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REACTION OF QUINOXALINES WITH β,γ-UNSATURATED GRIGNARD REAGENTS. SYNTHESIS OF ALLYL-, ALLENYL-, PROPARGYL-QUINOXALINE DERIVATIVES.

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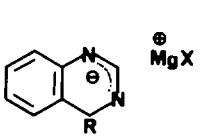
Abstract - Mono- and bis-addition reactions of the β,γ-unsaturated Grignard reagents 2 and 6 to the C=N bonds of quinoxalines 1 afford high yields of dihydroquinoxalines 4 and tetrahydroquinoxalines 3. Dehydrogenation of 4g-l and 3a-c with DDQ leads to allylic quinoxalines 1i-m and 1e-g respectively in very good yields. Allylic and propargylic quinoxalines 1m and 1s can conveniently be synthesized by "cross-coupling" of 2-chloro-3-methylquinoxaline with 2c and 6a.

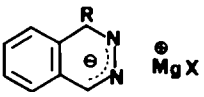
Quinoxalines have had a variety of uses such as insecticides,[1] fungicides,[2] bactericides[3] and many other significant biological effects.[4]

Quinoxaline derivatives are usually prepared from an aromatic o-diamine and an α-dicarbonyl, β,γ-acetylenic-α-ketoacid ester, or α-halophenylacetate, by intramolecular cyclisation reactions, and from alloxazines, diazepines, and quinone diimides.[3] Yields are not always very high and precursors sometimes are not easily available.

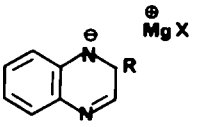
The behaviour of quinoxalines towards nucleophiles has been studied;[3] the reactions with C-nucleophiles have not been extensively investigated. Concerning the reaction with Grignard reagents quinoxaline has been shown to react with two equivalents of the allylmagnesium bromide to produce the related tetrahydroquinoxaline.[5] No mention was made about the geometry of such a tetrahydroquinoxaline nor does the possibility of obtaining monoaddition products seem to have been considered. Both quinazoline and phthalazine have been reported to react with Grignards affording mono-addition products, presumably owing to the deactivation of the second C=N bond by charge delocalisation in the intermediate metal complexes (see A and B). It has been suggested that in the case of quinoxaline charge delocalisation of this kind (see C) is minimal and double addition easily occurs.[6]



(A)



(B)



(C)

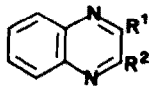
Organolithiums[7] and some alkyl and aryl Grignard reagents[8] have recently been shown to add to 2-methylquinoxaline affording both dihydro- and tetrahydro-methylquinoxaline but in very poor yields and with difficulty. Moreover, the good mobility of halogens[9] in the heterocyclic ring of quinoxalines does not appear to have been exploited for the cross-coupling reaction with organometallics.

As part of our continuing interest towards the reactivity of aza-aromatic heterocycles with organometallics[10] we have studied the reaction of some quinoxalines with a number of β,γ-unsaturated Grignard reagents. We report here a convenient synthesis of functionalised quinoxalines, dihydro- and tetrahydro-quinoxalines from commercially available precursors.

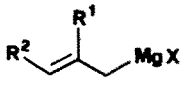
For our initial study we addressed our attention to the reaction of quinoxaline 1a with allylmagnesium bromide 2a. The addition of 2a (2.2 mole) to a THF solution of 1a (1 mole) at -78°C afforded, as reported,[5] 2,3-diallyl-1,2,-3,4-tetrahydroquinoxaline 3a.

We could not establish whether 3a had a trans or a cis configuration. The pro cedure described by Aguilera[11] could not be applied as in our hands we had just one isomer.

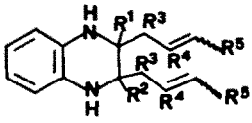
The reaction of 1a with an excess of methallylmagnesium chloride 2b (2.2 mole) furnished a quite good yield of the bis-adduct 3b. Attempts to control the reaction in order to obtain the mono-addition product 4b either at low or room temperature and using a 1:1 reactants molar ratio failed. When we used a 1:1 molar ratio we could isolate also a small amount of 2-methallyl-1,2,3,4-tetrahydroquinoxaline 5a and 2-methallylquinoxaline 1n, both possibly arising from a dismutation reaction of 4b.[7] Compound 3b turned out to be configurationally pure; we established its structure by X-Ray analysis. Torsion angles (see experimental part) clearly indicate that the six membered heterocyclic ring adopts the half-chair conformation. Moreover, the crystallographic study shows that the two methallylic groups in 3b are in a trans arrangement.



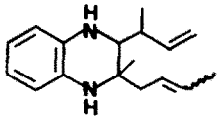
1a: $R^1 = R^2 = H$
1b: $R^1 = Me$; $R^2 = H$
1c: $R^1 = R^2 = Me$
1d: $R^1 = Me$; $R^2 = Cl$
1e: $R^1 = R^2 = -CH_2-CH=CH_2$
1f: $R^1 = R^2 = -CH_2-C(CH_3)=CH_2$
1g: $R^1 = R^2 = -CH(CH_3)-CH=CH_2$
1i: $R^1 = Me$; $R^2 = -CH_2-CH=CH_2$
1l: $R^1 = Me$; $R^2 = -CH_2-C(CH_3)=CH_2$
1m: $R^1 = Me$; $R^2 = -CH(CH_3)-CH=CH_2$
1n: $R^1 = H$; $R^2 = -CH_2-C(CH_3)=CH_2$
1o: $R^1 = H$; $R^2 = -CH(CH_3)-CH=CH_2$
1p: $R^1 = H$; $R^2 = -C(CH_3)_2-C\equiv CH$
1q: $R^1 = Me$; $R^2 = -C(CH_3)=CH-CH_3$
1r: $R^1 = Me$; $R^2 = -CH=C=CH_2$
1s: $R^1 = Me$; $R^2 = -CH_2-C\equiv CH$
1t: $R^1 = CH_2-CH=CH_2$; $R^2 = -CH=CH-CH_3$
1u: $R^1 = Me$; $R^2 = -CH=CH-CH_3$



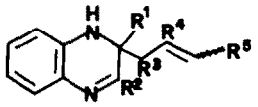
2a: $R^1 = R^2 = H$
2b: $R^1 = Me$; $R^2 = H$
2c: $R^1 = H$; $R^2 = Me$



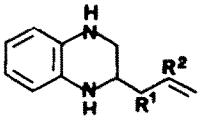
3a: $R^1 = R^2 = R^3 = R^4 = R^5 = H$
3b: $R^1 = R^2 = R^3 = R^5 = H$; $R^4 = Me$
3c: $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Me$
3d: $R^1 = R^2 = Me$; $R^3 = R^4 = R^5 = H$
3e: $R^1 = R^2 = R^4 = Me$; $R^3 = R^5 = H$
3f: $R^1 = R^2 = R^3 = Me$; $R^4 = R^5 = H$
3g: $R^1 = R^2 = R^5 = Me$; $R^3 = R^4 = H$
3i: $R^1 = Me$; $R^2 = R^3 = R^4 = R^5 = H$
3l: $R^1 = R^4 = Me$; $R^2 = R^3 = R^5 = H$
3m: $R^1 = R^3 = Me$; $R^2 = R^4 = R^5 = H$



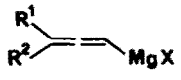
3n



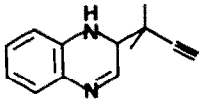
4a: $R^1 = R^2 = R^3 = R^4 = R^5 = H$
4b: $R^1 = R^2 = R^3 = R^5 = H$; $R^4 = Me$
4c: $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Me$
4d: $R^1 = R^2 = Me$; $R^3 = R^4 = R^5 = H$
4e: $R^1 = R^2 = R^4 = Me$; $R^3 = R^5 = H$
4f: $R^1 = R^2 = R^3 = Me$; $R^4 = R^5 = H$
4g: $R^1 = R^3 = R^4 = R^5 = H$; $R^2 = Me$
4i: $R^1 = R^3 = R^5 = H$; $R^2 = R^4 = Me$
4l: $R^1 = R^4 = R^5 = H$; $R^2 = R^3 = Me$
4m: $R^1 = R^3 = Me$; $R^2 = Cl$; $R^4 = R^5 = H$



5a: $R^1 = H$; $R^2 = Me$
5b: $R^1 = Me$; $R^2 = H$



6a: $R^1 = R^2 = H$
6b: $R^1 = R^2 = Me$



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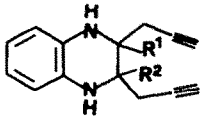
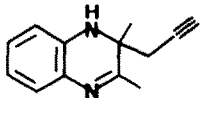


8a: $R^1 = R^2 = H$
8b: $R^1 = R^2 = Me$



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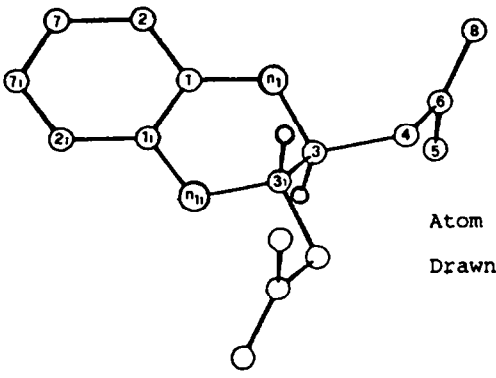


Atom numbering and molecular conformation. Drawn by graphic section of Caos 1986.[20]

The reaction of 1a with the crotylmagnesium bromide 2c using a 1:1 reactants molar ratio gave both 2,3-di-α-methylallyl-1,2,3,4-tetrahydroquinoxaline 3c and 2-α-methylallyl-1,2-dihydroquinoxaline 4c, which undergoes dismutation to 5b and to 2-α-methylallylquinoxaline 1o.

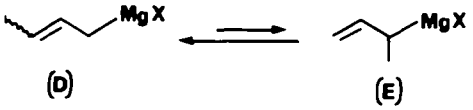
Compound 3c was the sole product (diastereomeric mixture) when the reaction was carried out with an excess of 2c (2.2 mole). In both cases the reaction proceeded with complete regioselectivity as the allylic group turned out to be attached through the more substituted carbon atom. A six-center intermediate involving the coordination of crotyl Grignard reagent to the nitrogen atom of the heterocyclic ring and the allylic rearrangement might explain the observed regioselectivity according to a S_Ei' or S_E2' mechanism.[12]

That the mono-addition product 4c could be obtained in this case might likely be attributed to steric interactions. The α-methylallyl group in the mono-addition product 4c could somewhat slow down the second addition. Accordingly treatment of quinoxaline 1a with dimethylallenylmagnesium bromide 6b furnished 2-dimethylpropargyl-1,2-dihydroquinoxaline 7, that easily converted to 2-dimethylpropargylquinoxaline 1p, while the reaction of 1a with allenylmagnesium bromide 6a gave exclusively 2,3-dipropargyl-1,2,3,4-tetrahydroquinoxaline 8a.

In order to evaluate the substituent effect in the heterocyclic ring we studied the reaction of 2,3-dimethylquinoxaline 1c with Grignards 2 and 6. We found that the Grignards 2a-c react with 1c to give almost exclusively and in excellent yields mono-addition compounds 4d-f or bis addition products 3d-g just choosing the appropriate experimental conditions in terms of temperature and reactants molar ratio.

These results clearly indicate that substituents in the heterocyclic ring and in the Grignard reagent markedly affect the addition reaction to the azomethine linkages of quinoxalines. Accordingly, the bis-addition product 3g (E and Z) derived from the reaction between 1c and crotylmagnesium bromide 2c has the allylic group attached through the less substituted carbon atom. A possible explanation for this might be that, due to steric reasons the less abundant form

D[13] of the Grignard reagent acts as the reacting species.



(D) (E)

Alternatively one may think that the di-α-methylallyl derivative 3f actually forms as a result of the nucleophilic attack of the crotyl form (D) of the Grignard reagent but soon after undergoes rearrangement to the less sterically hindered isomer 3g. Due to the smaller steric interaction 2-α-methylallyl-1,2-dihydroquinoxaline 4f forms in the reaction of 1c and 2c using a 1:1 molar ratio.

Quinoxaline 1c when treated with an excess of the allenylmagnesium bromide 6a afforded the dimethylpropargyldihydroquinoxaline 9 accompanied by a small amount of the bis-addition product 8b. No reaction occurred when quinoxaline 1c was treated with dimethylallenylmagnesium bromide 6b. It is likely that the steric hindrance between the methyl groups of the Grignard reagent and those of the heterocyclic ring of quinoxaline 1c are responsible for such a failure.

We found that tetrahydroquinoxalines 3a-c can easily be converted into quinoxalines 1e-g simply by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

The reaction of methylquinoxaline 1b with allylic Grignard reagents 2a-c has also been studied. Treatment of 1b with 2.2 moles of allylmagnesium bromide 2a gives the diallylmethyltetrahydroquinoxaline 3i in quite good yield. Similarly 1b reacts with methallylmagnesium chloride 2b affording the dimethallylmethyltetrahydroquinoxaline 3l. The diastereomeric mixture of the di-α-methylallylmethyltetrahydroquinoxaline 3m forms substantially in the reaction of 1b with 2c.

Eventually we could observe, via NMR, that a small amount of the α-methylallyl crotylmethyltetrahydroquinoxaline 3n accompanies compound 3m, possibly derived from the attack of the (D) form of the Grignard reagent 2c to the C=N bond bearing the methyl group.

As in the case of 1c, the quinoxaline 1b undergoes mono-addition reaction with the allylic Grignards 2a-c to give very high yields of the dihydroquinoxalines 4g-l. Acceptable yields of allylquinoxalines 1i-m were obtained upon dehydrogenation of 4g-l with DDQ.

Finally, we studied the reaction of chloroquinoxaline 1d with the Grignard 2 and 6. We found that 1d reacts quickly with 2c producing a satisfactory yield of the cross-coupled product 1m together with a small amount of the vinyl isomer 1q. Moreover, 1d reacts with allenylmagnesium bromide 6a at -78°C in ether to give 2-allenylquinoxaline 1r together with a small percentage of 2-a-

cetylenic quinoxaline 1s. However, repeating the reaction at 0°C in THF and using a 50% excess of the Grignard reagent furnished the acetylenic derivative 1s as the main product which surprisingly was the sole product when the reaction was carried out at -50° in ether.

In conclusion our results actually confirm that quinoxalines are more prone to undergo bis-addition of C-nucleophiles than quinazolines and phthalazines. This, as mentioned above, might presumably be due to the minimal stabilisation by charge delocalisation of the dihydroquinoxalinemagnesium bromide (C) that leaves the second addition substantially unaffected.

However we have found that the addition of β,γ-unsaturated Grignards to the C=N bonds of quinoxalines can be stopped at the first step to give mono-addition products. This depends upon the experimental conditions and the substitution either in the Grignard reagent or in the starting quinoxaline.

The reaction of quinoxalines with β,γ-unsaturated Grignard reagents appears of interest from the synthetic viewpoint as it allows a convenient and easy synthesis of substituted dihydroquinoxalines, and tetrahydroquinoxalines all of potential interest in pharmacology. Related quinoxalines can usefully be obtained through dehydrogenation with DDQ.

Alternatively allyl-, allenyl- or propargylquinoxalines can be obtained by cross-coupling of the chloroquinoxaline 1d with allylic and allenic Grignard reagents.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Varian EM-360A or a Varian XL-200 spectrometer and chemical shifts are reported in parts per million (δ) from internal Me_4Si. ^{13}C-NMR spectra were performed on a Varian XL-200 spectrometer. Melting points were determined on a Electrothermal apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 681 spectrometer. Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator (Stratocrom SIF, Carlo Erba). Column chromatography was carried out by using 70-230 mesh silica gel from Merck. Flash chromatographies were done with Baker 40 μm silica gel.

Materials.- Tetrahydrofuran (THF) and diethyl ether (ether) from commercial sources (RS, C.E.) were purified by distillation (twice) from sodium wire in a N_2 atmosphere. Petroleum ether (RS, C.E.) refers to the 40-60°C boiling fraction. Dichloromethane (RS, C.E.) was purified by distillation. 2-Methyl- 1b, 2,3-dimethyl- 1c and 2-chloro-3-methyl-quinoxaline 1d were commercial grade and were purified by flash chromatography[14] [eluants: petroleum ether-ether (8:2) for 1b and 1c and petroleum ether-ether (9:1) for 1d]. All other chemicals were commercial grade and were used without further purification.

The Grignard reagents 2a-c and 6a-b were prepared as reported.[15,16]

All the novel compounds showed satisfactory microanalytical data.

Reaction of quinoxalines 1a-c with allylic Grignard reagents 2a-c. The reaction of 1a with 2a is described as an example. To a stirred solution of 1a (0.65 g, 5.0 mmol) in THF (30 ml) was added dropwise an ether solution of 2a (13 ml, 0.88 M; 11.44 mmol) at -78°C under nitrogen. After 30 min the reaction mixture was warmed to room temperature and quenched with a saturated aqueous NH_4Cl (30 ml) solution. Extraction with ether (3 x 25 ml), drying over Na_2SO_4 and removal of the solvent in vacuo gave 2,3-di-(2-propenyl)-1,2,3,4-tetrahydroquinoxaline 3a (1.04 g,97%) as an oil, which was purified by flash chromatography on silica gel using petroleum ether-ether (95:5) as eluant. ν_{max}(film) 3280-3460br (NHs) and 1640 cm^{-1} (C=C).
δ_H ($CDCl_3$) 1.8-2.7 (4H, m), 2.9-3.3 (2H, m), 3.75 (2H, br signal, ex-

change with D_2O), 5.0-5.4 (4H, m), 5.55-6.3 (2H, m), and 6.4-6.8 (4H, m)
The reaction of 1a (1 mole) with 2b (2.2 mole) carried out as above yielded 2,3-di-(2-methyl-2-propenyl)-1,2,3,4-tetrahydroquinoxaline 3b (1.1 g, 91%) as a solid which was recrystallized from pentane, m.p. 77-78°C; ν_{max} (nujol) 3385 cm^{-1} (NHs), and 1639 cm^{-1} (C=C); δ_H (200 MHz; $CDCl_3$) 1.78 (6H, s), 2.08 (2H, dd, J 9.8 and 13.4 Hz), 4.13 (2H, m), 3.5-4.1 (2H, br s, exchange with D_2O), 4.84-4.95 (4H, m), and 6.5-6.6 (4H, m) δ_C ($CDCl_3$, Me_4Si as internal standard) 22.25, 41.69, 51.4, 113.7, 113.9, 118.35, 132.4, and 141.9.
The reaction of 1a (1 mole) with 2b (1.1 mole) in THF (21 ml, gave a crude oily residue. Flash chromatography of the mixture with petroleum ether-ether (9:1) gave 3b (0.69 g, 39%); 2-(2-methyl-2-propenyl)quinoxaline 1n (traces) as an oil, δ_H ($CDCl_3$) 1.9 (3H, s), 3.8 (2H, s), 4.8-5.2 (2H, m), 7.8-8.4 (4H, m),and 9.0 (1H, s); and 2-(2-methyl-2-propenyl)-1,2,3,4-tetrahydroquinoxaline 5a (traces) as a solid, ν_{max} (nujol) 3140-3380br (NHs), and 1640 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.8 (3H, s), 2.15 (2H, d, J 7 Hz), 2.86-3.75 (5H, series of m which simplified by adding D_2O), 4.8-5.1 (2H, m), and 6.5-6.8 (4H, m).
The reaction of 1a (1 mole) with 2c (2.2 mole) gave an oil mainly constituted of 2,3-di-(1-methyl-2-propenyl)-1,2,3,4-tetrahydroquinoxaline 3c (0.7 g; 77%) which was further purified by flash chromatography on silica gel using petroleum ether-ether (8:2) as eluant. δ_H ($CDCl_3$) 0.8-1.2 (6H, m), 2.2-2.75 (2H, m), 2.8-3.1 (2H, m), 3.7-4.1 (2H, br signal, exchange with D_2O) 4.8-5.3 (4H, m), 5.5-6.1 (2H, m), and 6.4-6.7 (4H, m).
When to a solution of 1a (0.5 g, 4 mmol) in THF (30 ml) was added an ether solution of 2c (10.1 ml, 0.42 M; 4.2 mmol) at room temperature it was obtained an oily residue. Flash chromatography with petroleum ether-ethyl acetate (8:2) gave 3c (0.063 g, 13%), 2-(1-methyl-2-propenyl)quinoxaline 1o (0.061 g, 17% yield) as an oil; ν_{max} (film) 1638 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.6 (3H, d, J 7 Hz), 3.75-4.25 (1H, m), 5.1-5.5 (2H, m), 6.0-6.7 (1H, m), 7.8-8.3 (4H, m), and 8.9 (1H, s), and 2-(1-methyl-2-propenyl)-1,2,3,4-tetrahydroquinoxaline 5b (0.043 g, 12% yield) as an oil; δ_H ($CDCl_3$) 0.9-1.2 (3H, m), 2.0-3.5 (1H, m), 3.0-3.5 (3H, m), 3.5 (2H, br signal), 4.9-5.3 (2H, m), 5.4-6.0 (1H, m), and 6.6 (4H, br s).
The reaction of 2,3-dimethylquinoxaline 1c (1 mole) with 2a (2.2 mole) carried out and worked up in the standard way gave 2,3-di-(2-propenyl)-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline 3d (0.66 g, 87%) as a dark residue which was purified by flash chromatography using petroleum ether-ether (9:1) as eluant; ν_{max} (film) 3390br (NHs), and 1635 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.09 (6H, s), 1.8-2.8 (4H, m), 3.4-3.8 (2H, br s, exch. with D_2O), 4.8-5.4 (4H, m), 5.6-6.2 (2H, m), and 6.4-6.8 (4H, m).
The reaction of 2,3-dimethylquinoxaline 1c (1mole) with 2b (2.2 mole) led to an oil mainly made of 2,3-di-(2-methyl-2-propenyl)-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline 3e (0.96 g, 94%) which was purified by flash chromatography using petroleum ether-ether (9:1) as eluant; ν_{max} (film) 3480br(NHs), and 1640 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.1 (6H, s), 1.8 (6H, s), 2.1 (2H, d, J 13 Hz), 2.55 (2H, d, J 13 Hz), 3.75 (2H, br signal, exch. with D_2O), 4.7-5.1 (4H, m), and 6.4-6.8 (4H, m).
The reaction of 2,3-dimethylquinoxaline 1c (1 mole) with 2c (3 mole) afforded 2,3-di-(2-butenyl)-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline 3g (0.9 g, 87%) as an oil which was purified by flash chromatography using petroleum ether-acetone (9:1) as eluant; ν_{max} 3480br (NHs), and 1650 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.15 (6H, s), 1.45 (6H, d, J 6 Hz), 2.0-2.8 (4H, m), 3.6 (2H, br s, exchange with D_2O), 5.4-6.05 (4H, m), and 6.35-6.75 (4H, m).
The reaction of 1b (1 mole) with 2a (2.2 mole) gave an oily product which was purified by column chromatography on silica gel using petroleum ether-acetone (8:2) to afford the pure 2,3-di-(2-propenyl)-3-methyl-1,2,3,4-tetrahydroquinoxaline 3i (73% yield); ν_{max} 3320-3460 (broad band), and 1635 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.03 (3H, s), 1.7-2.5 (4H, m), 3.4 (1H, dd, J 3.0 Hz and 11.0 Hz), 3.65 (2H, br s, exchange with D_2O), 5.0-5.4 (4H, m), 5.5-6.2 (2H, m), and 6.5-6.8 (4H, m).
The reaction of 1b (1 mole) with 2b (2.2 mole) gave 2,3-di-(2-methyl-2-propenyl)-3-methyl-1,2,3,4-tetrahydroquinoxaline 3l (71% yield); ν_{max} 3400br (NHs), and 1640 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.1 (3H, s), 1.78 (3H, s), 1.88 (3H, s), 1.8-2.5 (4H, m), 3.15 (1H, dd, J 3 Hz and 11 Hz), 3.7 (2H, br signal), 4.8-5.2 (4H, m), and 6.5-6.8 (4H, m).
The reaction of 1b (1 mole) with 2c (2.2 mole afforded 2,3-di-(1-methyl-2-propenyl)-3-methyl-1,2,3,4-tetrahydroquinoxaline 3m (74% yield); ν_{max} 3400br (NHs), and 1630w cm^{-1} (C=C); δ_H ($CDCl_3$) 0.9-1.3 (9H, m), 2.5-2.9 (2H, m), 3.2 (1H, m), 4.9-5.3 (4H, m), 5.5-6.2 (2H, m), and 6.5-6.8 (4H, br s).
The reaction of 2,3-dimethylquinoxaline 1c (1 mole) with 2a (1.1 mole) afforded the 2-(2-propenyl)-2,3-dimethyl-1,2-dihydroquinoxaline 4d (86%): m.p. 109--111°C (petroleum ether); ν_{max} (nujol) 3100-3300br (NH), 1637w (C=C) and 1605 cm^{-1} (C=N); δ_H ($CDCl_3$) 1.33 (3H, s), 2.18 (3H, s), 2.1-2.5 (2H, m), 3.7-4.0 (1H, br s, exch. with D_2O), 4.9-5.4 (2H, m), 5.5-6.2 (1H, m), and 6.5-7-5 (4H, m).

The reaction of 1c (1 mole) with 2b (1.1 mole) led to 2-methallyl-2,3-dimethyl-1,2-dihydroquinoxaline 4e (85%): ν_{max} (nujol) 3300-3120br (NH), 1640 (C=C), and 1618 cm^{-1} (C=N); δ_H ($CDCl_3$) 1.37 (3H,s), 1.8 (3H, s) 2.04 (1H, d, J 13 Hz), 2.2 (3H, s), 2.49 (1H, d, J 13 Hz), 3.8-4.1 (1H, br signal, exch. with D_2O), 4.8-5.2 (2H, m), and 6.5-7.5 (4H, m).
The reaction of 1c (1 mole) with 2c (1.1 mole) produced 2-α-methylallyl-2,3-dimethyl-1,2-dihydroquinoxaline 4f (83%): m.p. 85-87°C (petroleum ether); ν_{max} (nujol) 3340-3120br cm^{-1} (NH); δ_H ($CDCl_3$) 1.02 (3H, d, J6 Hz), 1.37 (3H, s), 2.2 (3H, s), 2.6 (1H, q, J 6 Hz), 3.6-3.9 (1H, s, exchange with D_2O), 5.0-5.4 (2H, m), 5.6-6.3 (1H, m), 6.5-7.4 (4H, m).
The reaction of 2-methylquinoxaline 1b (1 mole) with 2a (1.0 mole) gave a crude solid residue that was mainly 2-(2-propenyl)-3-methyl-1,2-dihydroquinoxaline 4g (0.55 g, 84%) which was purified by washing with petroleum ether, m.p. 88-89°C; ν_{max} (nujol) 3240br (NH), and 1630 cm^{-1} (C=C); δ_H ($CDCl_3$) 2.2 (3H, s), 2.3 (2H, m), 3.85 (1H, t, J 7 Hz), 4.1-4.3 (1H, br s, exchange with D_2O), 4.9-5.4 (2H, m), 5.5 6.3 (1H, m), and 6.5-7.4 (4H,m).
The reaction of 1b (1 mole) with 2b (1.1 mole) formed 2-(2-Methyl-2-propenyl)-3-methyl-1,2-dihydroquinoxaline 4i (0.48 g, 86.5%) was purified as 4g, m.p. 94-96°C; ν_{max} (nujol) 3240br (NH), and 1634 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.8 (3H, s), 2.25 (3H, s), 2.2-2.9 (2H, m), 3.8-4.1 (1H, dd), 4.75-5.1 (2H, m), and 6.5-7.5 (4H, m).
The reaction of 1b (1 mole) with 2c (1.1 mole) led to 2-(1-Methyl-2-propenyl)-3-methyl-1,2-dihydroquinoxaline 4l (0.62 g, 89%) m.p. 92-93°C (petroleum ether); δ_H ($CDCl_3$) 1.0 (3H, d, J 7 Hz), 2.2 (3H, s), 2.5-2.85 (1H, m), 4.05 (1H, d), 5.0-5.4 (2H, m), 5.5-6.2 (1H, m), and 6.5-7.4 (4H, m).
Reaction of quinoxaline 1a, 1c with allenylmagnesium bromide 6a-b The reaction of 1a with 6a is described as an example. The solution of 1a (1.0 g, 7.7 mmol) in ether (20 ml) was treated with the ether solution of the allenyl Grignard 6a (6.0 ml, 1.39 M; 8.3 mmol) at -78°C affording an oily residue, which was purified by flash chromatography with petroleum ether-ether (8:2) to afford 2,3-di-(2-propynyl)-1,2,3,4-tetrahydroquinoxaline 8a (0.33 g, 41%) as a solid which was recrystallized from petroleum ether (60-80°C) m.p.56-57°C; ν_{max} (nujol) 3390 (≡C-H), 3280 (NH), and 2117 cm^{-1} (C≡C); δ_H ($CDCl_3$) 2.1 (2H, t, J 2 Hz), 2.3-2.7 (4H, m), 3.3-4.7 (2H, m), 3.8-4.3 (2H, br signal, exc. with D_2O), and 6.5-6.9 (4H, br s).
The reaction of 2,3-dimethylquinoxaline 1c (1 mole) with 6a (5 mole) afforded a crude residue which, after flash chromatography on silica gel using petroleum ether-ether (8:2) as eluant, gave: 2,3-di-(2-propynyl)-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline 8b (0.06 g, 4%) as an oil; δ_H 1.17 (3H, s), 1.96 (2H, t, J 2 Hz), 2.3-2.6 (4H, m), 3.6-4.0 (2H, br signal, exch. with D_2O) 6.4-6.7 (4H, br signal); and 2-(2-propynyl)-2,3-dimethyl-1,2-dihydroquinoxaline 9 (0.37 g, 59%) as a solid m.p. 104-106°C; ν_{max} (nujol) 3300 (≡C-H), 3240br (NH), and 2110w cm^{-1} (C=C); δ_H ($CDCl_3$) 1.5 (3H, s), 2.1-2.2 (1H, m), 2.28 (3H, s), 2.5-2.6 (2H, m), 4.1-4.4 (1H, br s, exchange with D_2O), 6.6-7.5 (4H, m).
The reaction of quinoxaline 1a (1 mole) with 6b (1.1 mole) gave a solid residue; its ^{1}H-NMR spectrum was consistent with 2-(1,1-dimethyl-2-propynyl)-1,2-dihydroquinoxaline 7 (67%); δ_H ($CDCl_3$) 1.26 (3H, s), 1.3 (3H, s) 2.26 (1H, s), 4.15 (1H, d, J 3 Hz), 4.1-4.5 (1H, br signal, exchange with D_2O), 6.5-7.4 (4H, m), and 7.7 (1H, m). Compound 7 could not be isolated, because, during flash chromatography, it converted to 2-(1,1-dimethyl-2-propynyl)quinoxaline 1p: δ_H ($CDCl_3$) 1.7 (6H, m), 2.4 (1H, s), 7.7-8.3 (4H, m), and 9.5 (1H, s).
Reaction of 2-chloro-3-methylquinoxaline 1d with 2c - To a stirred solution of 1d (0.7 g, 4.0 mmol) in THF (20 ml) was added dropwise an ether solution of 2c (5.6 ml, 0.90 M; 5.0 mmol) at -80°C, under nitrogen. After 15 min, the reaction mixture was worked up in the standard way to give a crude oily residue constituted of starting material and 2-(1-methyl-2-propenyl)-3-methylquinoxaline 1m. After flash chromatography using petroleum ether-ether (95:5) as eluant it was obtained the pure 1m (0.415 g, 67% yield) as an oil; ν_{max} (film) 1630 cm^{-1} (C=C); δ_H($CDCl_3$) 1.55 (3H, d, J 7 Hz), 2.8 (3H s), 3.8- 4.3 (1H, m), 4.9-5.3 (2H, m), 5.9-6.5 (1H, m) and 7.6-8.3 (4H, m). When to a solution of 1d (0.5 g, 3.0 mmol) in CH_2Cl_2 (15 ml) was added an ether solution of 2c (10.6 ml, 1.1 M; 12 mmol) at -78°C, under nitrogen, it was obtained a crude oily residue, which was flash chromatographied (petroleum ether-ether 95:5) to give 1m (0.306 g, 51%), and 2-(1-methyl-1-propenyl)-3-methylquinoxaline 1q (0.053 g, 9%): δ_H ($CDCl_3$) 1.9 (3H, d, J 7 Hz), 2.15 (3H, s), 2.77 (3H, s), 5.7-6.1 (2H, q, J 7 Hz), 7.7-8.3 (4H, m).
Reaction of 2-chloro-3-methylquinoxaline 1d with 6a - To a stirred solution of 1d (0.5 g, 2.8 mmol) in Et_2O (30 ml) was added dropwise an ether solution of 6a (2.8 ml, 1.1 M; 3.1 mmol) at -78°C, under nitrogen. After 15 min the red reaction mixture was worked up as above to afford a crude solid residue which was purified by flash chromatography on silica gel, using petroleum ether-ether (9:1) as eluant to give starting material 1d; 2-allenyl-3-methylquinoxaline 1r (0.155 g, 37% yield) m.p. 98-100°C (dec.) (acetone-petroleum ether): ν_{max} (nujol) 1940 cm^{-1} (C=C=C); δ_H ($CDCl_3$)

2.8 (3H, s), 5.4 (2H, d, J 7 Hz), 6.72 (1H, t, J 7 Hz), 7.6-8.2 (4H, m); 2-(2-propynyl)-3-methylquinoxaline 1s (0.044 g, 10% yield) m.p. 63-65°C, ν_{max} (nujol) 3245 cm^{-1} (C-H); δ_H ($CDCl_3$) 2.27 (1H, t, J 3 Hz), 2.88 (3H, s), 3.98 (2H, d, J 3 Hz), 7.7-8.8 (4H, m).

When to a solution of 1d (0.5 g, 2.8 mmol) in THF (30 ml) was added an ether solution of 6a (6.8 ml, 0,9 M; 6.1 mmol) at 0°C, under nitrogen, it was obtained a crude residue which was purified by flash chromatography on silica gel, using petroleum ether-ether (8:2) as eluant to give 1r (0.06 g, 11%), and 1s (0.252 g, 46%); when to a solution of (1d) (0.23 g, 1.3 mmol) in Et_2O (20 ml) was added 6a (2.2 ml, 0,9 M; 2.0 mmol) at -50°C it was obtained a crude solid residue constituted of starting material 1d, and 1s (0.168 g, 86% yield).

Preparation of the quinoxaline derivatives 1e-m. - To a stirred solution of DDQ (0.54 g, 2.4 mmol), or (0.27 g, 1.2 mmol) in dioxane (15 ml) was added slowly a solution of 3a-c, or 4g,i,l (1.2 mmol) respectively in dioxane (15 ml) at room temperature. The dark reaction mixture was stirred up to the disappearance of the starting material (TLC). Then the solvent was removed under reduced pressure to give a dark residue which was treated with ether. The ether suspension was filtered and the filtrate was evaporated in vacuo to afford the crude oily products 1e-m, which were purified by column chromatography on silica gel using petroleum ether-acetone (8:2) for 1e-g,l,m or petroleum ether-ether (1:1) for 1i.

2,3-Di-(2-propenyl)quinoxaline 1e[17] (21% yield); δ_H ($CDCl_3$) 3.8 -4.0 (4H, m), 5.0-5.4 (4H, m), 5.9-6.7 (2H, m), and 7.7-8.3 (4H, m).

2,3-Di-(2-methyl-2-propenyl)quinoxaline 1f (35% yield); δ_H ($CDCl_3$) 1.8 (6H, s), 3.8 (4H, s), 4.5-5.1 (4H, m), and 7.7-8.3 (4H, m).

2,3-Di-(1-methyl-2-propenyl)quinoxaline 1g (40% yield); ν_{max} (neat) 1635 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.53 (6H, d, J 7 Hz), 3.9-4.4 (2H, m), 4.9-5.4 (4H, m), 6.0-6.7 (2H, m), and 7.7-8.3 (4H, m).

2-(2-Propenyl)-3-methylquinoxaline 1i[18] (86% yield); ν_{max} (neat) 1640 cm^{-1}; δ_H ($CDCl_3$) 2.7 (3H, s), 3.7-3.9 (2H, m), 5.0-5.4 (2H, m), 5.9-6.8 (1H, m), and 7.7-8.3 (4H, m).

2-(2-Methyl-2-propenyl)-3-methylquinoxaline 1l (95% yield); δ_H ($CDCl_3$) 1.94 (3H, s), 2.85 (3H, s), 3.87 (2H, s), 4.65-5.2 (2H, m), and 7.7-8.5 (4H, m).

2-(1-Methyl-2-propenyl)-3-methylquinoxaline 1m (87% yield).

Crystal Data

$C_{16}H_{22}N_2$, M = 242.36, monoclinic, C 2/c, a=13.127, b=13.493, c=9.237 Å, β=119.54°, V=1423.41 $Å^3$. Z=4, D_x=1.13 mg m^{-3}, MoKα = 0.71069Å, F(000)=528.

Colourless transparent crystal with dimensions 0.4 X 0.4 X 0.1 mm was used to measure the cell parameters and record 726 reflections (677 unique) by a PW 1100 Philips four-circles diffractometer; $\vartheta \leq 25°$; ω-2ϑ scan mode.

LP correction, no absorption and secondary extinction correction. The space group from systematic absences (hkl, h+k = 2n+1 and h0l, l = 2n+1) could have been either C 2/c or Cc; however a E statistic test indicated a centro-symmetric space group. Structure solved by direct methods using SIR package,[19] refined by SHELX 76 (Sheldric, 1976). In the final stage of refinement 558 reflections with Fo > 4σ (Fo) were considered significant, six additional reflections omitted. Most H atoms located from difference Fourier synthesis, methyl group refined as rigid group. Anisotropic thermal parameters for non-H atoms and isotropic for H-atoms. The isotropic temperature factors of the H-atoms were not refined and fixed at the last value of U_{iso} for the atom to which they are attached. Final R = 0.060.

Crystal structure solution and discussion

Data affected by the bad quality of crystals which changed their colour into a dusky one caused some difficulties in the crystals structure solutions. The structure was solved first in non-centrosymmetric Cc space group by application of so called P10 formula[20] (usual tangent formula was unsuccessfull) The best figure of merit was developed into a E-map containing 10 non-H peaks. Completing structure by successive Fourier synthesis revealed the existence of a two-fold axis in the molecule. However the refinement of the structure was continued in Cc s.g., yielding the lowest R index = 0.068. Bond lenghts and angles calculated were unsatisfactory. The refinement of the structure was later thied on the assumption that the space group was centrosymmetric C 2/c with satisfactory results (R = 0.060). No atoms in special positions. In particular, normal N-C aromatic bonds were obtained. The half chair conformation of the 6-membered heterocyclic ring is shown by the torsion angles: N1-C3-C31-N11 = 63.67° and C1-C11-N11-C31 = 17.94°.

The main result of crystallographic study is that trans geometry of heterocyclic ring was revealed with respect to the two allylic groups.

Tables of atom coordinates, isotropic temperature factors, bond lenghts and angles are available on request.

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17) Compound 1e partly isomerises in $CDCl_3$ to 2-(2-propenyl)-3-(1-propenyl)quinoxaline 1t. ^{1}H-NMR, infact, indicates the appearance of signals at: 2.03 (3H, d), 6.9-7.3 (2H, m).
18) Compound 1i tends to isomerise in $CDCl_3$ to 2-(1-propenyl)-3-methylquinoxaline 1u as can be seen in the ^{1}H-NMR spectrum signals at: 2.05 (3H, d), 2.74 (3H, s), 6.9-7.4 (2H, m).
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