

Synthesis Characterization and Stereostructures of the Pyridazino[6,1-b]Quinazolinones

Abdullah G.M. Al-Sehemi

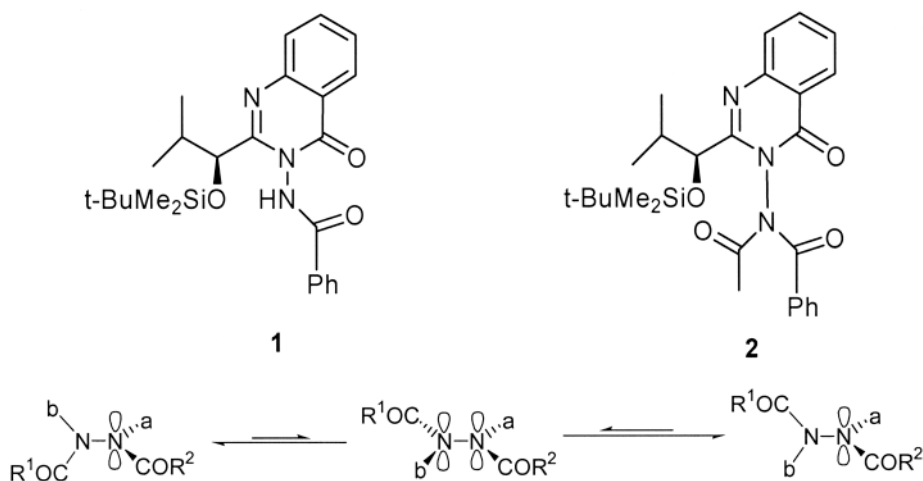
*Department of Chemistry, Teacher's College
Abha, Saudi Arabia*

Abstract. The title compounds pyridazino[6,1-b]quinazolinones were prepared in five steps from succinic anhydride in good yield without the need for chromatography. The barrier to rotation around the *N-N* bond and concurrent ring-inversion in 7 and 15, was so low at room temperature by comparison with 3-diacylaminoquinazolinone. The preferred geometries have been determined by a Hartree-Fock and Density Function Theory calculation [RHF/6-31G**(d), B3LYP/6-311G**(d)].

Introduction

Certain compounds containing quinazolinone ring system are known to possess a large variety of biological effects, particularly in the areas of antiinflammatory^[1], anticonvulsive^[2], antibacterial^[3], antitumor^[4] and antihypertensive^[5].

The barrier to rotation about the *N-N* bond is not sufficient to allow for separation of stereoisomers in monoacylaminoquinazolinones such as 1 unless the exocyclic nitrogen is additionally substituted. We have shown previously that 3-diacylaminoquinazolin-4(3*H*)-ones, when the two acyl groups on the exocyclic nitrogen are different, the *N-N* bond is a chiral axis with the two planes containing the quinazolinone and imide moieties orthogonal to one another^[6-10]. The barrier to *N-N* bond rotation is sufficiently high to allow separation of diastereoisomers (atropisomers) as in 2^[11]. The activation barrier to rotation arises from an unfavourable eclipsing interaction during the transition state, involving the field p-orbitals in each of the sp²-hybridised nitrogens and also due to steric interaction between the *N*-substituent (Scheme 1)^[12].

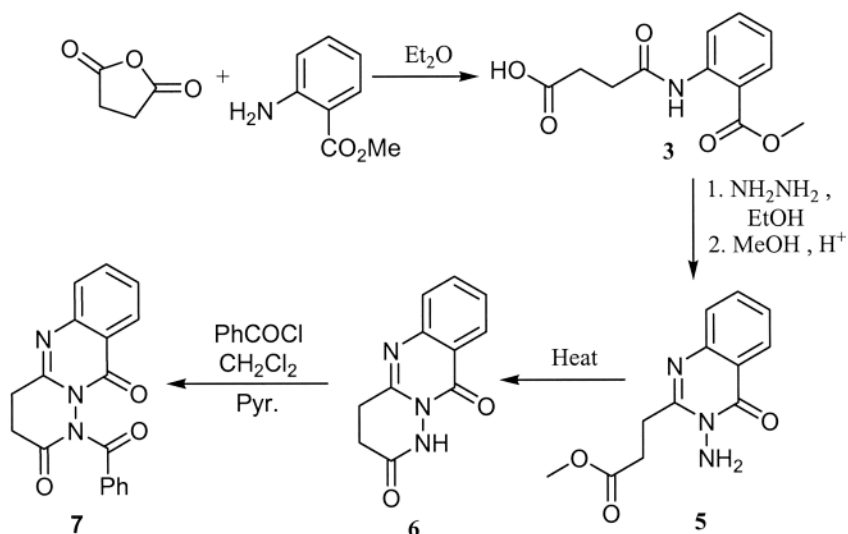


Scheme 1

Results and Discussion

Compounds 7 and 15 were of interest due to their structural similarity to the diacylaminopyridazinone such as 2. In these compounds, however, incorporation of one of the acyl groups into the dihydropyridazinone ring holds it in an *endo* position and quinazolinone and imide planes cannot be orthogonal.

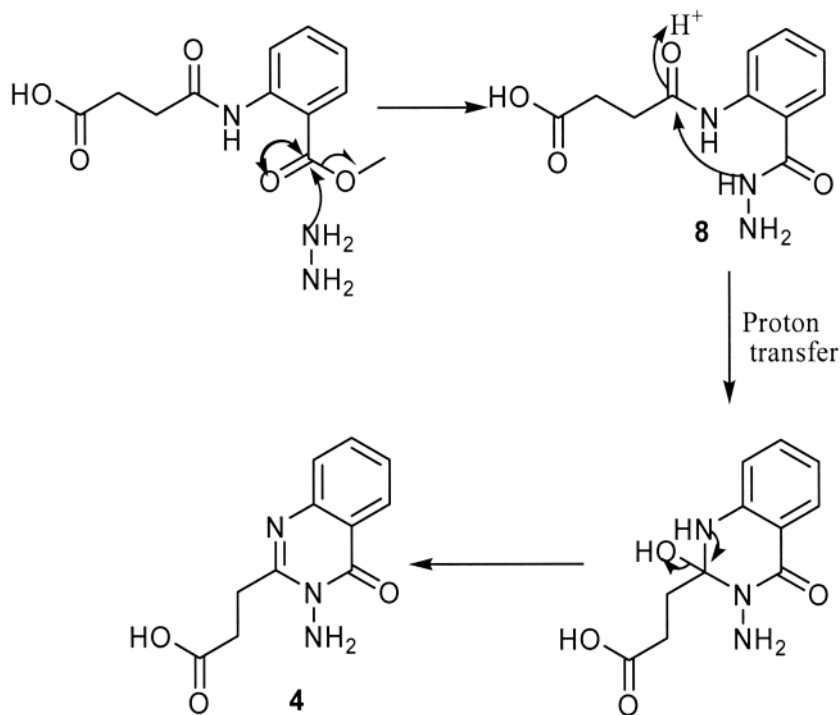
Pyridazinone 7 was prepared from succinic anhydride by the route shown in Scheme 2 in good yield (72%) without need for chromatographic separation at any stage.



Scheme 2

The proton NMR spectrum of **3** was of particular interest since the two methylene groups of the side-chain appeared equivalent, giving a sharp 4H-singlet at 2.79. The two environments of these methylene groups were, however, sufficiently different to allow their identification in the ^{13}C -NMR spectrum where there is a 3.4 ppm difference in chemical shift.

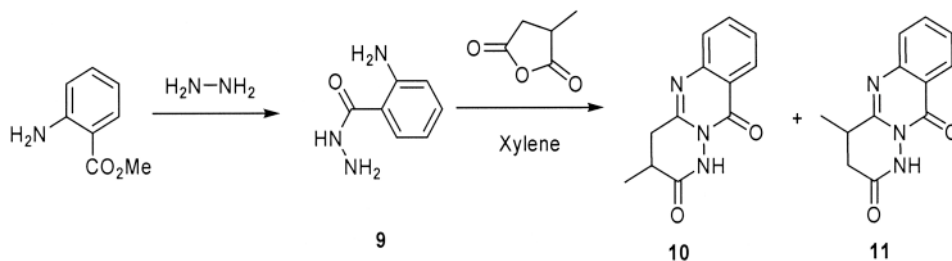
Cyclisation of the anthranilate **3** to give their respective 3-aminoquinazoliones **4** was achieved efficiently by heating the former in ethanol under reflux and in the presence of an excess of hydrazine monohydrate. On cooling, the hydrazine salt was collected in quantitative yield. Dissolution in water followed by neutralization using glacial acetic acid gave the free acid-containing 3-aminoquinazoliones in good yields and as crystalline white solids, without the need for subsequent purification. If, in the neutralization step the solution was made too acidic, the yields were observed to decrease suggesting that protonation of the quinazolinone ring occurred so reforming a water-soluble species. The mechanism for cyclisation is thought to involve initial attack of hydrazine on the more electrophilic ester carbonyl carbon to give an anthranil hydrazide **8** which intramolecularly attacks the amide carbonyl carbon. Subsequent dehydration affords the 3-aminoquinazolinone as its hydrazine salt (Scheme 3).



Scheme 3

Methyl Substituted Pyridazinone

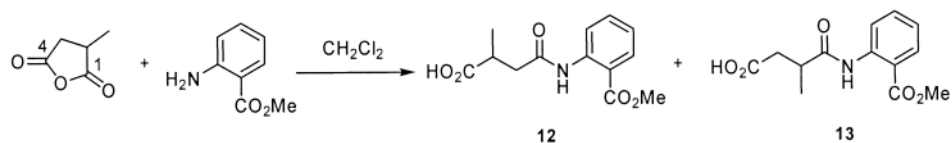
Racemic methyl succinic anhydride would provide the starting material for introduction of the methyl group into the side chain. Unlike succinic anhydride, methyl succinic anhydride is non-symmetrical so attack of a nucleophile on the two inequivalent carbonyl carbons results in two regioisomeric products. Direct synthesis of the required isomeric pyridazinone 10 and 11 is possible *via* nucleophilic attack of the anthranil hydrazide 9 in refluxing dry xylene as illustrated in (Scheme 4).



Scheme 4

However, this synthesis would require the subsequent separation of regioisomers 10 and 11 which was expected to be difficult. Consequently, the longer but reliable method that was used to prepare pyridazinone 6 was employed.

Reaction of methyl anthranilate with racemic methyl succinic anhydride gave methyl-N-(3-carboxymethylpropanoyl)anthranilate 12 and 13 (Scheme 5), easily distinguishable by NMR spectroscopy by comparison of the two distinct methyl signal doublets at 1.30 and 1.38 ppm respectively (the sense of regioselectivity will be discussed later). The major regioisomer 12 (33%) was separated by crystallisation.

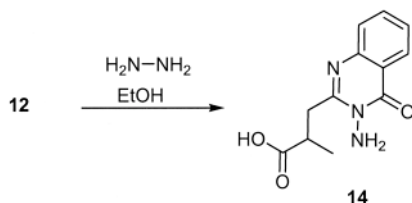


Scheme 5

The 3-aminoquinazolinone 14 was also synthesized *via* direct reaction of 12 with slightly excess amount of hydrazine monohydrate (Scheme 6).

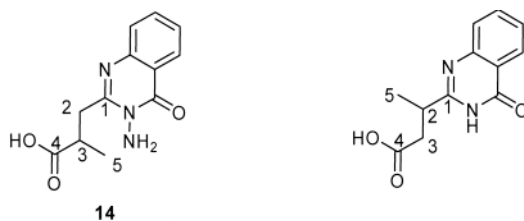
Regioselectivity in the Anthranil Ester Formation

From the proton NMR spectra of the crude reaction product in (Scheme 5) the overall ratio of 12 to 13 was calculated at 8:1. Evidence that 12 and hence



Scheme 6

quinazolinone 14, was the major regioisomer which formed from attack of methyl anthranilate on methyl succinic anhydride was obtained from several sources. Tentatively, relative chemical shift changes of the side-chain groups on converting 13 to 11 indicated 12 as being the major product. Additionally, nucleophilic attack by methyl anthranilate would be expected to occur at the less hindered carbonyl of methyl succinic anhydride, *i.e.*, C(4) to give 12 (Scheme 5). Such observations though have only been shown to manifest themselves when small nucleophiles such as the hydride ions are employed. More conclusive evidence came from 2D-NMR and mass spectrometry experiments, carried out on the pure 3-aminoquinazolinone regioisomer 14 that had been isolated, as follows:



Interpretation of the recorded Heteronuclear Multiple Bond Correlation (HMBC) spectrum is based upon the assignments of C(1) and C(4), which are believed to be correct. The relative magnitudes of cross-peaks between these quaternary carbons and the protons of the side-chain are in agreement with 3-aminoquinazolinone 14 as being the regioisomer present, as described below.

There are large cross-peaks at δ 3.0 and 3.4 ppm arising from a 2-bond coupling between C(1) and the two diastereotopic C(2)H₂ protons. Similarly, there are weak cross-peaks at δ 1.2 and 3.1 due 4-bond [to C(5)H₃] and 3-bond [to C(3)H] couplings respectively, involving C(1). For C(4) the situation is reversed: it shows strong 2-bond and 3-bond cross-peaks at 3.1 and 1.2 ppm to C(3)H and C(5)H₃, respectively. The cross peak with C(2)H₂ (3-bond) is weaker comparison to the case of C(1).

With regard to mass spectroscopy, specific breakage of the C(2)-C(3) bond would release fragments of differing molecular mass. By use of electron ionization such a cleavage was accomplished, resulting in an intense signal at m/z 175 corresponding to loss of the fragment $\text{CH}(\text{CH}_3)\text{CO}_2^-$ as can occur in 14. The lack of a peak at m/z 189 resulting from loss of CH_2CO_2^- in the alternative regioisomer, provided mass spectral evidence that 14 was the preferentially formed regioisomer.

Geometry optimization by *ab initio* quantum mechanical calculations were carried out on the two possible regioisomers 12 and 13, using the GAUSSIAN 98W package^[12]. The geometries were optimized in vacuum on the levels of both Hartree-Fock (HF/6-31G) and Density Functional Theory (DFT/B3LYP/6-31G).^[13] To obtain improved energy comparisons second-order (MP2) and fourth-order Moller-Pleset perturbation (MP4) calculations were also carried out on the HF optimized geometries. The results of quantum mechanical calculations show that Methyl-N-(3-carboxy-2-methylpropanoyl)anthranilate (12) is the global energy minimum structure (Table 1).

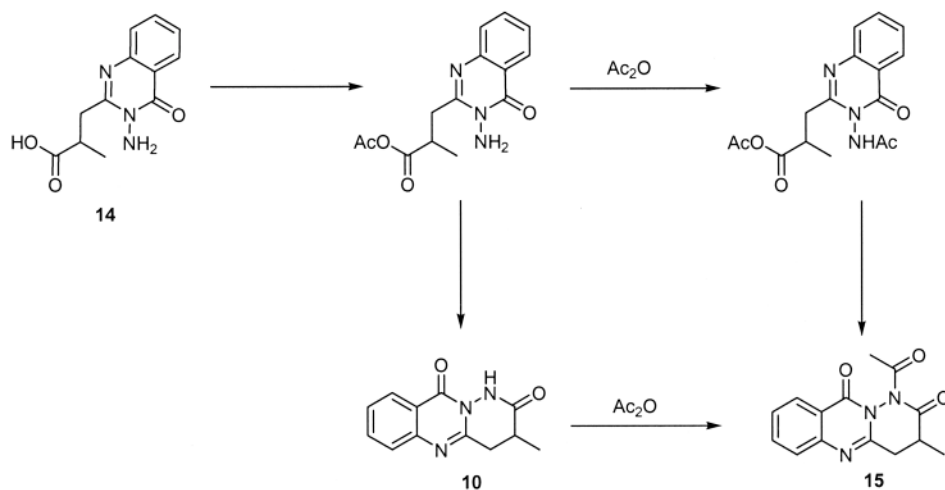
Table 1. The relative energies of two regioisomers from the various quantum mechanical methods.

Compounds	ΔE (kca/mol)			
	HF	MP2	MP4	DFT
12	0.0	0.0	0.0	0.0
13	9.7	19.0	21.2	12.5

The total energies for global minimum structure of 12 are HF = -929.4483259 hartree, MP2 = -931.2981677 hartree, MP4 = -929.448341222 hartree and DFT = -935.0676402 hartree. The MP2 and MP4 energies are obtained using the HF optimized structures.

Cyclisation 14 to Provide its Pyridazinone Compound 10

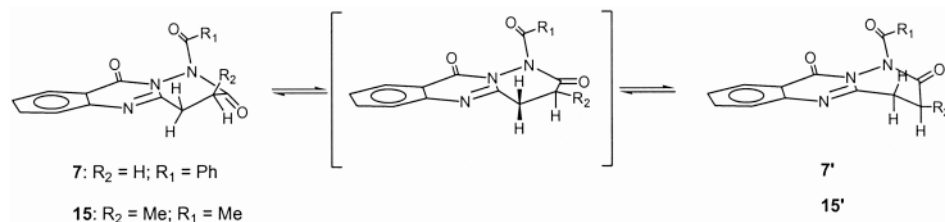
Conversion of 14 to pyridazinone 10 following the method described in (Scheme 2) would have involved initial formation of the methyl ester followed by pyrolysis to induce the intramolecular cyclisation. In an attempt to bring about a more direct synthesis^[14], was heated in acetic anhydride. Not surprisingly, the isolated product was the N-acetyl pyridazinone 15, formed by acetylation of nitrogen either before or after cyclisation to give the pyridazinone had occurred (Scheme 7).



Scheme 7

Stereostructures of Pyridazinonequinazolinone 7 and 15

The synthesis of the parent pyridazinone compound 6, formation of the new six-membered ring is favorable, however, the two filled p-orbitals from the adjacent sp^2 -hybridized nitrogens in the ring are orientated in a near eclipsing fashion *cf.* the preferred orthogonal arrangement found in DAQS^[6-11]. This unfavourable interaction could provide an inherent stereoelectronic barrier to ring-formation. The small angle between these p-orbitals in 7 and 15, is expected to raise the energy of the ground state conformation thereby making *N-N* bond rotation comparatively easy to achieve, at least in comparison to DAQs. In the presumed transition state between the two rotamers (diastereoisomers) 15 and 15' not only are the two p-orbitals directly eclipsing but the pyridazinone ring system becomes planar (Scheme 8). The two species inter converting *via* this transition state are diastereoisomeric, having different configurations for their *N-N* Chiral axis. The nature of the transition state suggests that *N-N* bond rotation and ring-inversion occur concurrently so providing a torsional as well as stereoelectronic barrier to interconversion.



Scheme 8

Consequently, a high-energy ground state may be compensated to some degree by a high-energy transition state leading to a high activation barrier for interconversion, albeit less than that believed to be present in DAQs. If the activation energy for interconversion in (Scheme 8) were large enough, then the *N-N* bond would constitute a chiral axis, making identification and/or isolation of the two diastereoisomers possible. The barrier to *N-N* bond rotation is considerably augmented in 3-diacylaminoquinazolinones by comparison with 3-monacylaminoquinazolinones. Consequently, a higher barrier to *N-N* bond rotation is anticipated in *N*-acylated pyridazinone 7 and 15 than their parent compound 6.

The proton NMR spectrum of *N*-acetylpyridazinone 15 was present as only one doublet signal for the methyl group. This seemed to disprove the initial suggestion that *N-N* bond rotation would be sufficiently retarded on the NMR timescale to allow identification of the two diastereoisomers, where the methyl group is in an axial or equatorial position. The presence of a single methyl doublet signal can be explained if the energy difference between the two diastereoisomers is large enough such that only one (the preferred) diastereoisomer was observable on the NMR timescale. It was, however, noticed that all quinazolinone ring systems. This broadening suggested an alternative explanation for the single methyl doublet the existence of two diastereoisomers that were rapidly interconverting on the NMR timescale due to a low barrier to *N-N* bond rotation and concurrent ring-inversion. Lowering the temperature would be expected to retard the rate of interconversion making it possible to observe the two diastereoisomers. Decreasing the temperature to 0°C resulted in the methyl doublet broadening to a broad singlet. Simultaneously, the complex resonances due to the three ring protons also broadened and began to coalesce at -20°C. By the time the temperature had reached -40°C the methyl resonances had reformed a well-defined doublet and the ring protons had begun to sharpen to a complex multiplet. It was anticipated that complete resolution of the latter signal could have been achieved by decreasing the temperature further, to the point where ring-inversion ceases to occur. Although the barrier to interconversion of the two species indicated (presumably the two diastereoisomers shown in (Scheme 8) has not been quantified it is clearly an order of magnitude less than that present in DAQs where analogous diastereoisomers can be separated and do not interconvert at room temperature. Again, the presence of only one methyl signal doublet at a temperature of -40°C was unexpected. This suggested that the two doublets, resulting from the methyl group being in the axial or equatorial position had coincidentally at the same chemical shift. It is likely that the two methyl signals would have been more non-equivalent in a ¹³C-NMR spectrum also recorded at -40°C, though unfortunately this was also not performed. From this work it appears that the barrier for *N-N* bond rotation in pyridazinones is much lower than for DAQs to the extent that a temperature of

-40°C is required to slow the process sufficiently for it to become visible on the NMR timescale.

In order to find whether a possible correlation could be established between the stereochemical *endo* (*endo* \equiv C = O *trans* to quinazolinone group) and *exo* (*exo* \equiv C = O *cis* to quinazolinone group) preference of two rotamers 7a and 7b determined experimentally (NMR) and their relative stabilities, the estimation of the total energies for the model compound 7 was carried out, using several basis sets to evaluate basis set effects using the GAUSSIAN98 program^[13]. For all calculations the most stable rotamers correspond to the *endo* structure 7b. The computational *endo* and *exo* configurations are illustrated in Fig. 1 along with their relative energies.

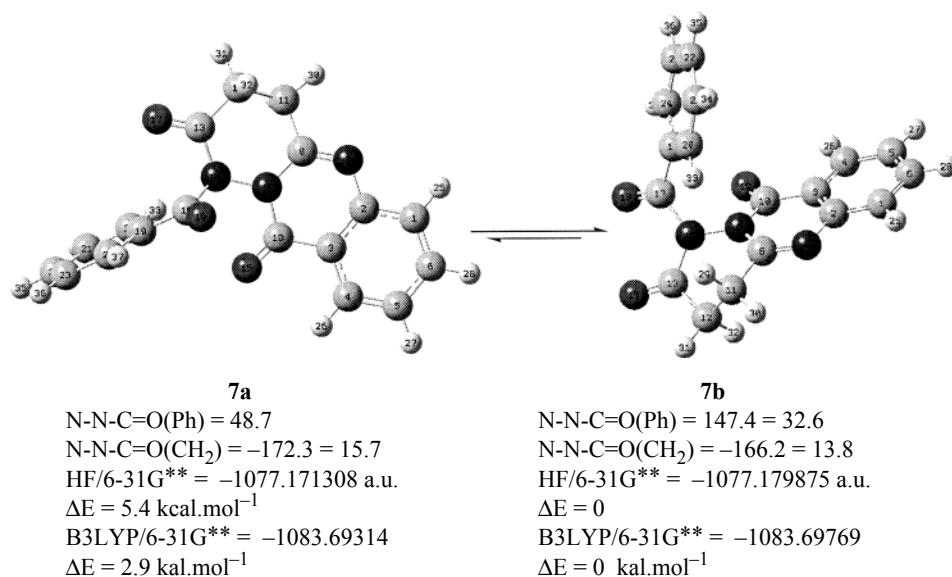


Fig. 1. Optimized geometries structure of pyridazinonequinazolinone (7a) and (7b) rotamers obtained at the *ab initio* (HF/6-31G**) levels and B3LYP/6-31G**; dihedral angles ($^{\circ}$) and relative energies (kcal/mol) shown.

Energy profile for rotation about dihedral angle N-N-C=O(Ph) for the 7a rotamer was studied. The calculations were performed at the semiempirical level (AM1) first and the minima points of the resulting energetic profile were further optimized at the level of *ab initio* (HF/6-31G). The changes in the total energy with the dihedral angle between N-N-C=O of the *endo* and *exo* rotamers were calculated by a stepwise variation of the dihedral angle. The calculation gave two ground state conformations corresponding to the rotamers 7a with the C=O group of the N-N-C=O(Ph) dihedral angle *exo*-oriented and 7b the C=O *endo*-oriented. These two conformations for the *endo* and *exo* rotamers are illustrated

in Fig. 2. As shown the *endo* rotamer 7b is the most stable conformer in this profile ($N-N-C=O = 147.4^\circ$) and the two ground state conformations for *endo*- and *exo* can be converted into each other. The optimized structural information is shown in Scheme 9.

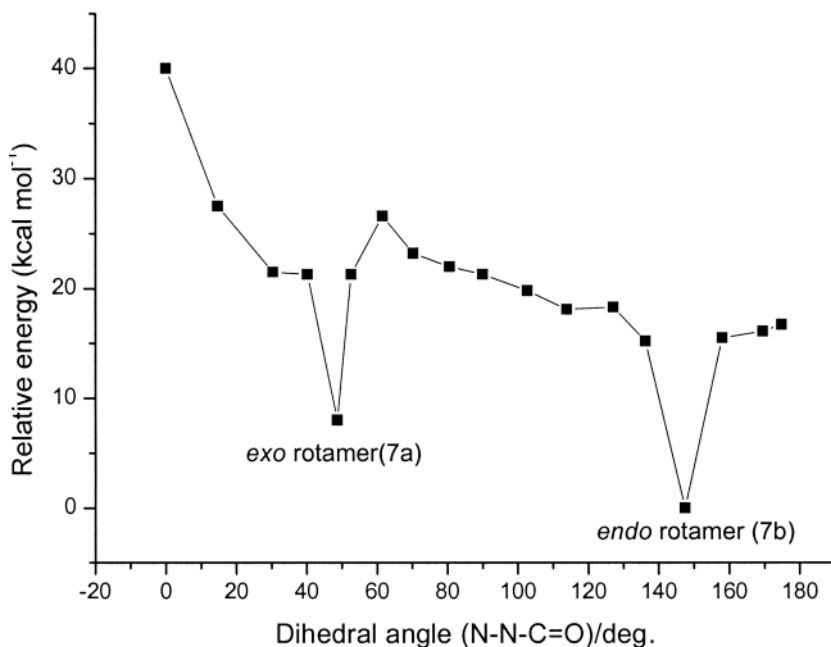
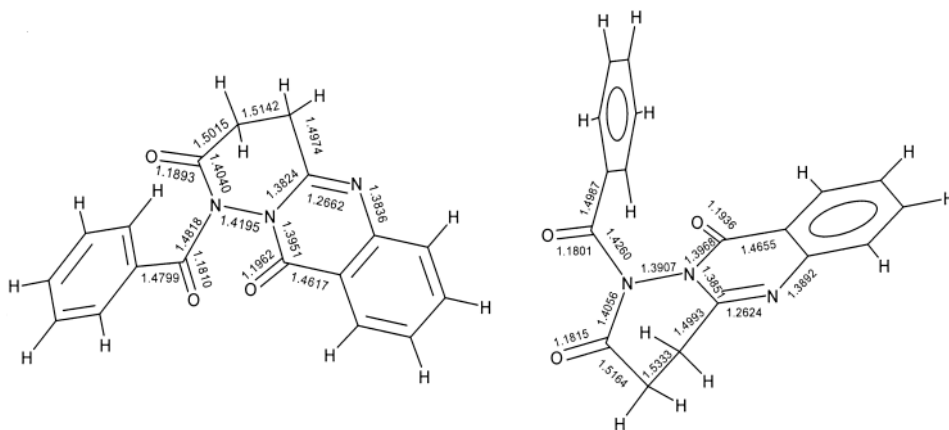


Fig. 2. Energy profile for the rotation about dihedral angle ($N-N-C=O(Ph)$) of 7, obtained at the semiempirical (AM1) level. The minima points in each case were optimized at the *ab initio* (HF/6-31G) level and the corresponding two stable rotamers for *exo* 7a and *endo* 7b.



Scheme 9

In summary, it can be speculated that at room temperature the barrier to *N-N* bond rotation and concurrent ring-inversion is so low that interconversion between the comparable amounts of the two *N-N* bond rotamers (diastereoisomers) present results in a time-averaged NMR spectrum. The broadening-sharpening observed in the signals as the temperature was lowered to -40°C suggests the existence of a barrier between two species, conceivably two diastereoisomers as in (Scheme 8).

Experimental

General

^1H NMR spectra were recorded with Bruker ARX 250 and DRX 300 NMR spectrometers respectively. ^{13}C NMR spectra were recorded at room temperature at 75 MHz. NMR spectra were recorded at room temperature in deuterated chloroform. *J* values are given in Hz using a Bruker DRX 400 spectrometer. IR spectra of crystalline compounds were recorded at room temperature in dichloromethane and of liquids as thin films using a Perkin-Elmer 298 spectrometer. Standard mass spectra were recorded on a Kratos Concept 1H Magnetic Sector Mass Spectrometer with fast atomic bombardment (FAB). Elemental analysis was carried out by CHN analysis. Melting point were determined on a Kofler hot stage and are uncorrected. Dichloromethane was distilled from calcium hydride. Routine drying of organic solutions was carried out using magnesium sulfate. All reaction products were dried under vacuum (\sim mmHg) prior to spectroscopic analysis and further use. Removal of solvent under reduced pressure was accomplished by using a rotary evaporator (Buchi) at (\sim 15 mmHg) water pump.

Preparation of Methyl-*N*-(3-Carboxypropanoyl) Anthranilate (3)

To solution of Succinic anhydride (12 g, 0.12 mol) was dissolved in sodium dried ether (300 cm^3) was added methyl anthranilate (34 ml, 0.26 mol, 2.2 equiv.) dropwise and allowed to stir overnight and the solvent removed by evaporation under reduced pressure to give cloudy oil which solidified overnight. Crystallisation of the product gave anthranilate 3 (24.51 g, 81%) as colourless crystals, m.p. $131\text{--}133^{\circ}\text{C}$ (from ethanol) (Found: MH^+ , 252.0872. $\text{C}_{12}\text{H}_{14}\text{NO}_5$ requires MH, 252.0872); δ_{H} 2.79 (4H, s, CH_2CH_2), 3.90 (3H, s, OCH_3), 7.07 (1H, ddd, *J* 1.6, 7.1 and 8.3, Ar 5-H), 7.52 (1H, ddd, *J* 1.6, 7.1 and 8.7, Ar 4-H), 8.0 (1H, dd, *J* 1.6 and 8.3, Ar 6-H) 8.68 (1H, dd, *J* 1.6 and 8.7 Ar 3-H), 9.45 and 11.04 (2H, br s and s, NH or CO_2H); δ_{C} 29.5 and 32.8 (CH_2CH_2), 52.7 (CO_2CH_3), 115.5 [CCO_2CH_3 (Ar)], 120.9, 123.1, 131.1 and 135.0 [$4 \times \text{CH}(\text{Ar})$], 141.5 [$\text{CNHCO}(\text{Ar})$], 169.2 and 170.9 (C=O); $\nu_{\text{max}}/\text{cm}^{-1}$ 3200vbr, 1720brs, 1590s and 1580s.

3-Amino-2-(2-Carboxyethyl)Quinazolin-4(3H)-One (4)

Anthranilate 3 (22 g) was dissolved in ethanol (30 cm³) and heat with hydrazine (24 cm³, 5.5 equiv.) in a closed steel container at 135°C for 12 h. The solution was cooled to room temperature and then in an ice-water bath for 0.5 h, yielding the hydrazine salt in quantitative yield. Dissolving of the salt in water and neutralization using glacial acetic acid gave the 3-aminoquinazolinone 4 (15 g, 73%) as colourless crystals mp 135-137°C (from ethanol) (Found: MH⁺, 234.0878. C₁₁H₁₁N₃O₃ requires MH 234.0879); δ_H (²H₆-DMSO), 2.87 (2H, t, *J* 7.1 QCH₂CH₂), 3.32 (2H, t, *J* 7.1, QCH₂CH₂), 5.85 (2H, br, s, NH₂), 7.58 (1H, dd, *J* 1.4, 7, 1 and 8.0, Q6-H), 7.69 (1H, d, *J* 8.0, Q8H), 7.88 (1H, ddd, *J* 1.4, 7.1 and 8.0, Q7-H) and 8.21 (1H, dd, *J* 0.9 and 8.0, Q5-H); δ_C (²H₆-DMSO) 28.8 (CH₂CH₂), 30.2 (CH₂CH₂) 120.0 [CC=O (Q)], 126.2, 126.4, and 134.3 [4 × CH (Q)], 146.6 [CN=C (Q)], 157.3 [C=N (Q)], 160.7 [C=O (Q)] and 174.3 (CO₂H); ν_{max}/cm⁻¹ 3320m, 3295w, 3200m, 1700s, 1680s, 1640s and 1605s; m/z 232(M⁻¹, 100%), 214 (29), 188 (59) and 172 (78).

3-Amino-2-(2-Ethoxycarbonylethyl)Quinazolin-4(3H)-One (5)

3-Aminoquinazolinone 4 (10 g) was added to an excess of methanol (150 ml) containing sulphuric acid (2 ml) and heated at reflux for 3 h. Neutralization of the solution using saturated sodium hydrogen carbonate afforded the 3-aminoquinazolinone methyl ester 5 (9.2 g, 86%) as colourless crystals, mp 179-181°C (from ethanol) (Found: MH⁺ 248.1036. C₁₂H₁₃N₃O₃ requires MH 248.1035); δ_H 2.93 (2H, t, *J* 6.9, QCH₂CH₂), 3.36 (2H, t, *J* 6.9, QCH₂CH₂), 3.71 (3H, s, CO₂CH₃), 4.96 (2H, br s, NH₂), 7, 44 (1H, ddd, *J* 1.2, 6.9 and 8.0, Q6-H), 7.62 (1H, d, *J* 8.3, Q8-H), 7.72 (1H, ddd, *J* 1.4, 6.9 and 8.3, Q7-H) and 8.23 (1H, dd, *J* 1.4 and 8.0, Q5-H); δ_C 34.0 (QCH₂CH₂), 35.1 (QCH₂CH₂), 57.0 (CO₂CH₃), 125.3 [CC=O (Q)], 131.5, 131.8, 132.5 and 139.6 [4 × CH (Q)] 151.9 [CN=C (Q)], 162.3 [C=N (Q)], 165, 9 [C=O (Q)] and 178,5 (CO₂CH₃); ν_{max}/cm⁻¹ 3310m, 3200m, 1735s, 1685s, 1660m, 1610 and 1600m.

3,4-Dihydro-1H-Pyridazino[6,1-b]Quinazline-2,10-Dione (6)

3-Aminoquinazolinone 5 (5 g) was heated at 190°C until methanol evolution ceased (5 min). On cooling to room temperature, the solid mass was digested in ethanol (20 ml) to provide the pyridazinone 6 (4 g, 87%) as a light-brown solid, crystallization from glacial acetic acid. (Found: MH⁺, 216.0773. C₁₁H₉N₃O₂ requires MH 216.0773) δ_H 2.83 (2H, m, QCH₂CH₂), 3.30 (2H, m, QCH₂CH₂), 7.54 (1H, ddd, *J* 1.6, 7.1 and 8.3, Q6-H), 7.72 (1H, dd, *J* 1.6 and 8.3, Q8-H), 7.81 (1H, ddd, *J* 71.6, 7.1 and 8.3, Q7-H), 8.30 (1H, dd, *J* 1.6 and 8.3, Q5-H) and 9.70 (1H, br s, NH); δ_C 28.9 and 29.2 (CH₂CH₂), 121.0 [CC=O (Q)], 126.9,

127.8 and 134.5 [$3 \times \text{CH}$ (Q) one peak overlaid], 146.9 (CN=C (Q)), 149.2 [CN (Q)], 155.5 [C=O (Q)] and 168.8 (CONH); $\nu_{\text{max}}/\text{cm}^{-1}$ 1670brs and 1600s.

N-Benzoylation of Pyridasinon[6,1-*b*]Quinazoline 7

Pyridazinone 6 (0.1 g, 0.47 mmol) was dissolved in dry dichloromethane (2 cm^3) containing dry pyridine (0.07 g, 0.94 mmol). Benzoyl chloride (0.131 g, 0.94 mmol) was added dropwise over 10 min with subsequent stirring at room temperature for 24 h. A further quantity of dichloromethane (10 ml) was added and the solution washed consecutively with sodium hydrogen carbonate, water and brine solution before being dried over magnesium sulphate. Removal of the solvent under reduced pressure afforded a black oil. Purification by flash chromatography eluting with light petroleum-ethyl acetate (4:1) provided the *N*-benzoylpyridazinone 7 as colourless crystals (0.11 g, 72%) (Found: M^+ , 319.0957). $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_3$ requires M 319.0957); δ_{H} 2.91(2H, m, $\text{CH}_2\text{C}=\text{N}$), 3.27 (2H, m, CH_2CO), 7.40-7.54 [4H, m, $3 \times \text{CH}(\text{Ph})$ and 6-H(Q)], 7.57-8.0 [4H, m, $2 \times \text{CH}(\text{pH})$, 7- and 8-H(Q)], and 8.22 [1H, d, J 8.2, 5-H(Q)]; δ_{C} (100 MHz) 28.7 and 32.9 (CH_2CH_2), 121.6 [CC=O (Q)], 122.4, 127.6, 127, 7, 127.9, 128.7, 128.9, 132.2, 134.2 and 135 [$5 \times \text{CH}(\text{Ph})$ and $4 \times \text{CH}(\text{Q})$] 146.3 [CN=C (Q)], 157.3 [C=N (Q)], 159.5 [C=O (Q), and 170.9 and 179.0 ($2 \times \text{CO}$).

Methyl-N-(3-Carboxy-2-Methylpropanoyl)Anthranilate (12) and *Methyl-N*-(3-Carboxy-3-Methylpropanoyl)Anthranilate (13)

To racemic methyl succinic anhydride (6 g) dissolved in sodium dried ether (200 cm^3) was added methyl anthranilate (9.5 g, 1.2 equiv.) dropwise and allowed to stir at room and allowed to stir at room temperature for 48 h and the solvent removed by evaporation under reduced to give cloudy oil which solidified over 12 h. A proton NMR spectrum of the crude product showed the presence of 8:1 mixture of regioisomers by comparison of the signals at δ_{H} and 1.31 and 1.37, respectively. Crystallization of the crude product (5.2 g) from ethanol provided the major regioisomer 2-methyl anthranil ester 12 (4.00 g, 33%) as a colourless solid mp 70-71°C (from ethanol) (Found: C, 58.76; H, 5.71; N, 5.27. $\text{C}_{13}\text{H}_{15}\text{NO}_5$ requires C, 58.86; H, 5.70; N, 5.28%); δ_{H} 1.31 (3H, d, J 7.1, CH (CH_3), 2.55 [1H, dd, J 76.0 and 15.6, CHHCH), 2.90 [1H, dd, J 7.8 and 15.6, CHH(CH)] 3.10 [1H, app. septet, J 6.9 and 7.6 CH(CH_3)] 3.91 (3H, s, CO_2CH_3), 7.07 (1H, dd, J 1.2, 7.1 and 8.0, Ar 5-H), 7.51 (1H, ddd, J 7 1.6, 7.1 and 8.5, Ar 4-H), 8.00 (1H, dd, J 1.6 and 8.0, Ar 6-H), 8.66 (1H, d, J 7 8.5, Ar 3-H), 9.10 and 11.14 (2H, br s and s, NH or CO_2H); δ_{C} 17.3 [CH(CH_3)]. 36.2 [CH $_2$ CH(CH_3)], 41.5 [CH $_2$ CH(CH_3)], 52.8 (CO_2CH_3), 115.4 [CCO $_2$ CH $_3$ (Ar)], 120.9, 123.0, 131.2 and 135.0 [$4 \times \text{CH}$ (Ar)], 141.6 [CNHCO (Ar)], 169.1 and

170.5 [CO_2CH_3 (Ar) and NHCO (Ar)] and 181.3 (CO_2H); $\nu_{\text{max}}/\text{cm}^{-1}$ 3260w, 1690s, 1700s, 1600s and 1590s.

3-Amino-2-(2-Carboxypropyl)Quinazolin-4(3H)-One QNH₂ (14)

To anthranilate 12 (2 g) was dissolved in ethanol (10 cm³) were added hydrazine monohydrate (2 g, 5.4 equiv.) but the reaction mixture heated under reflux for 5 h. Subsequent stirring at room temperature overnight, the bulk of the solvent was removed under reduced pressure and the residue digested in water. Neutralisation using glacial acetic acid gave the 3-aminoquinazolinone 14 (1.23 g, 65%) as colourless crystals, m.p. 145-146°C (from ethanol) (Found: C, 58.24; H, 5.33; 16.98. $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_3$ requires C, 58.29; H, 5.30; N, 16.99%); δ_{H} (²H₆]-DMSO) 1.42 [3H, d, *J* 7.1, $\text{CH}(\text{CH}_3)$], 3.16 (1H, dd, *J* 6.0 and 16.3, $\text{CHH}(\text{CH})$], 3.33 [app. sextet, *J* 7.1, $\text{CH}(\text{CH}_3)$], 3.57 [1H, dd, *J* 7.8 d, 16.3, $\text{CHH}(\text{CH})$], 5.94 (2H, br s, NH_2), 7.64 (1H, ddd, *J* 0.9, 7.1 -and 8.0, Q 6-H), 7.76 (1H, d, *J* 8.5, Q 8-H), 7.94 (1H, ddd, *J* 1.6, 7.1 and 8.5, Q 7-H) and 8.29 (1H, dd, *J* 1.6 and 8.0 Q 5-H); δ_{C} (²H₆]-DMSO) 17.6 [$\text{CH}(\text{CH}_3)$], 36.2 [$\text{CH}(\text{CH}_3)$], 37.0 [$\text{CH}_2\text{CH}(\text{CH}_3)$], 120.1 [$\text{CC}=\text{O}$ (Q)], 126.2, 126.4, 127.2 and 134.2 (4 × CH (Q)), 146.6 (CN=C (Q)), 156.7 [C=N (Q)], 160.7 [C=O (Q)] and 177.3 (CO_2H); $\nu_{\text{max}}/\text{cm}^{-1}$, 3345w, 1700m, 1680m and 1605m.

3-Methyl-4-Dihydro-1-Acetylpyridazino[6,1-b]Quinazoline-2,10-Dione (15)

3-Aminoquinazolinone 14 (0.1 g, 0.4 mmol) was allowed to stir in acetic anhydride (3 ml) at 100°C for 2 h. The excess acetic anhydride was removed under reduced pressure resulting viscous yellow oil (89 mg). Purification by flash chromatography eluting with neat ethyl acetate gave a sample (52 mg) which possessed two spots on TLC (*R_f* 0.44 and 0.22). Repeat elution using light petroleum-ethyl acetate (1:3) afforded the product pyridazinone 15 as a viscous colourless oil *R_f* 0.44 (27 mg, 24.5%) (Found: MH^+ , 272.1035. $\text{C}_{14}\text{H}_{14}\text{N}_3\text{O}_3$ requires MH. 272.1035); δ_{H} 1.37 (3H, d, *J* 6.2, CHCH_3), 2.72 (3H, s, NCOCH_3), 2.94 [2H, m, $\text{CH}_2\text{CH}(\text{CH}_3)$], 3.12 [1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)$]. 7.51 (1H, ddd, *J* 1.2, 7.1 and 8.0, Q 6-H), 7.66 (1H, d, *J* 8.0, Q 8-H), 7.79 (1H, ddd, *J* 1.6, 7.1 and 8.0, Q 7-H) and 8.26 (1H, dd, *J* 1.6 and 8.0, Q 5-H); δ_{C} (100 MHz) 14.6 (CHCH_3), 26.2 [$\text{CH}_2\text{CH}(\text{CH}_3)$] 36.3 [$\text{CH}_2\text{CH}(\text{CH}_3)$], 37.5 (NCOCH_3), 121.7 [$\text{CC}=\text{O}$ (Q)], 127.5, 127.8, 127.9 and 135.4 [4 × CH (Q)], 146.2 [CN=C (Q)], 151.7 [C=N (Q)], 156.8 [C=O (Q)], 166.6 [$\text{CH}(\text{CH}_3)\text{C}=\text{O}$] and 172.9 [N(O=CCH₃)]; $\nu_{\text{max}}/\text{cm}^{-1}$ 1745m, 1700m, 1630w and 1610w.

References

- [1] Chao, Q., Deng, L., Shih, H., Leoni, L., Genini, D., Cason, D.A. and Cattam, H.B., *J. Med. Chem.*, **42**: 3860 (1999).
- [2] Mannschreck, A., Koller, H., Stuhler, G. and Davies, M.A., *Eur. J. Med. Chem.*, **19**: 381 (1984).
- [3] Hess, H.J., Cromin, T.H. and Scriabine, A., *J. Med. Chem.*, **11**: 130 (1968).
- [4] Xia, Y., Yang, Z., Hour, M., Kuo, S., Xia, P., Bastow, K.F., Nakanishi, Y., Nam-poothiri, P., Hackt, T., Hamel, E. and Lee, K., *Med. Chem. Lett.*, **11**: 1193 (2001).
- [5] Bandurco, V., Wong, E.M., Levine, S.D. and Hajos, Z.G., *J. Med. Chem.*, **24**: 1456 (1981).
- [6] Al-Sehemi, A.G., Atkinson, R.S., Fawcett, J. and Russell, D.R., *Chem. Commun.*, **43** (2000).
- [7] Al-Sehemi, A.G., Atkinson, R.S., Fawcett, J. and Russell, D.R., *Tetrahedron Lett.*, **41**: 2239 (2000).
- [8] Al-Sehemi, A.G., Atkinson, R.S., Fawcett, J. and Russell, D.R., *Tetrahedron Lett.*, **41**: 2243 (2000).
- [9] Al-Sehemi, A.G., Atkinson, R.S., Fawcett, J. and Russell, D.R., *J. Chem. Soc., Perkin Trans.*, **1**: 4413 (2000).
- [10] Al-Sehemi, A.G., Atkinson, R.S. and Fawcett, J., *J. Chem. Soc., Perkin Trans.*, **1**: 257 (2002).
- [11] Al-Sehemi, A.G., Atkinson, R.S. and Meades, C.K., *Chem. Commun.*, 2684 (2001).
- [12] Al-Sehemi, A.G., *J. Saudi Chem. Soc.*, **8**: 461 (2004).
- [13] Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Zakrzewski, V.G., Montgomery, J.A., Jr., Stratmann, R.E., Burant, J.C., Dapprich, S., Millam, J.M., Daniels, A.D., Kudin, R.N., Strain, M.C., Farkas, O., Tomasi, J., Barone, V., Cossi, M., Cammi, R., Mennucci, B., Pomelli, C., Adamo, C., Clifford, S., Ochterski, J., Petersson, C.A., Ayala, P.Y., Cui, Q., Morokuma, K., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Cioslowski, J., Ortiz, J.V., Baboul, A.G., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Gomperts, R., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Gonzalez, C., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Andres, J.L., Gonzalez, C., Head-Gordon, M., Replogle, E.S. and Pople, J.A., Gaussian, Inc., Pittsburgh PA (1998).
- [14] Binkley, J.S., Pople, J.A. and Hehre, W.J., *J. Am. Chem. Soc.*, **102**: 939 (1980).

تخصير وتوصيف ودراسة فراغية لمركبات بيريدازين (6,1-b) كينازولينون

عبدالله السحيمي

قسم الكيمياء ، كلية أبها للمعلمين ، أبها - المملكة العربية السعودية

المستخلص. تم تخصير مركبات pyridazino[6,1-b]quinazolinones في خمس خطوات ابتداءً من السكسنك انهيدرايد ، وكان الناتج جيداً من غير الحاجة إلى كروماتوجرافي للفصل أو التنقية خلال أي من الخطوات الخمس . كما أن طاقة الإعاقاة الفراغية حول الرابطة *N-N* وانقلاب الحلقة في المركبين ٧ و ١٧ كانت منخفضة عند درجة حرارة الغرفة مقارنة ب diacylaminoquinazolinone . كما تم تعيين الوضع الهندسي المفضل لهذه المركبات باستخدام حسابات نظرية بواسطة Hartree-Fock وحسابات الكثافة الوظيفية النظرية (Density Function Theory calculation) [RHF/6-31G**(d), B3LYP/6-311G**(d)] .