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SYNTHESIS AND REACTIVITY OF A NEW PYRANOQUINOXALINE

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Abstract – 3-Methyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinoxalin-1-one (**2**) was prepared from a series of 3-methyl-4,5,10,11-tetrahydropyrano[4,3-*b*][1,5]benzodiazepin-1(3*H*)-one derivatives (**1**) bearing various substituents at position 11. The formation of this quinoxaline is initiated by oxidation of the diazepine-4',11'-double bond to give an unstable epoxide intermediate, followed by a ring contraction which releases a carben species that has been trapped in the presence of cyclohexene. Reactivity of this new quinoxaline (**2**) with various primary and secondary amines was investigated.

INTRODUCTION

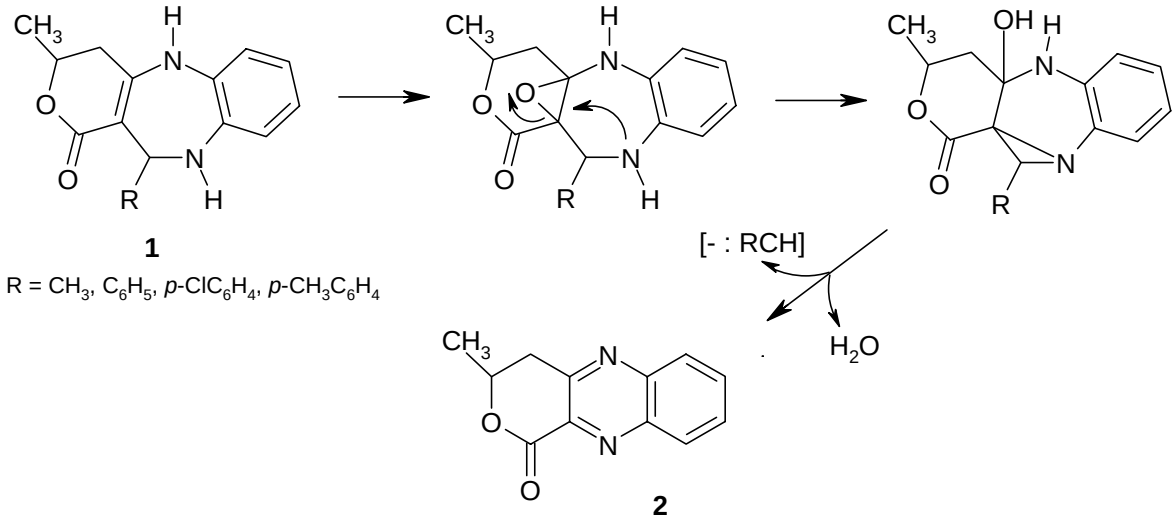
A variety of heterocyclic compounds, including indole or benzimidazole derivatives, have been obtained by rearrangement of substituted benzodiazepines.[1] The mechanism of these rearrangements involves in most of the cases either ring opening, or intermediates in which the 7-membered ring of the diazepine is bridged. In the latter case, the rather unstable bridged intermediates often undergo a ring contraction leading to heterocyclic skeletal changes, aromatization being most of the time the driving force of these rearrangements. Ring contraction reactions involving radical processes leading to quinoxalines as major products were also observed when 2,3-dihydro-1,4-diazepines were submitted to flash vacuum pyrolysis at high temperature.[2,3] In preceeding studies, 5,6-dihydro-4-hydroxy-6-methyl-2-pyrone was used as starting compound to versatilely prepare a series of benzimidazole, benzimidazolone and benzodiazepine (**1**) derivatives fused to the dihydropyrone moiety.[4,5] All these heterocyclic derivatives, as well as quinoxaline

compounds, are known to exhibit a large number of biological activities, including antibacterial, antiviral, antifungal or antihelmintic properties.[6] Quinoxalines are mainly prepared by condensation of *o*-phenylenediamines with various α-dicarbonyl derivatives, although other procedures have been reported such as the condensation of aryldiamines with 2,3-dibromo compounds[7] or the rearrangement of benzimidazole under thermal conditions.[8] As part of a study examining the reactivity of benzodiazepine compounds, the present paper describes the synthesis of 3-methyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]-quinoxalin-1-one (**2**) starting from various tetrahydrobenzodiazepine derivatives which were found to undergo an unusual rearrangement involving a ring contraction on treatment with sodium hypochlorite. On treatment with some primary amines, this new quinoxalinone leads to the formation of compounds having an *N*-alkylated dihydro-2-pyridone moiety fused to the quinoxaline cycle.

RESULTS AND DISCUSSION

Synthesis of quinoxaline (**2**).

The oxidation of benzodiazepine derivatives (**1**) using sodium hypochlorite as oxygen source under slight acid catalytic conditions (pH = 5-6) gave spontaneously the pyranoquinoxaline (**2**). A proposed mechanism for this conversion is depicted in Scheme 1.



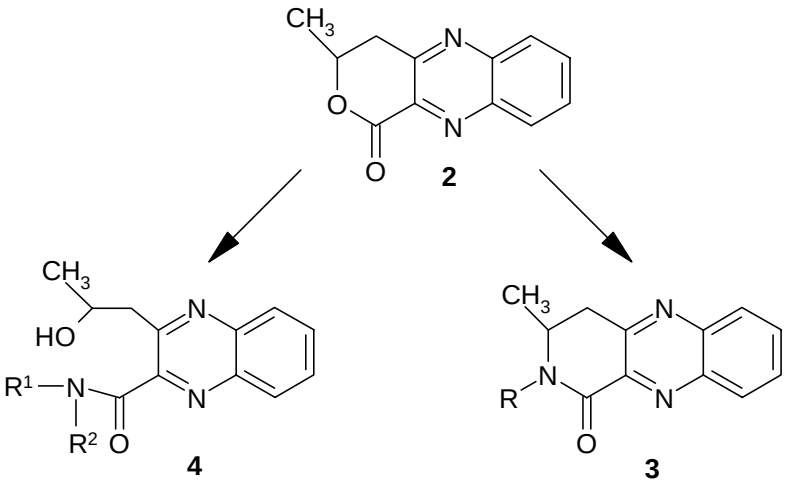
Scheme 1

In a first step, incorporation of oxygen could occur allowing conversion of benzodiazepines to their corresponding epoxide derivatives, which could not be isolated due to their instability under the experimental conditions. Unfortunately, attempts to isolate or identify the epoxide intermediate by using various oxidants such as *m*-chloroperbenzoic acid failed. The formation of quinoxaline (**2**) may be then explained by an epoxide openning by nucleophilic attack of the N^{10}-atom, leading to an aziridine intermediate. A further concomitant dehydration and diazepine ring contraction could finally account for

the quinoxaline formation. Since carbenes are likely intermediates in the course of these ring contraction reactions, the reaction (in the case of R = C_6H_5) was conducted in the presence of cyclohexene in an attemp to trap the reactive carbene intermediate. As expected, in that case 7-phenylbicyclo[4.1.0]heptane was *in situ* evidenced by ^{1}H-NMR spectrometry, thus proving that a carbene was expulsed during the quinoxaline formation. Beside the formation of the expected trapped carbene, trace amounts of benzaldehyde, arising from carbene oxidation, were also detected in the reaction mixture. Depending on the nature of the substituents, yields ranging from 40 to 80 % were typically obtained, the best yields being reached when substituents were aryl groups, probably due to the intrinsic stability of the carbene intermediates.

Reactivity of quinoxaline (**2**).

The synthetic potential of pyranoquinoxaline (**2**) was investigated. Treatment of **2** with several primary amines (Scheme 2) in refluxing ethyl acetate in the presence of catalytic amounts of acetic acid afforded different products, depending on the strutures of amines.



Scheme 2

However in all cases, the carbonyl of the pyrone was the initial target of the amino group attack. But while reactions with aliphatic primary amines gave in high yield tricyclic *N*-alkylated pyridoquinoxalinone derivatives (**3**), primary amines such as benzylamine or isopropylamine led to compounds (**4**) after ring opening of the 2-pyrone moiety. Cyclization was not observed in the latter case despite of the acidic conditions used that could have promote the cyclization / dehydration reaction. Similarly, uncyclized compounds (**4**) were obtained in all cases when quinoxaline (**2**) was allowed to react with secondary amines.

All these compounds were fully characterized by NMR spectrum, elemental analysis and MS. The crystal structure of quinoxaline (**4d**) reveals an intramolecular hydrogen bond between the hydroxyl and carbonyl groups, which could ensure the stabilization of the observed non-cyclized form (Figure 1).

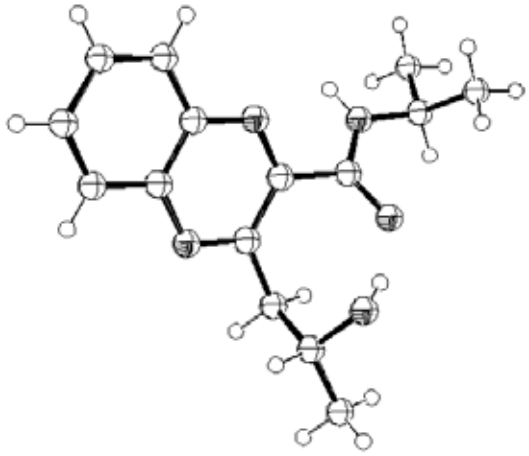


Figure 1. X-Ray crystallography of N^2-isopropyl-3-(2-hydroxypropyl)-2-quinoxalinecarboxamide (**4d**).

EXPERIMENTAL

NMR spectra were recorded on a Bruker AC 250 at 250 MHz (^{1}H) or 63 MHz (^{13}C). IR spectra were recorded on a Perkin–Elmer 883 spectrophotometer, and MS spectra on a Nermag R10-10C mass spectrometer. Mps points were determined on a Büchi 512 melting point apparatus and are uncorrected. Elemental analyses were performed at the *ENSC* in Toulouse, France. All chemicals were obtained from Aldrich or Acros Organics, and used without further purification. Benzodiazepines (**1**) were obtained as mixtures of diastereoisomers as described previously .[9]

General procedure for preparation of 3-methyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinoxalin-1-one (**2**). Quinoxalin (**2**) was obtained from diazepine derivatives (**1**) (Scheme I). A general procedure is as follows: To a solution of **1** (0.05 mol) in acetonitrile (20 mL) was added dropwise during 1.5 h under stirring an aqueous solution of 2.3 M sodium hypochloride (50 mL, 0.115 mol), and the reaction mixture was stirred at rt for 1 h. 2 N sulfuric acid was periodically added to the reaction mixture to maintain the pH around 5. Cold water was then added to the solution, leading to the precipitation of pyranoquinoxaline (**2**) as a yellow solid, which was separated by filtration. Yields were ranging from 40 to 83% depending of the starting benzodiazepine (40% for R = CH_3, 80% for R = C_6H_5, 75% for R = *p*-ClC_6H_4 and 83% for *p*-$CH_3C_6H_4$). mp 195 °C. IR (KBr) ν (cm^{-1}): 1750 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.63 (d, *J* = 6 Hz, 3H, C*H*$_3$); 3.45 (m, 2H, C*H*$_{2(4)}$); 5.00 (m, 1H, C*H*$_{(3)}$); 7.90-8.35 (m, 4H, arom-*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 21 (*C*H$_3$); 38 (*C*H$_{2(4)}$); 75 (*C*H$_{(3)}$); 128.5, 130, 130.5, 133.5 (arom-*C*H); 138 ($C_{(4a)}$); 142.5 ($C_{(9a)}$); 143 ($C_{(5a)}$); 153 ($C_{(10a)}$);

163 (*C*=O). MS (70 eV, electron impact) *m/z* (%): 214 (M^+, 75), 169 (100). *Anal.* Calcd for $C_{12}H_{10}O_2N_2$: C, 67.20; H, 4.84; N, 12.93. Found: C, 67.28; H, 4.67; N, 13.08.

General procedure for the synthesis of compounds (3) and (4): To a solution of quinoxaline (**2**) (428 mg, 2 mmol) in ethyl acetate (10 mL) was added the amine derivative (2.5 mmol) and 30 µL of acetic acid. The mixture was then heated to reflux with stirring for 4 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography with ethyl acetate as eluent to yield pure compounds (**3**) and (**4**):

2,3-Dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxalin-1-one (**3a**). Yield: 50%. mp 76-78 °C. IR (KBr) ν(cm^{-1}): 1780 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.26 (d, *J* = 6 Hz, 3H, C*H*$_3$); 3.05 (s, 3H, N-C*H*$_3$); 3.50 (m, 2H, C*H*$_{2(4)}$); 4.40 (m, 1H, C*H*$_{(3)}$); 7.90-8.00 (m, 4H, arom-*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.7 (*C*H$_3$); 28.5 (N-*C*H$_3$); 44.1 (*C*H$_{2(4)}$); 67.9 (*C*H$_{(3)}$); 128.5, 129.1, 130.1, 131.7 (arom-*C*H); 138.9 (*C*$_{(4a)}$); 142.4 (*C*$_{(9a)}$); 143.8 (*C*$_{(5a)}$); 155.3 (*C*$_{(10a)}$); 165.9 (*C*=O). MS (70 eV, electron impact) *m/z* (%): 227 (M^+, 30), 169 (100). *Anal.* Calcd for $C_{13}H_{13}N_3O$: C, 68.71; H, 5.77; N, 18.49. Found: C, 68.80; H, 5.79; N, 18.51.

2-Ethyl-3-methyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxalin-1-one (**3b**). Yield: 60%. mp 80-82 °C. IR (KBr) ν(cm^{-1}): 1775 (C=O). ^{1}H NMR ($CDCl_3$) δ(ppm): 1.25 (t, *J* = 7 Hz, 3H, N-CH$_2$-C*H*$_3$); 1.35 (d, *J* = 6 Hz, 3H, C*H*$_3$); 3.40 (q, *J* = 7 Hz, 2H, N-C*H*$_2$-CH$_3$); 3.45 (m, 2H, C*H*$_{2(4)}$); 4.30 (m,1H, C*H*$_{(3)}$); 7.90-8.00 (m, 4H, arom-*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.7 (N-CH$_2$-*C*H$_3$); 22.8 (N-*C*H$_2$-CH$_3$); 23.6 (*C*H$_3$); 44.1 (*C*H$_{2(4)}$); 67.9 (*C*H$_{(3)}$); 128.4, 129.1, 130.2, 131.7 (arom-*C*H); 139.2 (*C*$_{(4a)}$); 142.4 (*C*$_{(9a)}$); 143.5 (*C*$_{(5a)}$); 155.8 (*C*$_{(10a)}$); 166.2 (*C*=O). MS (70 eV, electron impact) *m/z* (%): 241 (M^+, 40), 169 (100). *Anal.* Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.75; H, 6.31; N, 17.39.

3-Methyl-2-propyl -1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxalin-1-one (**3c**). Yield: 90%. mp 88-90 °C. IR (KBr) ν(cm^{-1}): 1760 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.05 (t, *J* = 7 Hz,3H, N(CH$_2$)$_2$C*H*$_3$); 1.25 (d, *J* = 6 Hz, 3H, C*H*$_3$); 1.90 (t, *J* = 7 Hz, 2H, C*H*$_2$); 3.20 (m, 2H, C*H*$_2$); 3.50 (m, 2H, C*H*$_{2(4)}$); 4.25 (m, 1H, C*H*); 7.80-8.00 (m, 4H, arom-*H*). ^{13}C NMR($CDCl_3$) δ (ppm): 14.5 (N-(CH$_2$)$_2$-*C*H$_3$); 22.8 (*C*H$_2$-N); 23.7 (*C*H$_3$); 41.6 (*C*H$_2$-CH$_2$-N); 44.1 (*C*H$_{2(4)}$); 67.7 (*C*H$_{(3)}$); 128.4, 128.9, 130.7, 132.1 (arom-*C*H); 138.2 (*C*$_{(4a)}$); 141.9 (*C*$_{(9a)}$); 143.4 (*C*$_{(5a)}$); 156.2 (*C*$_{(10a)}$); 166.5 (*C*=O). MS (70 eV, electron impact) *m/z* (%): 255 (M^+, 20), 169 (100). *Anal.* Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.60; H, 6.78; N, 16.51.

2-Butyl-3-methyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxalin-1-one (**3d**). Yield: 85%. mp 85-87 °C. IR (KBr) ν(cm^{-1}): 1770 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm): 0.95 (t, *J* = 7 Hz, 3H, N(CH$_2$)$_3$C*H*$_3$); 1.25 (d, *J* = 6 Hz, 3H, C*H*$_3$); 1.30 (t, *J* = 7 Hz, 2H, C*H*$_2$-N); 1.45 (m, 2H, C*H*$_2$); 1.70 (m, 2H, C*H*$_2$); 3.30 (m, 2H, C*H*$_{2(4)}$); 4.35 (m, 1H, C*H*$_{(3)}$); 7.75-8.00 (m, 4H, arom-C*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 13.8 (N(CH$_2$)$_3$*C*H3); 20.3 (*C*H$_2$-N); 23.7 (*C*H$_3$); 31.6 (*C*H$_2$); 38.6 (*C*H$_2$); 44.1 (*C*H$_{2(4)}$); 67.9 (*C*H$_{(3)}$); 128.4, 129.7, 130.4, 131.6 (arom-*C*H); 138.6 (*C*$_{(4a)}$); 142.4 (*C*$_{(9a)}$); 143.5 (*C*$_{(5a)}$); 155.8 (*C*$_{(10a)}$); 166.3 (*C*=O). MS (70 eV, electron

impact) *m/z* (%): 269 (M^+, 35), 169 (100). ***Anal.*** Calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.39; H, 7.17; N, 15.59.

N*²,*N*²-Diethyl-3-(2-hydroxypropyl)-2-quinoxalinecarboxamide** (**4a**). Yield: 70% (oil). IR (Nujol) ν(cm^{-1}): 1760 (C=O), 3300 (C-OH). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.15-1.20 (m, 6H, C*H*$_3$CH$_2$N); 1.35 (d, *J* = 6 Hz, 3H, C*H*$_3$); 3.10 (m, 4H, CH$_3$C*H*$_2$N); 3.20 (m, 2H, C*H*$_2$CHOH); 4.40 (m, 1H, C*H*-OH); 7.90-8.00 (m, 4H, arom-C*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.7 (*C*H$_3$CH$_2$-N); 23.6 (*C*H$_3$); 39.2 (CH$_3$*C*H$_2$-N); 39.3 (CH$_3$*C*H$_2$-N); 44.1 (*C*H$_2$CH-OH); 67.8 (*C*H-OH); 128.6, 129.1, 130.0, 132.1 (arom-*C*H); 139.0 ($C_{(3)}$); 142.5 ($C_{(8a)}$); 144.1 ($C_{(4a)}$); 155.5 ($C_{(2)}$); 166.2 (*C*=O). MS (70 eV, electron impact) *m/z* (%): 287 (M_+, 15), 187 (30), 169 (10), 144 (100). ***Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.91; H, 7.32; N, 14.69.

N*²-Benzyl-*N*²-methyl-3-(2-hydroxypropyl)-2-quinoxalinecarboxamide** (**4b**). Yield: 65% (oil). IR (Nujol) ν(cm^{-1}): 1770 (C=O), 3400 (C-OH). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.30 (d, *J* = 6 Hz, 3H, C*H*$_3$); 2.72 (s, 3H, N-C*H*$_3$); 2.75 (s, 2H, N-C*H*$_2$); 3.19 (m, 2H, C*H*$_2$-CH-OH); 3.90 (s, 1H, -O*H*); 4.40 (m, 1H, C*H*-OH); 7.20-7.90 (m, 9H, arom-C*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.7 (*C*H$_3$); 28.3 (N-*C*H$_3$); 22.8 (N-*C*H$_2$); 44.1 (*C*H$_2$-CH-OH); 67.9 (*C*H-OH); 128.4, 128.7, 129.1, 129.4, 130.1, 131.1, 131.9, 133.4, 134.1 (arom-*C*H); 138.2 ($C_{(3)}$); 142.4 ($C_{(8a)}$); 143.8 ($C_{(4a)}$); 155.3 ($C_{(2)}$); 165.9 (*C*=O). MS (70 eV, electron impact) *m/z* (%): 335 (M^+, 25), 187 (10), 169 (20), 144 (100). ***Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.66; H, 6.28; N, 12.49.

N*²-Benzyl-3-(2-hydroxypropyl)-2-quinoxalinecarboxamide** (**4c**). Yield: 72%; mp 90 °C. IR (KBr) ν(cm^{-1}): 1755 (C=O), 3300-3100 (C-NH / C-OH). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.40 (d, *J* = 6 Hz, 3H, C*H*$_3$); 3.60 (m, 2H, C*H*$_2$); 4.38 (d, *J* = 6 Hz, 2H, N-C*H*$_2$); 4.00 (s, 1H, -O*H*); 7.20-8.00 (m, 9H, arom-C*H*); 9.12 (t, *J* = 6 Hz, -N*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.6 (*C*H$_3$-CH-OH); 22.6 (N-*C*H$_2$); 44.3 (*C*H$_2$-CH-OH); 67.8 (*C*H-OH); 128.4, 128.7, 129.6, 129.7, 130.4, 130.8, 131.6, 133.4, 134.3 (arom-*C*H); 138.6 ($C_{(3)}$); 142.6 ($C_{(8a)}$); 143.7 ($C_{(4a)}$); 155.5 ($C_{(2)}$); 166.0 (*C*=O). MS (70 eV, electron impact) *m/z* (%): 321 (M^+, 25), 187 (10), 169 (20), 144 (100). ***Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 71.08; H, 6.03; N, 13.03.

N*²-Isopropyl-3-(2-hydroxypropyl)-2-quinoxalinecarboxamide** (**4d**). Yield: 85%; mp 83-85 °C. IR (KBr) ν(cm^{-1}): 1780 (C=O), 3400-3100(C-NH / C-OH). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.22-1.26 (m, 9H, 3C*H*$_3$); 3.60 (m, 2H, C*H*$_2$-CH-OH); 4.20 (m, 1H, C*H*-(CH$_3$)$_2$); 4.40 (m, 1H, C*H*-OH); 5.90-6.30 (s, 2H, -O*H* and -N*H*); 7.70-8.10 (m, 4H, arom-C*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.4, 22.7 (*C*H$_3$-CH-*C*H$_3$); 23.8 (*C*H$_3$.CH-OH); 44.2 (*C*H$_2$-CH-OH); 42.0 (CH$_3$-*C*H-CH$_3$); 67.7 (*C*H-OH); 128.5; 129.2; 130.1; 131.7 (arom-*C*H); 139.0 ($C_{(3)}$); 142.4 ($C_{(8a)}$); 143.8 ($C_{(4a)}$); 155.5 ($C_{(2)}$); 164.4 (*C*=O). MS (70 eV, electron impact) *m/z* (%): 273 (M^+, 30), 169 (100). ***Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.41; H, 7.01; N, 15.37. Found: C, 65.49; H, 7.08; N, 15.30.

Crystal data for 4d: ($C_{15}H_{19}N_3O_2$, M=273.33), monoclinic, $P2_1/c$. a = 6.033(1), b = 12.267(1), c = 18.873(2) Å, ß = 93.663(2)º, V = 1393.8(3) Å^3, Z = 4, ρ_{calcd} = 1.303 Mgm^{-3}, F(000) = 584, λ = 0.71073 Å, T = 173(2) K, μ(Mo_{Ka}) = 0.088 mm^{-1}, crystal dimensions 0.4x0.5x0.6 mm^3, 1.98≤θ≤26.41º; 8326 reflections (2858 independent,R_{int} = 0.0180) were collected at low temperature on an oil-coated shock-cooled crystal on a Bruker-AXS CCD 1000 diffractometer. The structure was solved by direct methods (SHELXS-97),[10] and 189 parameters were refined by the least-sqares method on F^2.[11] Maximum residual electron density: 0.254 eÅ^3, *R1*(for I>2σ(I)) = 0.0347 and *wR2*(all data) = 0.0954 with $R1 = \sum |F_O| - |F_C| / \sum |F_O|$ and $wR2 = (\sum w(\sum(F_O^2 - F_C^2)^2 / \sum w(F_O^2)^2)^{0.5}$.

Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre (CCDC reference number 235118). These data can be obtained free of charge from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk.

Carbene trapping by cyclohexene.

To a solution of **1** (R = C_6H_5) (3.06 g, 0.01 mol) and cyclohexene (4 mL, 0.04 mol) in acetonitrile (20 mL) was added dropwise during 3 h an aqueous solution of 2.3 M sodium hypochloride (60 mL). Periodically, a 2 M solution of sulfuric acid was added to the reaction mixture to maintain the pH around 5. Cold water was then added to the solution, leading to the precipitation of pyranoquinoxaline (**2**), which was separated by filtration. The filtrate was then concentrated under reduced pressure, and the residue was distillated to afford 7-phenyl-bicyclo[4.1.0]heptane. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.10-2.30 (m, 8H, CH_2); 3.15 (m, 1H, C$H_{(7)}$); 3.40 and 3.80 (m, 2H, C$H_{(1)}$ and C$H_{(6)}$); 7.40-7.90 (m, 5H, C_6H_5).

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