petroleum ether (bp 80-110°C).

TABLE 2. Compounds 7a-c.

No	Yield[a] %	m.p.[b](°C) (solvent)	^{1}H-NMR($CDCl_3$/TMS) ,J(Hz)[c]	^{13}C-NMR($CDCl_3$/TMS)[d] δ,J(Hz)	MS(70eV)[e] m/z(%)
7a	25	oil		total decoupling: 29.7(t,CH_2D,J_{CD}=19) total coupling: 29.7(tt,CH_2D,J_{CD}=19, J_{CH}=143).	313(M^+,4.5); 297(100)
7b	20	120 (PE)	0.88(d,3H,CH_3,J=7.3);0.89(t,3H,CH_3,J=7.2);1.62 and 1.95(m,1.5H,CH_2+CHD/2);2.31(s,3H,CH_3); 6.81(s,1H,H5);7.00(d,H7orH8,J=8);7.12(d,H7orH8, J=8);7.36(m,3H_{arom});7.83(m,2H_{arom}).		279(M^+,3.5); 250(100) 249(100)
7c	--	--	1.51(s,6H,CH_3);2.58(s,3H,CH_3);7.50(m,3H_{arom}); 7.67(dd,1H,H7,J_{7-8}=8.5,J_{7-5}=1.5);7.91(d,1H,H5, J_{5-7}=1.5);8.00(d,1H,H8,J_{8-7}=8.5);8.70(dd,2H, H2',H6',J=8 and 2).[g]		

a) Isolated analytically pure product, after chromatographic purification.

b) Uncorrected.

c) Recorded at 200 MHz on a Brucker AC200 spectrometer.

d) Recorded at 200 MHz on a Varian XL200 spectrometer.

e) Recorded with VG70 SE Q.

f) PE = petroleum ether (bp 80-110°C).

g) Compound **7c** was obtained in mixture with 3 ^{1}H-NMR spectrum was deduced from the spectrum of the mixture.

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