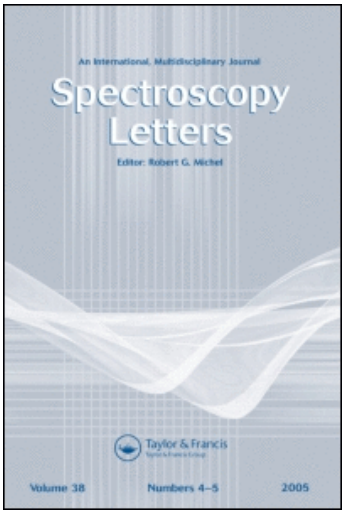

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Synthesis and Spectroscopic Structural Elucidation of New Quinoxaline Derivatives

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Abstract: A quinoxaline-2,3-dione derivative was synthesized, and its chemical structure was determined through spectral analysis. Alkylation of this compound under phase transfer catalysis (PTC) conditions yielded monoalkylated and diakylated adducts. The monolalkylation process was shown to be regioselective

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occurring on the quinoxalic nitrogen atom rather than on its pyrazolic analogue. The full characterization of the synthesized compounds was studied by concerted use of NMR and MS techniques. Assignments of proton and carbon atoms were achieved through analysis of the 1D ^{1}H and ^{13}C NMR spectra combined with homo- and hetero-nuclear 2D NMR experiments. Determination of the alkylation site was achieved through long-range proton–carbon coupling correlations spectroscopy.

Keywords: Alkylation, COSY, HMBC, HMQC, MS, NMR, quinoxaline, regioselectivity, structural elucidation

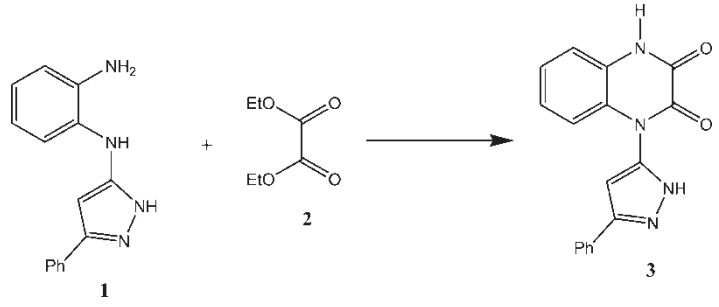
INTRODUCTION

Quinoxaline derivatives are of great importance because many applications have been reported for such adducts.[1–4] In addition to their use as metal detectors, [5] they are widely applied for medical use as antibiotics,[6] antidepressors,[7] and anticonvulsants. [8] They are also used in the agricultural field as fungicides,[9] herbicides, [10] and insecticides.[11] In cosmetology, many patents describe them as hair paint.[12] All these applications prompted us to investigate the synthesis of new quinoxalic derivatives. The current work was undertaken with the view to synthesize new heterocyclic systems of quinoxaline derivatives that may possess biological and pharmacological activities.

For this purpose, 3-*N*-(2-aminophenylamino)-5-phenylpyrazole (**1**) was chosen as starting material (Scheme 1). The synthesis of quinoxaline (**3**) was thus achieved and was used for the preparation of monoalkylated and diakylated derivatives. The structural elucidation of all the studied compounds was explored through IR, MS, and 1D and 2D NMR analysis.

MATERIALS AND METHODS

Melting points were determined on a Mettler FP 62 (Metler Toledo, Switzerland) in open capillary tubes or on a Koffler apparatus and are uncorrected. IR spectra



Scheme 1.

were recorded on a Perkin-Elmer 1600 spectrometer as KBr pellet. Mass spectra were recorded on a Varian Mat 311A spectrometer equipped with a Data System 2040. Spectra were acquired in EI or DCI/NH_3 modes. NMR spectra were acquired using a Bruker AC 200 and AC 250 spectrometers (Bruker, Germany) for 1D NMR analysis. 2D homo ($^1H-^1H$) and heteronuclear (HMQC, HMBC) coupling NMR analyses were acquired on a DPX 200 and 400 MHz apparatus. Chemical shifts are given in ppm using TMS as an internal standard and coupling constants are given in Hz. Elemental analysis was performed at CNRS service (Toulouse, France).

Synthesis of 1-(3-Phenylpyrazol-5-yl)-4-allyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (3)

Compound **1** 0.01 mole (3.04 g) was solubilized in 80 mL of ethyl oxalate. The obtained solution was concentrated and the residue was washed with ether. Compound **3** was then purified by recrystallization from ethanol with a yield of 90%: m.p. $> 260^\circ$C, IR (KBr): 1718 and 1722 (C═O). ^{1}H NMR ($DMSOd_6$): 6.71 (s, 1H, H–C4′), 6.88–7.41 (m, 9H, H-C aromatic). ^{13}C NMR ($DMSOd_6$): 100.5 (C4′), 115.5–129.1 (CH aromatic), 125.4, 126.0, 126.4, 144.2 (Cq), 144.5 (C═N), 153.7 (C═O), 155.1 (C═O). MS-DCI (NH_3): m/z 305 ($[M+H]^+$). Analysis: For $C_{17}H_{12}N_4O_2$, calculated C: 67.10%, H: 3.97%, N: 18.41%; found C: 66.92%, H: 4.18%, N: 18.27%.

Alkylation of Quinoxalin-2,3-dione

Compound **3** 0.01 mole was dissolved in 60 mL DMF; 0.02 mole each alkyl halide (CH_2═CH-Cl, HC≡C-CH_2-Br, Cl-CH_2COOEt), 0.02 mole of potassium carbonate, and tetrabutylammonium bromide were then added. The obtained mixture was stirred at room temperature. After filtration, the solvent was evaporated under reduced pressure and the resulting crude material was dissolved in CH_2Cl_2, concentrated under reduced pressure, and separated on Silicagel column chromatography using hexane/AcOEt 8/2 as eluent giving compounds **4**–**6** and **10**–**12** (Scheme 2).

1-(3′-Phenylpyrazol-5′-yl)-4-allyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (4)

The product was obtained by stirring the reaction mixture during 48 hr. Compound **4** was obtained with a yield of 81%: m.p. 228–230°C, IR (KBr): 1718 and 1722 (C═O). ^{1}H NMR ($CDCl_3$/TFA): 4.9 (d, 2H, N–CH_2, 7.2 Hz), 5.32 (dd, 1H, H_2C═, 2.7 and 9.6 Hz), 5.59 (m, 1H, HC═), 5.62 (dd, 1H, H_2C═, 1.4, 9.6 Hz), 6.84 (s, 1H, H–C4′), 6.88–7.41 (m, 9H,

H–C aromatic). ^{13}C NMR ($CDCl_3$/TFA): 46.8 (NCH_2), 102.6 (C4′), 108.7 (Cq), 119.4 (=CH_2), 125.7–131.2 (CH aromatic, =CH), 126.1 (C4a), 126.9 (C8a), 135.7 (Cq aromatic), 140.5 (C=N), 148.2 (Cq), 155.1 (C=O). MS (EI): m/z 344. Analysis: For $C_{20}H_{16}N_4O_2$, calculated C: 69.76%, H: 4.68%, N: 16.27%; found C: 69.60%, H: 4.88%, N: 16.32%.

1-(3′-Phenylpyrazol-5′-yl)-4-propargyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (5)

Compound **5** was obtained with a yield of 75% by stirring the reaction mixture during 12 h: m.p. 250–252°C, IR (KBr): 1718 and 1722 (C=O), 3260 (≡C-H), 2140 (C≡C). ^{1}H NMR ($CDCl_3$/TFA): 2.36 (t, 1H, HC≡, 2.6Hz), 5.05 (d, 2H, N–CH_2, 2.6 Hz), 6.67 (s, 1H, H–C4′), 6.85–7.59 (m, 9H, H–C aromatic). ^{13}C NMR ($CDCl_3$/TFA): 33.6 (NCH_2), 74.5 (≡CH), 75.3 (–C≡), 101.8 (C4′), 116.8–130.5 (CH aromatic), 123.1 (C4a), 125.2 (C8a), 125.7 (Cq), 141.7 (Cq(ar)), 147.2 (C=N), 155.0 (C=O), 159.6 (C=O). MS (EI): m/z 342. Analysis: For $C_{20}H_{14}N_4O_4$, calculated C: 70.17%, H: 4.12%, N: 16.37%; found C: 70.03%, H: 4.31%, N: 16.45%).

1-(3′-phenylpyrazol-5′-yl)-4-ethoxycarbonylmethyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (6)

Compound **6** was obtained with a yield of 70% according to the procedure described above by stirring the mixture during 72hr: m.p. 110–112°C, IR (KBr): 1718 and 1722 (C=O), 1750 (C=O ester). ^{1}H NMR ($CDCl_3$): 1.28 (t, 3H, CH_3, 7.1 Hz), 4.31 (q, 2H, OCH_2, 7.1 Hz), 5.00 (s, 2H, NCH_2), 6.34 (s, 1H, H–C4′), 6.81–7.23 (m, 9H, H–C(ar)). ^{13}C NMR ($CDCl_3$): 14.2 (CH_3), 44.7 (NCH_2), 62.3 (OCH_2), 99.8 (C4′), 114.1–128.8 (CH(ar)), 126.4 (C4a), 128.3 (C8a), 128.4 (Car), 143.6 (C3′), 145.8 (C=N), 154.6 (C=O), 155.0 (C=O), 167.2 (O-C=O). MS (EI): m/z 390. Analysis: For $C_{21}H_{18}N_4O_4$, calculated C: 64.61%, H: 4.65%, N: 16.39%; found C: 64.51%, H: 4.84%, N: 16.30%.

1-(1′-Allyl-3′-phenylpyrazol-5′-yl)-4-allyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (10)

The title product was obtained after stirring the mixture during 48 hr with a yield of 19%: m.p. 118–120°C, IR (KBr): 1718 and 1722 (C=O). ^{1}H NMR ($CDCl_3$): 6.67 (s, 1H, H–C(4)), 6.75–7.88 (m, 9H, H–C aromatic), 4.61 (d, 2H, N–CH_2, 7.4 Hz), 4.92 (d, 2H, N–CH_2, 7.4 Hz), 5.11 (m, 2H, H_2C=), 5.35 (m, 2H, H_2C=), 5.91 (m, 2H, HC=). ^{13}C NMR ($CDCl_3$): 45.8 (NCH_2), 52.6 (NCH_2), 102.0 (C4′), 108.7 (Cq), 118.7 (=CH_2), 118.9

(=CH_2), 124.5–131.8 (CH aromatic, =CH), 126.4 (C4a), 127.4 (C8a), 132.7 (Cq aromatic), 133.5 (C=N), 151.4 (C=O), 153.6 (C=O). MS-DCI (NH_3): m/z 385 ($[M+H]^+$). Analysis: For $C_{23}H_{20}N_4O_2$, calculated C: 71.86%, H: 5.24%, N: 14.57%; found C: 71.64%, H: 5.41%, N: 14.75%.

1-(1′-Propargyl-3′-phenylpyrazol-5′-yl)-4-propargyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (11)

Compound **11** was formed after stirring the reaction mixture during 12 hr. It was obtained with a yield of 25%: m.p. 205–207°C, IR (KBr): 1718 and 1722 (C=O), 3263 (≡C–H), 2143 (C≡C). ^{1}H NMR ($CDCl_3$/TFA): 6.78 (s, 1H, H–C4′), 6.91–7.75 (m, 9H, H–C(ar)), 4.96 (d, 2H, N–CH_2, 2.6 Hz), 5.11 (d, 2H, N–CH_2, 2.6 Hz), 2.24 (t, 1H, HC≡, 2.6Hz), 2.42 (t, 1H, HC≡, 2.6Hz). ^{13}C NMR ($CDCl_3$/TFA): 33.8 (NCH_2), 39.2 (NCH_2), 74.3 (≡CH), 74.8 (≡CH), 75.1 (–C≡), 75.7 (–C≡), 103.3 (C4′), 116.5–130.0 (CH aromatic), 125.2 (C4a), 126.4 (C8a), 129.9 (Cq), 134.1 (Cq aromatic), 152.9 (C=N), 154.2 (C=O), 154.3 (C=O). MS (EI): m/z 380. Analysis: For $C_{23}H_{16}N_4O_2$, calculated C: 72.62%, H: 4.24%, N: 14.73%; found C: 72.45%, H: 4.38%, N: 14.55%.

1-(1′-Ethoxycarbonylmethyl-3′-phenylpyrazol-5′-yl)-4-ethoxycarbonylmethyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (12)

Compound **12** was isolated through column chromatography after 72hr reaction. Reaction yield 30%, m.p. 128–130°C, IR (KBr): 1718 and 1722 (C=O), 1750 (CO ester). ^{1}H NMR ($CDCl_3$): 6.67 (s, 1H, H–C4′), 6.99–7.83 (m, 9H, H–C aromatic), 4.74 (s, 2H, NCH_2), 4.91 (s, 2H, NCH_2), 4.05 (q, 2H, OCH_2, 7.12 Hz), 4.27 (q, 2H, OCH_2, 7.12 Hz), 1.12 (t, 3H, CH_3, 7.12 Hz), 1.31 (t, 3H, CH_3, 7.12 Hz). ^{13}C NMR ($CDCl_3$): 14.0 (CH_3), 14.2 (CH_3), 44.7 (NCH_2), 51.0 (NCH_2), 62.0 (OCH_2), 62.4 (OCH_2), 102.0 (C4′), 108.5–128.8 (CH aromatic), 126.5 (C4a), 127.2 (C8a), 128.1 (Cq), 132.5 (Cq aromatic), 134.6 (C=N), 152.0 (C=O), 153.8 (C=O), 166.8 (O–C=O), 167.0 (O–C=O). MS (EI): m/z 476. Analysis: For $C_{24}H_{24}N_4O_6$, calculated C: 63.02%, H: 5.08%, N: 11.76%; found C: 62.80%, H: 5.25%, N: 11.92%.

RESULTS AND DISCUSSION

Synthesis of Quinoxaline-2,3-dione

Synthesis of the quinoxaline derivative **3** was performed, as indicated in Scheme 1, by action of ethyl oxalate **2** on the amino pyrazole **1**.[13] The latter was obtained from the 4-phenyl-1,5-benzodiazepin-2-thione by

hydrazinolysis. Structural elucidation of compound **3** was achieved through IR, MS, and NMR analysis. Thus, ^{1}H NMR spectrum recorded in DMSO showed in particular a signal at 6.71 ppm corresponding with the 4′ pyrazolic proton,[14] while the aromatic protons were observed between 6.65 and 7.68 ppm. Among the signals observed in the ^{13}C NMR spectrum were those located at 100.5 and 144.5 ppm assigned to the 4′ and 5′ pyrazolic carbon atoms while the two carbonyl carbon atoms were observed at 153.7 and 155.1 ppm. The presence of the latter was also confirmed through IR spectroscopy where absorptions were observed at 1718 and 1722 cm^{-1}.

The mass spectrum of compound **3** showed molecular ion at 304 in agreement with the proposed chemical structure. Various signals were also observed corresponding with the fragmentations shown in Fig. 1.

Alkylation of Quinoxaline-2,3-dione

In order to prepare new quinoxaline derivatives, alkylation of compound **3** by various alkyl halides (allyl bromide, propargyl bromide, ethyl chloroacetate) was explored under solid–liquid phase transfer catalysis in DMF, in presence of potassium carbonate and with tetra *n*-butylammonium bromide as catalyst. The formation of monoalkylated derivatives which were obtained as major compounds in addition to dialkylated derivatives was observed in all the studied cases (Scheme 2). It may be noted that two nitrogen atoms could be involved in the alkylation process. Thus, monoalkylation could occur on the pyrazolic nitrogen giving compounds **4**–**6** or on the quinoxalic one giving compounds **7**–**9**, while both nitrogen atoms are involved in the dilakylated derivatives yielding compounds **10**–**12**. The fact that only one monoalkylated derivative was obtained in all the studied cases showed

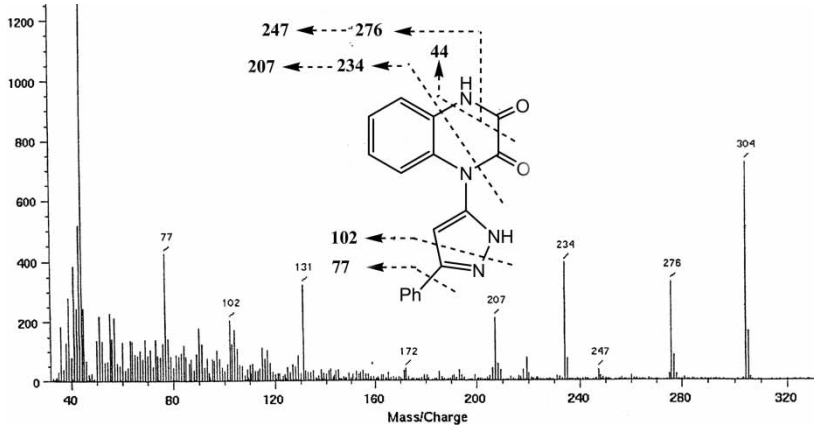
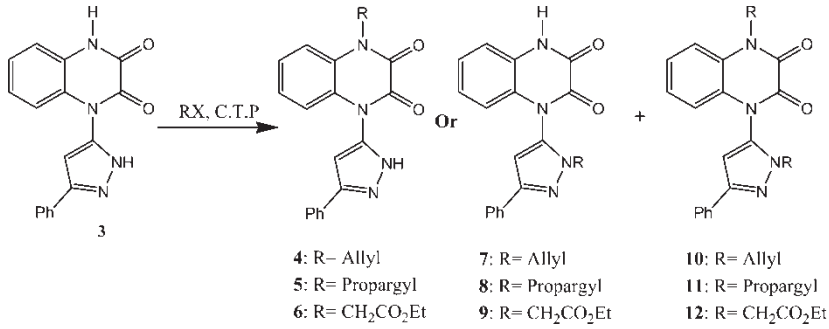


Figure 1. Mass spectrum and main fragmentations observed in compound 3.



Scheme 2.

that only one nitrogen atom was involved in the alkylation process suggesting that the reaction is regioselective.

In order to elucidate the regioselectivity of the reaction by determining which nitrogen atom was involved in the monoalkyllation process, the structures of the obtained compounds were investigated through IR, MS, 1D (^{1}H, ^{13}C), and 2D (COSY, HMQC, HMBC) NMR analysis. In the ^{1}H NMR spectra, the presence of signals corresponding with the alky groups (allyl, propargyl, CH_2COOEt) were observed. These data were also confirmed through ^{13}C NMR analysis, and the obtained results are gathered in the "Materials and Methods" section.

As indicated above, monolakylation could occur at the pyrazolic nitrogen giving products **4**–**6** or at the quinoxalic nitrogen yielding compounds **7**–**9**. In order to determine the alkylation site in each case, homonuclear (COSY) and heteronuclear (HMQC, HMBC) 2D NMR analyses were used. Only the monolakylated derivatives having the CH_2COOEt as alkyl group will be detailed here as an example. The structures of the two monoalkylated derivatives involving the allyl and the propargyl groups were determined through similar reasoning.

The possible monoalkylated derivatives involving the CH_2COOEt group are presented as structures A and B reported in Fig. 2.

The chemical shifts of all proton and carbon atoms in addition to the proton–proton coupling constants were determined through 1D (^{1}H, ^{13}C) and 2D (^{1}H–^{1}H COSY, ^{1}H–^{13}C HMQC, and HMBC) NMR analysis.

NMR analysis of the monoalkylated derivative (structure A or B) was initiated by ^{1}H NMR analysis. The obtained spectrum showed two singlets at 6.34 and 5.00 ppm integrating respectively one and two protons and corresponding with H–C4′ and NCH_2. The presence of the ethoxy group was easily confirmed by the presence in the obtained spectrum of one triplet (1.28 ppm, 3 protons) and quadruplet (4.31 ppm, 2 protons) with the same coupling constant (7.12 Hz) and corresponding respectively with the CH_3 and OCH_2 protons. Finally, the ^{1}H spectrum showed a multiplet between

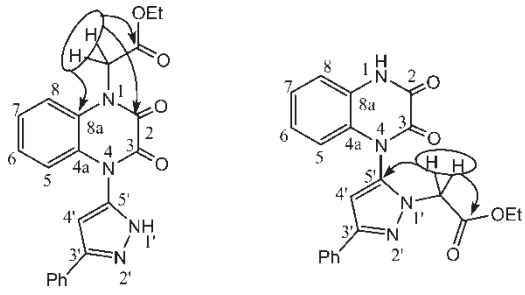


Figure 2. The two possible monoalkylated quinoxaline structures A and B.

6.81 and 7.23 ppm integrating 9 protons and corresponding with the aromatic protons. The 2D COSY NMR spectrum showed correlations involving the aromatic protons, and the 2D HMQC spectrum showed cross peaks between protons and their corresponding carbon atoms. Thus, the NCH_2 carbon atom was easily assigned to the signal located at 44.7 ppm due to the presence of a correlation with the signal located at 5.00 ppm attributed above to the CH_2 protons linked to the quinoxalic nitrogen atom. By the same reasoning, the signal located at 99.8 ppm was attributed to the C4′ carbon atom due to its correlation with the pyrazolic proton signal. Finally, the signals located at 14.2 and 62.3 ppm were attributed to the carbon atoms of the ethyl methylene and methyl group, respectively.

However, all these data did not allow us to distinguish between the two possible structures A and B, which are expected to show similar signals in 1D (^{1}H, ^{13}C) and 2D (COSY, HMQC) NMR analysis. In order to differentiate between the two structures, this requires long-range proton carbon correlations, which will clearly distinguish between the two hypothetical structures as indicated in Table 1 where the long-range correlations (^2J and ^3J) involving the NCH_2 protons expected to be observed in each structure are specified. As can be noticed, the ^2J correlations could not allow us to distinguish between the two structures because the only ^2J correlation possible is similar for both structures A and B and involves the carbonyl of the CO–OEt group. On the other hand, Table 1 shows that ^3J correlations expected to be

Table 1. Long-range correlations involving the NCH_2 protons expected to be observed in structures A and B

	^2J (^{1}H,^{13}C)	^3J (^{1}H,^{13}C)
Structure A	CO–OEt	C2, C8a
Structure B	CO–OEt	C5′

observed are different for structures A and B. Thus, in structure A where the alkyl group is located on the quinoxalic nitrogen, the methylene protons (NCH_2) should show cross peaks with the carbons 8a, 2, and the O–CO carbonyl carbon atom while only two correlations are expected to occur in the case of structure B, the 5′ carbon and the O–CO carbonyl carbon atom.

The obtained spectrum (Fig. 3) showed that the two methylene groups located around 5.0 ppm showed three correlations with carbon atoms located at 128.4, 154.6, and 155.0 ppm corresponding respectively with the C8a carbon, the C2 group, and the carbonyl of the CO–O–Et moiety in agreement with the structure A. This univocally demonstrates that the monoalkylation occurred at the quinoxalic nitrogen atom and not on the pyrazolic one.

The results concerning the main long-range correlations observed in the three monoalkylated derivatives are shown in Fig. 4. The observed correlations allowed us to confirm that the monoalkylation occurred at the quinoxalic nitrogen atom yielding compounds **4**, **5**, and **6**.

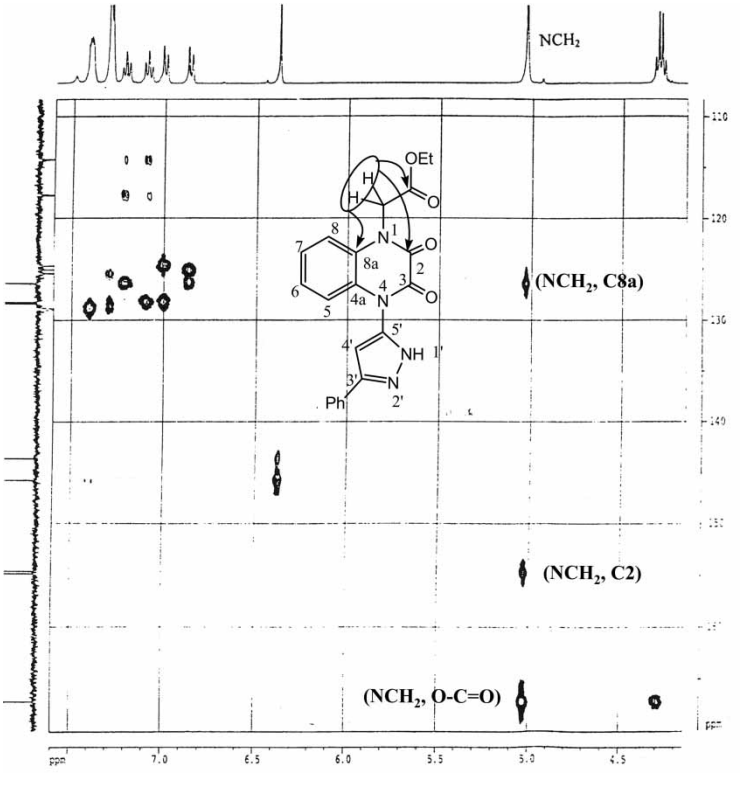


Figure 3. HMBC spectrum of compound 6.

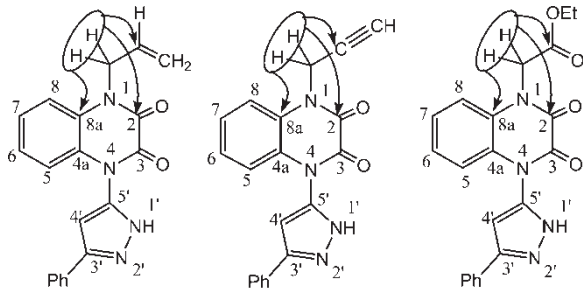


Figure 4. Long-range correlations involving the NCH_2 protons observed in compounds 4–6.

This demonstrated that the monoalkylation occurred at the quinoxalic nitrogen position, which could be considered as more reactive than the pyrazolic one. This led us to conclude that the obtained compounds corresponded thus with structures **4–6** and not to **7–9**.

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