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THE KORNBLUM REACTION OF α-SUBSTITUTED 3-BENZYL-1,2-DIHYDRO-2-OXOQUINOXALINES. SYNTHESIS AND STRUCTURE OF 3-BENZOYL-2-OXO-1,2-DIHYDROQUINOXALINE

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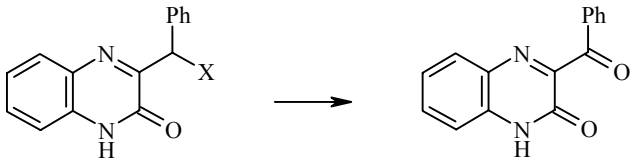
A method has been developed for the preparation of 3-benzoyl-2-oxo-1,2-dihydroquinoxaline by the reaction of 3-(α-chlorobenzyl)-1,2-dihydroquinoxaline under Kornblum reaction conditions to the corresponding α-azido derivative and then acid fission of the latter. The structure of the target ketone has been confirmed by X-ray analysis.

Keywords: 3-(α-azidobenzyl)-2-oxo-1,2-dihydroquinoxaline, 3-benzoyl-2-oxo-1,2-dihydroquinoxaline, 2-oxo-3-(α-thiocyanatobenzyl)-1,2-dihydroquinoxaline, 3-(α-chlorobenzyl)-2-oxo-1,2-dihydroquinoxaline, Kornblum reaction.

The 3-chlorobenzyl function in 3-(α-chlorobenzyl)-2-oxo-1,2-dihydroquinoxaline (**1**) offers a high synthetic potential for this compound thanks to the possibility of the easy introduction in place of the chlorine atom of various active groups which can further take part in annelation reaction of the heterocyclic systems on the a and b sides of the quinoxaline ring [1-3]. Transformation of the PhCHCl group to benzoyl then allows the 3-benzoyl-2-oxo-1,2-dihydroquinoxaline (**2**) formed to be used not only in various nucleophilic addition reactions at the carbonyl group but also as a promising synthon with a β-dicarbonyl system. In fact, the ready availability of compound **1** [4] makes this an attractive proposition upon which to base the method of synthesis of ketone **2**. Up to now the latter has been obtained in only 30% yield by the oxidation of 3-benzyl-2-oxo-1,2-dihydroquinoxaline with CrO_3 or by separation in 70% yield by fractional recrystallization from the mixture of products formed when heating 2-oxo-3-(α-thiocyano)-1,2-dihydroquinoxaline **3** in DMSO [3].

This work is concerned with the development of a method for the preparation of compound **2** based on compound **1** and an investigation of its structure.



1, 3, 5 **2**

1 X = Cl, **3** X = SCN, **5** X = N_3

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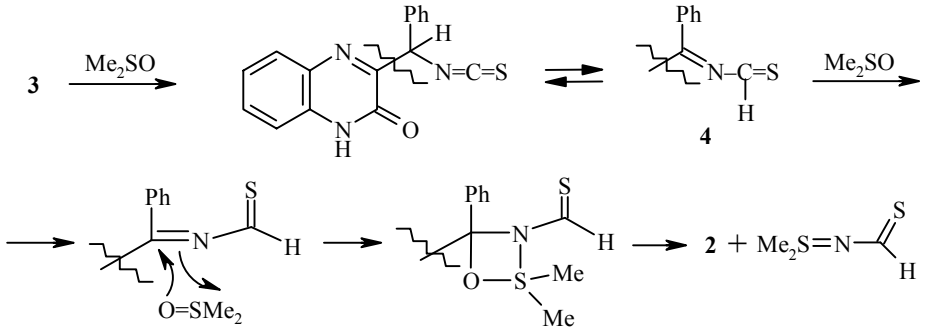
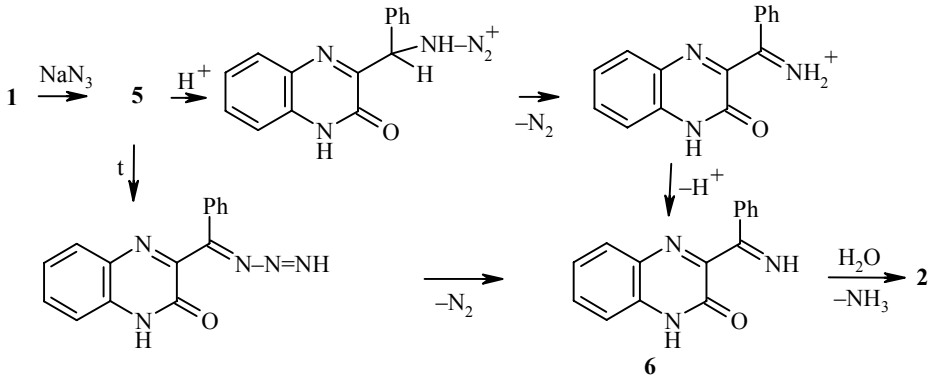
Under the conditions usually used for a Kornblum oxidation (heating an organic halide or its analog in DMSO in the presence of sodium acetate [6, 7]) the yield of the benzoylquinoxalinone **2** from chloride **1** reaches 84% while in the absence of the acetate (and independently of the reagent levels and reaction time) it does not exceed 30%. This implies that the success of the synthesis mentioned above for compound **2** by heating the thiocyanate **3** at 150°C for 1 h in DMSO without addition of base cannot be explained solely by the scheme quoted in the study [3] where the heterocyclic fragment of molecule **3** acts as the base. It is possible that another route occurs in parallel leading to product **2** specifically for the thiocyanate derivative **3** and this may include a thiocyanate-isothiocyanate isomerization, prototropic reaction, and reaction of the intermediately formed thioformylimino derivative **4** with DMSO.



The most convenient method for the preparation appears to be a two-stage reaction of the chloro derivative **1** to the benzoyl derivative **2** *via* the 3-α-azidobenzylquinoxalin-2-one with a direct thermal or acid treatment of the latter. The reaction of azide **5** to the ketone **2**, as in the reaction discussed above, leading to the benzoyl derivative **2** is a modification of the Kornblum reaction. The conversion of azide **5**, its acid fission, and thermolysis take place in high yields. Evidently the fission occurs *via* intermediate formation of the imine **6** according to a scheme which is similar in general outlines to that usually adopted in a discussion of the formation of imines [8], or with an initial prototropic shift as in the scheme given above involving the isothiocyanate.



The discrepancy of 20°C in the melting points of the benzoyldihydroquinoxalinones **2** as synthesized by us by various methods based on the α-chlorobenzyl derivative **1** and that reported in the study [4] prompted us to determine the structure of the material obtained by carrying out an X-ray structural analysis.

The geometry of compound **2** (Fig. 1) confirms the proposed structure, including the existence of compound **2** in the lactam form. The geometrical parameters for the molecule **2** are given in the Tables 1-3.

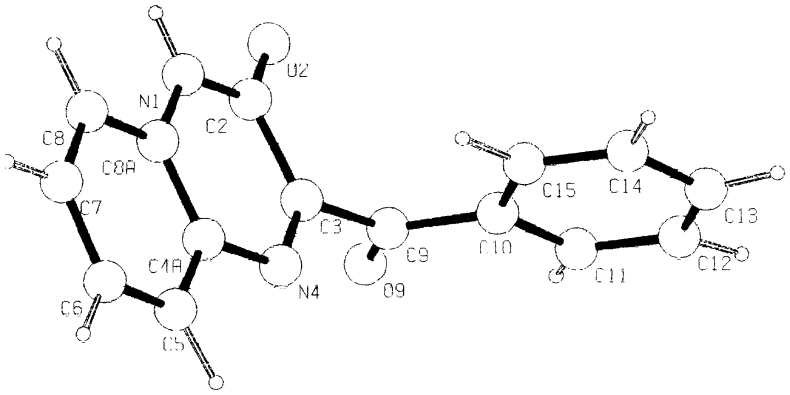


Fig. 1. Geometry of the molecular crystal of compound **2**.

The dihydroquinoxaline ring is planar within the limits of experimental error (0.07(1) Å) and it forms a dihedral angle with the plane of the phenyl substituent C(10)–C(15) of 85.39(6)°. Moreover, the plane of the benzene ring is virtually coplanar with the carbonyl group oxygen (torsional angle O(9)C(9)C(10)C(11) equal to -5.4(2)°) and this permits the formation of an intramolecular C–H···O contact-distance O(9)···H(11) of 2.46(2) Å.

The H(1) proton at atom N(1) of the quinoxaline ring is unambiguously revealed by electron density difference synthesis in the refined structure. The formation of hydrogen bonds between this proton and the O(2) atom (d (H(1)···O(2)) 1.99(2) Å, N(1)–H(1)···O(2) angle 171.6(1)°) for two centrosymmetric molecules gives rise to the formation of hydrogen-bonded dimers (Fig. 2).

The packing of the molecule in the crystal (Fig. 2) is evidently influenced to a significant degree by π-π type interactions between the electronic systems of the quinoxaline rings. The mutual geometry of the dimers enables the benzene fragment of the molecule to take part in an interaction with the pyrazine ring of a neighboring molecule bound by this translational operation of -1 along the OY axis and a pyrazine ring with the benzene molecular fragment shifted by +1 along the same axis. This leads to the formation of a sloping stack of molecular dimers in the direction of the crystallographic *b* axis (Fig. 3). Moreover, the phenyl groups of the benzoyl substituent of the molecule, associated with the binding symmetry operation (2-*x*, 1-*y*, 1-*z*), also take part in a π-π interaction.

TABLE 1. Bond Lengths (*d*) in the Molecule **2**

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
O(2)–C(2)	1.225(1)	C(5)–C(6)	1.373(2)	C(10)–C(15)	1.396(2)
O(9)–C(9)	1.210(2)	C(5)–H(5)	1.08(3)	C(11)–C(12)	1.377(2)
N(1)–C(2)	1.358(1)	C(6)–C(7)	1.400(2)	C(11)–H(11)	0.90(2)
N(1)–C(8a)	1.376(1)	C(6)–H(6)	0.97(2)	C(12)–C(13)	1.386(3)
N(1)–H(1)	0.88(2)	C(7)–C(8)	1.374(2)	C(12)–H(12)	1.05(2)
N(4)–C(3)	1.290(1)	C(7)–H(7)	0.96(2)	C(13)–C(14)	1.389(2)
N(4)–C(4a)	1.392(2)	C(8)–C(8a)	1.408(2)	C(13)–H(13)	0.97(2)
C(2)–C(3)	1.475(2)	C(8)–H(8)	0.97(2)	C(14)–C(15)	1.379(2)
C(3)–C(9)	1.522(2)	C(9)–C(10)	1.479(2)	C(14)–H(14)	1.00(2)
C(4a)–C(5)	1.399(2)	C(10)–C(11)	1.396(2)	C(15)–H(15)	1.07(2)
C(4a)–C(8a)	1.396(2)				

TABLE 2. Valence Angles (ω) in the Molecule **2**

Valence angle	ω, deg	Valence angle	ω, deg
C(2)–N(1)–C(8a)	123.4(1)	C(7)–C(8)–C(8a)	119.1(1)
C(2)–N(1)–H(1)	113.4(9)	C(7)–C(8)–H(8)	119(1)
C(8a)–N(1)–H(1)	123.2(9)	C(8a)–C(8)–H(8)	122(1)
C(3)–N(4)–C(4a)	117.8(1)	N(1)–C(8a)–C(4a)	118.9(1)
O(2)–C(2)–N(1)	124.2(1)	N(1)–C(8a)–C(8)	121.1(1)
O(2)–C(2)–C(3)	122.8(1)	C(4a)–C(8a)–C(8)	120.0(1)
N(1)–C(2)–C(3)	113.04(9)	O(9)–C(9)–C(3)	119.2(1)
N(4)–C(3)–C(2)	125.8(1)	O(9)–C(9)–C(10)	122.3(1)
N(4)–C(3)–C(9)	117.4(1)	C(3)–C(9)–C(10)	118.5(1)
C(2)–C(3)–C(9)	116.85(9)	C(9)–C(10)–C(11)	118.5(1)
N(4)–C(4a)–C(5)	119.8(1)	C(9)–C(10)–C(15)	122.6(1)
N(4)–C(4a)–C(8a)	120.49(9)	C(11)–C(10)–C(15)	118.9(1)
C(5)–C(4a)–C(8a)	119.7(1)	C(10)–C(11)–C(12)	120.5(1)
C(4a)–C(5)–C(6)	120.2(1)	C(10)–C(11)–H(11)	116(1)
C(4a)–C(5)–H(5)	112(1)	C(12)–C(11)–H(11)	123(1)
C(6)–C(5)–H(5)	127(1)	C(11)–C(12)–C(13)	120.5(2)
C(5)–C(6)–C(7)	119.8(1)	C(11)–C(12)–H(12)	124(1)
C(5)–C(6)–H(6)	118(1)	C(13)–C(12)–H(12)	116(1)
C(7)–C(6)–H(6)	122(1)	C(12)–C(13)–C(14)	119.2(2)
C(6)–C(7)–C(8)	121.1(1)	C(12)–C(13)–H(13)	123(1)
C(6)–C(7)–H(7)	121.9(9)	C(14)–C(13)–H(13)	117(1)
C(8)–C(7)–H(7)	116.6(9)	C(13)–C(14)–C(15)	120.7(2)
C(13)–C(14)–H(14)	118.(1)	C(10)–C(15)–H(15)	118(1)
C(15)–C(14)–H(14)	121(1)	C(14)–C(15)–H(15)	122(1)
C(10)–C(15)–C(14)	120.1(1)		

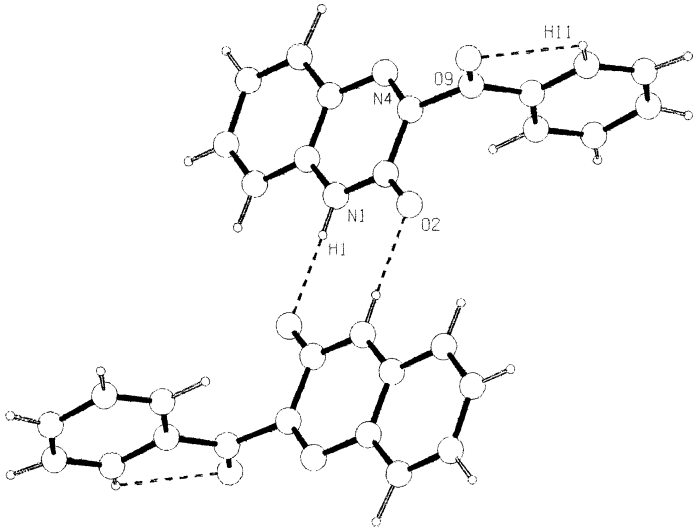


Fig. 2. Formation of dimers in the crystal of compound **1**.
The hydrogen bonds are shown dashed and the numbering is given only for the nitrogen and oxygen atoms and protons which are involved in the hydrogen bonds.

TABLE 3. Torsional Angles (τ) in the Molecule **2.**

Torsional angle	τ, deg.	Torsional angle	τ, deg.
C(8a)–N(1)–C(2)–O(2)	175.2(1)	H(6)–C(6)–C(7)–H(7)	-1(1)
C(8a)–N(1)–C(2)–C(3)	-6.5(2)	C(6)–C(7)–C(8)–C(8a)	0.2(2)
H(1)–N(1)–C(2)–O(2)	-2(1)	C(6)–C(7)–C(8)–H(8)	178(1)
H(1)–N(1)–C(2)–C(3)	176(1)	H(7)–C(7)–C(8)–C(8a)	-174(1)
C(2)–N(1)–C(8a)–C(4a)	1.1(2)	H(7)–C(7)–C(8)–H(8)	5(2)
C(2)–N(1)–C(8a)–C(8)	-179.5(1)	C(7)–C(8)–C(8a)–N(1)	178.2(1)
H(1)–N(1)–C(8a)–C(4a)	178(1)	C(7)–C(8)–C(8a)–C(4a)	-2.4(2)
H(1)–N(1)–C(8a)–C(8)	-3(1)	H(8)–C(8)–C(8a)–N(1)	0(1)
C(4a)–N(4)–C(3)–C(2)	-1.3(2)	H(8)–C(8)–C(8a)–C(4a)	180(1)
C(4a)–N(4)–C(3)–C(9)	178.1(1)	O(9)–C(9)–C(10)–C(11)	-5.4(2)
C(3)–N(4)–C(4a)–C(5)	177.7(1)	O(9)–C(9)–C(10)–C(15)	174.0(1)
C(3)–N(4)–C(4a)–C(8a)	-4.9(2)	C(3)–C(9)–C(10)–C(11)	173.5(1)
O(2)–C(2)–C(3)–N(4)	-174.8(1)	C(3)–C(9)–C(10)–C(15)	-7.0(2)
O(2)–C(2)–C(3)–C(9)	5.8(2)	C(9)–C(10)–C(11)–C(12)	-179.9(2)
N(1)–C(2)–C(3)–N(4)	6.8(2)	C(15)–C(10)–C(11)–C(12)	0.6(2)
N(1)–C(2)–C(3)–C(9)	-172.6(1)	C(9)–C(10)–C(15)–C(14)	-179.7(1)
N(4)–C(3)–C(9)–O(9)	99.5(1)	C(11)–C(10)–C(15)–C(14)	-0.3(2)
N(4)–C(3)–C(9)–C(10)	-79.5(1)	C(10)–C(11)–C(12)–C(13)	0.5(2)
C(2)–C(3)–C(9)–O(9)	-81.1(1)	C(11)–C(12)–C(13)–C(14)	-1.9(3)
C(2)–C(3)–C(9)–C(10)	99.9(1)	C(12)–C(13)–C(14)–C(15)	2.2(2)
N(4)–C(4a)–C(5)–C(6)	175.7(1)	C(13)–C(14)–C(15)–C(10)	-1.1(2)
N(4)–C(4a)–C(5)–H(5)	-4(1)	C(4a)–C(5)–C(6)–C(7)	-0.6(2)
C(8a)–C(4a)–C(5)–C(6)	-1.6(2)	C(4a)–C(5)–C(6)–H(6)	175(1)
C(8a)–C(4a)–C(5)–H(5)	179(1)	H(5)–C(5)–C(6)–C(7)	179(1)
N(4)–C(4a)–C(8a)–N(1)	5.2(2)	H(5)–C(5)–C(6)–H(6)	-6(2)
N(4)–C(4a)–C(8a)–C(8)	-174.2(1)	C(5)–C(6)–C(7)–C(8)	1.3(2)
C(5)–C(4a)–C(8a)–N(1)	-177.5(1)	C(5)–C(6)–C(7)–H(7)	175(1)
C(5)–C(4a)–C(8a)–C(8)	3.1(2)	H(6)–C(6)–C(7)–C(8)	-175(1)

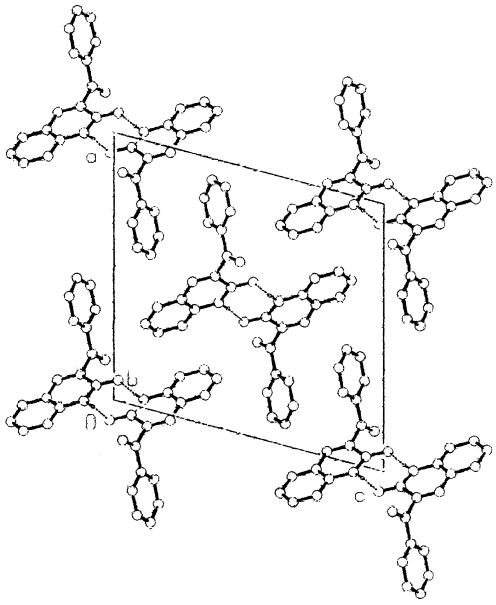


Fig. 3. Packing of the molecules of compound **1** in the crystal. View along the OY axis.

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer. ^{1}H NMR spectra were recorded on a Bruker MCL-250 (250 MHz) spectrometer with DMSO-d_6 as internal standard. In the synthesis of compound **2** by the different methods, the identity of the samples obtained was established by a comparison of physical and spectroscopic properties and also by the absence of a depression of melting point for mixed samples.

Melting points were determined on a Boetius stage.

X-ray Analysis was performed on an Enraf-Nonius CAD-4 automatic, four circle diffractometer. Crystals of compound **2** are monoclinic, $C_{15}H_{10}N_2O_2$. At 20°C a = 14.47(3), b = 5.604(2), c = 15.09(1) Å; β = 105.02(7)°; V = 1182(2) Å^3; Z = 4; d_{calc} = 1.41 g/cm^3; space group $P2_1/n$. Cell parameters and intensities of 3076 reflections (of which 2386 had $I \geq 3\sigma$) were measured at 20°C using λCuKα, graphite monochromator, $\omega/2\theta$ scanning, with $\theta \leq 26.3°$. A decrease in the intensity of three control reflections with exposure time was not observed. An empirical calculation of absorption was carried out (μCu 7.40 cm^{-1}). The structure was solved by a direct method using the SIR program [9] and refined initially in the isotropic and then the anisotropic approximation. Subsequently, difference array electron density revealed the hydrogen atoms which were refined in the isotropic approximation in the final least squares cycles. The final difference factor values were: R = 0.048, R_w = 0.064 for 1795 independent reflections with $F^2 \geq 3\sigma$. All of the calculations were carried out using the MolEN program package [10] on an AlphaStation 200 computer. The Figures were realized using the PLATON program [11].

3-(α-Azidobenzyl)-2-oxo-1,2-dihydroquinoxaline (5). A solution of compound **1** (2.10 g, 8 mmol) in DMSO (20 ml) was stirred for 6 h at room temperature with NaN_3 (0.78 g, 12 mmol). The latter gradually dissolved and a precipitate was then formed. The reaction mixture has held at the same temperature for about 16 h, poured into water, and the precipitated product **5** was filtered off and washed with water and propan-2-ol to give 2.11 g (98%); mp 206-208°C (dioxane). IR spectrum (vaseline), ν, cm^{-1}: 1655 (C=O), 2120 (N_3), 2580-3220 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, J (Hz): 6.18 (1H, s, C<u>H</u>Ph); 7.41-7.52 (7H, m, H_{Bz}, H_{Ph}-7, H_{Ph}-8); 7.67 (1H, ddd, J = 7.48, 7.48, 1.27, H_{Ph}-6); 7.96 (1H, d, J = 7.75, H_{Ph}-5); 12.70 (1H, s, NH). Found, %: C 65.36; H 3.90; N 25.43. $C_{15}H_{11}N_5O$. Calculated, %: C 64.97; H 4.00; N 25.26.

3-Benzoyl-2-oxo-1,2-dihydroquinoxaline (2). A. A solution of compound **1** (0.50 g, 1.80 mmol) in DMSO (5 ml) was refluxed for 1 h, cooled, poured into ice, and a solution of sodium carbonate was added. The precipitated crystals of the product **2** were filtered and washed with water. Yield 0.14 g (30%).

B. A solution of compound **1** (0.50 g, 1.80 mmol) and sodium acetate (0.18 g, 2.0 mmol) in DMSO (5 ml) was refluxed for 45 min. The reaction mixture was then cooled and poured into water. Yield 0.39 g (84%).

C. A solution of azide **5** (0.30 g, 1.10 mmol) in DMSO (5 ml) was refluxed for 30 min, cooled, poured into water, and the precipitated crystals of product **2** were filtered off, and washed with water. Yield 0.22 g (81%).

D. A solution of azide **5** (1.10 g, 4.0 mmol) in AcOH (10 ml) was refluxed for 30 min, cooled, the precipitated crystals of product **2** filtered off, and washed with 2-propanol. The filtrate was poured into water and the precipitated crystals of product **2** were filtered off and washed with water and 2-propanol. Overall yield 0.9 g (95%).

E. A solution of azide **5** (1.10 g, 4.0 mmol) in 6.1 M HCl (20 ml) was refluxed for 30 min, cooled, and the precipitated crystals of product **2** were filtered and washed with water, 5% aqueous sodium carbonate, and again water. Yield 0.97 g (98%).

Parameters for compound **2** and a method for its purification are given in the study [3].

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