CHEMICAL MODIFICATION OF THE ALKALOID 2,3-TETRAMETHYLENE-3,4-DIHYDROQUINAZOL-4-ONE

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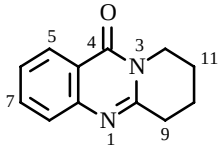
The 1,2-dihydro derivative of 2,3-tetramethylene-3,4-dihydroquinazol-4-one was produced by reduction and characterized using NMR spectra. 1-Acyl-1,2,3,4-tetrahydroquinazol-4-ones and ureas were synthesized by acylation of 2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one with acid chlorides and arylisocyanates, respectively. The molecular structures of 1-acetyl- and -m-*chlorophenylaminocarbonyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-ones were established using x-ray structure analyses.*

Key words: 2,3-tetramethylene-2,3-dihydro(1,2,3,4-tetrahydro)quinazol-4-one, alkaloids, PMR and ^{13}C NMR spectroscopy, XSA, acylation, reduction, nucleophilic substitution.

The chemistry of 2,3-tetramethylene-3,4-dihydroquinazol-4-one (6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one) (**1**) and quinazoline (**2**) alkaloids is little studied. These compounds are isolated from the plants *Mackinlaya subulata* Philipson and *M. makrosciadia* (Araliaceae) and are six-membered analogs of the alkaloids deoxyvasicinone and deoxypeganine [1, 2]. Mutual transformations of **1** into **2** by reduction with zinc in acidic medium or oxidation of **2** into **1** are known [1-3].



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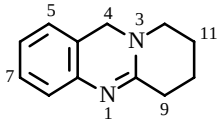


2

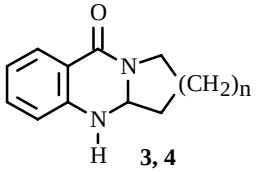
Alkaloids **1** and **2** have been synthesized. A simple and convenient preparation of them has been developed [3, 4].

The presence of N1 and N3, the activated N1=C2 double bond of the α-methylene, the carbonyl, and the benzene ring make it possible to perform reactions at N1, C=O, α-CH_2, and the aromatic ring [2, 4, 5].

Although reactions of these functional groups have been well investigated [4, 5], little attention has been paid to the reactivity of the N=C bond.

Herein we report the reduction of the N=C bond of **1**, the elucidation of the structural features of the resulting 2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one using PMR and ^{13}C NMR spectroscopy, and the study of its chemical transformations.

Reduction of **1** and deoxyvasicinone by $NaBH_4$ formed their 1,2-dihydro derivatives 2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (**3**) and 1,2-dihydrodeoxyvasicinone (**4**).



3, 4

3: n = 2; **4:** n = 1

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TABLE 1. NMR Spectra of **3**, CD_3OD, H_0 = 400 MHz, 0 = TMS

Atom	^1H chemical shifts, ppm	J/Hz*	^{13}C chemical shifts, ppm
2	4.77	3.02 (He-9), 10.37 (Ha-9)	70.19
4			166.49
4a			114.75
5	7.68	7.85 (H-6), 1.57 (H-7), 0.51 (H-8)	128.95
6	6.67	7.85 (H-5), 7.20 (H-7), 1.07 (H-8)	118.63
7	7.23	1.57 (H-5), 7.20 (H-6), 8.16 (H-8)	134.92
8	6.61	0.51 (H-5), 1.07 (H-6), 8.16 (H-7)	114.93
8a			148.68
9e	1.92	3.02 (H-2), 12.49 (Ha-9), 3.26 (He-10), 2.80 (Ha-10), 1.48 (He-11)	34.26
9a	1.77	10.37 (H-2), 12.49 (He-9), 3.58 (He-10), 12.70 (Ha-10)	
10e	1.74	3.26 (He-9), 3.58 (Ha-9), 12.65 (Ha-10), 1.63 (He-11), 3.20 (Ha-11), 1.95 (He-12)	23.36
10a	1.55	2.80 (He-9), 12.70 (Ha-9), 12.65 (He-10), 3.20 (He-11), 12.70 (Ha-11)	
11e	1.87	1.48 (He-9), 1.63 (He-10), 3.20 (Ha-10), 12.70 (Ha-11), 2.04 (He-12), 3.58 (Ha-12)	25.45
11a	1.47	3.20 (He-10), 12.70 (Ha-10), 12.70 (He-11), 4.40 (He-12), 12.61 (Ha-12)	
12e	4.50	1.95 (He-10), 2.04 (He-11), 4.40 (Ha-11), 13.48 (Ha-12)	13.48
12a	2.65	3.58 (He-11), 12.61 (Ha-11), 13.48 (He-12)	

*The coupling partner is indicated in parentheses next to the SSCC.

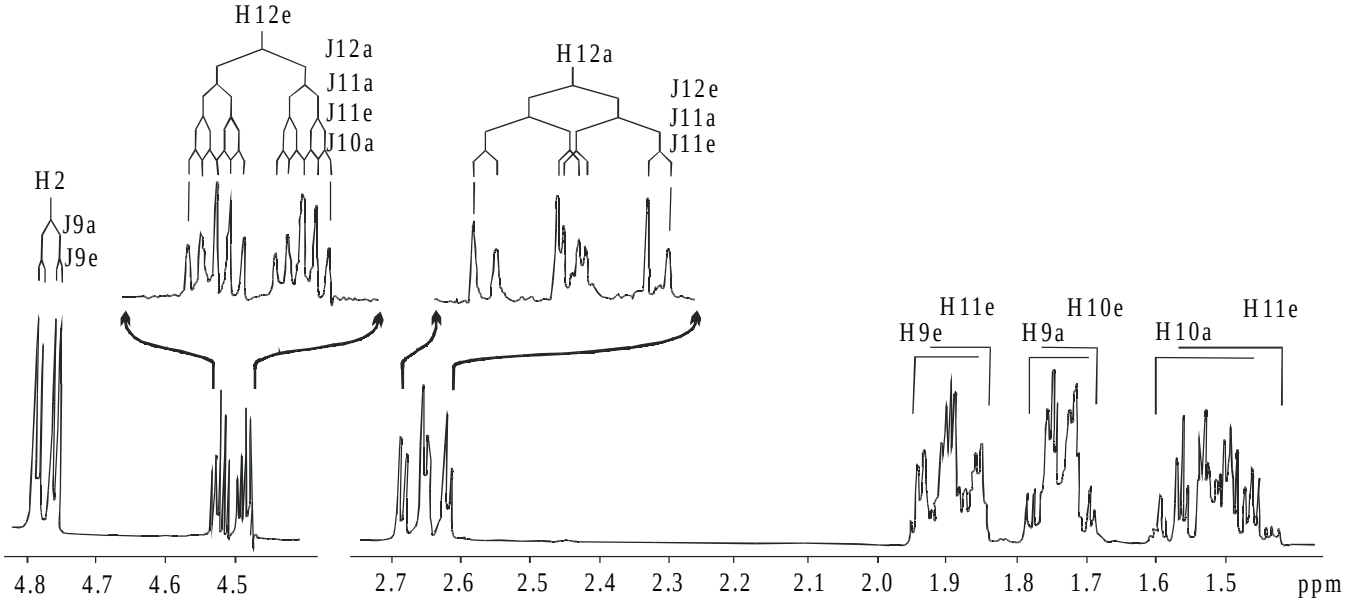


Fig. 1. Proton resonances of the cyclohexane ring in the PMR spectrum of **3**.

The PMR spectrum of **3** in CD_3OD exhibited several characteristic groups of resonances. The aromatic protons appeared as a typical four-spin system for an *o*-substituted benzene ring.

Table 1 and Fig. 1 show the PMR spectrum of **3**.

All SSCC were clearly visible in the resonances of aromatic protons. Chemical shifts of aromatic protons of **3** showed a slight weak-field shift compared with those of its five-membered analog 1,2-dihydrodeoxyvasicinone (**4**). Protons H-6 and H-8 underwent the greatest shifts (0.12 and 0.13 ppm, respectively). Therefore, these protons were sensitive to the electronic state of the molecule in general and to the conformation of the cyclopentane and cyclohexane rings, with the first factor perhaps being dominant. The resonance of H-2 was a doublet of doublets at 4.77 ppm with ^3J = 3.02 and 10.37 Hz with two vicinal SSCC to H_e-9 and H_a-9, respectively.

Of the four cycloalkane methylenes, only protons H-12 exhibited isolated and non-overlapping multiplets for H_e-12 at 4.50 and H_a-12 at 2.65 ppm.

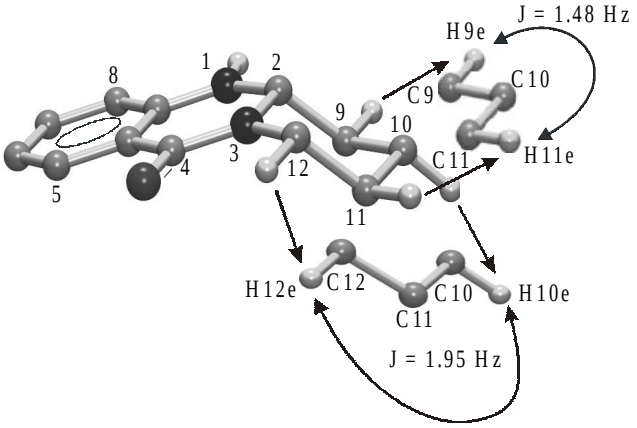


Fig. 2. Two W-fragments in the structure of **3**.

The resonance of equatorial proton H_e-12 was split into 10 lines due to coupling with four protons; ^2J = 13.48, ^3J = 4.40, 2.04 Hz, and ^4J = 1.95 Hz. The observation of SSCC ^4J = 1.95 Hz between H_e-12 and H_e-10 indicated that the planar fragment consisting of H_e-12, C12, C11, C10, and H_e-10 was conformationally rigid with a W-configuration. Axial proton H_a-12 formed a typical multiplet with three SSCC ^2J = 13.48 and ^3J = 12.61 and 3.58 Hz with H_e-12, H_a-11, and H_e-11, respectively.

The remaining six methylene protons on C9, C10, and C11 formed three groups of 2H overlapping multiplets. A series of differential double resonance experiments and calculation of resonance structures using the integration program LAME for calculating PMR spectra managed to reproduce the spectral properties of all coupled protons (Table 1).

Through-space spin—spin coupling through four bonds ^4J = 1.48 Hz was observed for H_e-9 and H_e-11. Therefore, two W-shaped couplings were formed in the saturated ring. This fact and the clearly resolved SSCC structure confirmed that this cyclohexane ring had a relatively stable chair conformation. Furthermore, the SSCC of H-2 with two H-9 protons agreed well with trans-axial ($^3J_{H_a\text{-}9}$ = 10.37 Hz) and gauche ($^3J_{H_e\text{-}9}$ = 3.02 Hz) couplings between them (Fig. 2).

The ^{13}C NMR spectrum of **3** in CD_3OD showed 12 resonances, 7 in the aromatic region and 5 in the cyclohexane region. Table 1 gives the resonance assignments. Their properties were consistent with the proposed structure of the compound.

Comparison of the spectral properties of **3** and **4** showed that resonances of the methylenes situated in the α-position to N-3 (H-12 in **3** and H-11 in **4**) underwent the greatest changes. In **3**, the difference in chemical shifts for the protons of this geminal pair was 1.85 ppm. The reason for this was the more distinct axial and equatorial orientation of H_a-12 and H_e-12 relative to the carbonyl and the unshared pair of the N atom than in **4**. In **4**, this difference in chemical shifts was 0.1 ppm. For all remaining geminal pairs in both **3** (Table 1) and **4** [6], the shift was less than 0.4 ppm.

Acylation of 2-aryl-3*H*-(benzyl, aryl)-1,2,3,4-tetrahydroquinazol-4-ones by acetic or trifluoroacetic anhydrides and adamantylcarboxylic and acetic acid chlorides is known to give the N-1 acyl derivatives [7]. Acylation of other simple 1,2,3,4-tetrahydroquinazol-4-ones has not been reported. It has been reported that acylation of 1,2,3,4-tetrahydroquinazol-4-one by chloroacetylchloride in acetone in the presence of K_2CO_3 formed the 1-chloroacetyl derivative [8]. Acylation of 1,2-dihydro-deoxyvasicinone (**4**) with acetic anhydride and benzoylchloride also occurred at N-1 [9].

We investigated acylation of **3** with acetic anhydride, benzoylchloride, 4-nitrobenzoylchloride, and chloroacetylchloride. Acylation with acetic anhydride occurred without a catalyst if an excess of the anhydride was used and formed 1-acetyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (**5**).

3 **5 - 7**

X = CH_3COO, Cl

5: R = CH_3; **6:** R = C_6H_5; **7:** *p*-NO_2-C_6H_4

TABLE 2. Bond Lengths (r, Å) and Angles (ω, deg) in **5** and **16**

Bond	r_5	R_{16}	Angle	ω_5	ω_{16}
O(1)-C(4)	1.229 (3)	1.241 (3)	C(13)-N(1)-C(8a)	124.58 (19)	127.1 (2)
O(2)-C(13)	1.215 (3)	1.219 (3)	C(13)-N(1)-C(2)	118.65 (18)	114.7 (2)
N(1)-C(13)	1.375 (3)	1.396 (3)	C(8a)-N(1)-C(2)	116.25 (17)	118.1 (2)
N(1)-C(8a)	1.422 (3)	1.422 (3)	C(4)-N(3)-C(12)	119.9 (2)	121.1 (2)
N(1)-C(2)	1.456 (3)	1.465 (3)	C(4)-N(3)-C(2)	123.34 (19)	123.8 (2)
N(3)-C(4)	1.355 (3)	1.343 (3)	C(12)-N(3)-C(2)	112.52 (19)	112.2 (2)
N(3)-C(12)	1.461 (3)	1.473 (3)	N(1)-C(2)-N(3)	109.86 (17)	110.9 (2)
N(3)-C(2)	1.469 (3)	1.464 (3)	N(1)-C(2)-C(9)	115.21 (19)	115.6 (2)
C(2)-C(9)	1.515 (3)	1.520 (4)	N(3)-C(2)-C(9)	109.46 (18)	109.0 (2)
C(4)-C(4a)	1.479 (3)	1.491 (4)	O(1)-C(4)-N(3)	122.4 (2)	122.3 (3)
C(4a)-C(5)	1.391 (3)	1.391 (4)	O(1)-C(4)-C(4a)	121.7 (2)	121.7 (2)
C(4a)-C(8a)	1.393 (3)	1.403 (4)	N(3)-C(4)-C(4a)	115.9 (2)	116.0 (2)
C(5)-C(6)	1.370 (4)	1.378 (4)	C(5)-C(4a)-C(8a)	119.0 (2)	119.5 (3)
C(6)-C(7)	1.376 (4)	1.378 (5)	C(5)-C(4a)-C(4)	119.7 (2)	119.0 (2)
C(7)-C(8)	1.383 (4)	1.387 (4)	C(8a)-C(4a)-C(4)	121.2 (2)	121.5 (2)
C(8)-C(8a)	1.380 (3)	1.391 (4)	C(6)-C(5)-C(4a)	120.7 (3)	120.9 (3)
C(9)-C(10)	1.520 (3)	1.536 (4)	C(5)-C(6)-C(7)	119.5 (2)	119.3 (3)
C(10)-C(11)	1.520 (4)	1.527 (4)	C(8)-C(7)-C(6)	121.1 (3)	121.1 (3)
C(11)-C(12)	1.515 (4)	1.522 (4)	C(8a)-C(8)-C(7)	119.1 (2)	119.7 (3)
C(13)-C(14)		1.498 (4)	C(8)-C(8a)-C(4a)	120.4 (2)	119.3 (2)
C(13)-N(14)		1.362 (3)	C(8)-C(8a)-N(1)	122.6 (2)	123.4 (2)
C(14)-C(19)		1.390 (3)	C(4a)-C(8a)-N(1)	117.0 (2)	117.2 (2)
C(14)-C(15)		1.396 (4)	C(10)-C(9)-C(2)	109.6 (2)	108.5 (3)
C(14)-N(14)		1.411 (3)	C(9)-C(10)-C(11)	111.4 (2)	111.8 (2)
C(15)-C(16)		1.376 (4)	C(12)-C(11)-C(10)	111.2 (2)	111.8 (3)
C(16)-C(17)		1.382 (4)	N(3)-C(12)-C(11)	109.2 (2)	109.2 (3)
C(17)-C(18)		1.375 (4)	O(2)-C(13)-N(1)	120.3 (2)	
C(18)-C(19)		1.378 (4)	O(2)-C(13)-C(14)	120.4 (2)	
C(18)-C1(1)		1.748 (3)	N(1)-C(13)-C(14)	119.2 (2)	
			O(2)-C(13)-N(14)		123.9 (2)
			O(2)-C(13)-N(1)		120.0 (2)
			N(14)-C(13)-N(1)		116.1 (2)
			C(19)-C(14)-C(15)		119.4 (2)
			C(19)-C(14)-N(14)		122.9 (2)
			C(15)-C(14)-N(14)		117.7 (2)
			C(16)-C(15)-C(14)		120.0 (3)
			C(15)-C(16)-C(17)		121.3 (3)
			C(18)-C(17)-C(16)		117.9 (3)
			C(17)-C(18)-C(19)		122.6 (3)
			C(17)-C(18)-C1(1)		119.3 (2)
			C(19)-C(18)-C1(1)		118.1 (2)
			C(18)-C(19)-C(14)		118.9 (3)
			C(13)-N(14)-C(14)		124.9 (2)

TABLE 3. Chemical Shifts in PMR Spectra of **6**, **7**, and **17** (DMSO, HMDS = 0, ppm, J/Hz)

Atom	Compound			Atom	Compound		
	6	**7**	**17**		**6**	**7**	**17**
2	5.66	5.67	5.66	12a	2.87	2.29	2.86
5	7.85	7.88	7.84	NH			9.00
6	7.16	7.20	7.10	CH_3			2.19
7	7.16	7.20	7.40	$-COC_6H_5$	5H, 7.35		
8	6.63	6.72	7.29	$-COC_6H_4NO_2$-*p*		2H, 7.63, 2H, 8.14	
9-11	1.10-1.90	1.10-1.90	1.10-1.90	$-CONHC_6H_4CH_3$-*p*			2H, 7.02, 2H, 7.28
12e	5.48	4.52	4.48				

TABLE 4. Spin-Spin Coupling Constants for Protons of **6**, **7**, and **17**

Atom	SSCC, Hz	Atom	SSCC, Hz
2	9.4 (H-9)	8	1.0 (H-6), 8.0 (H-7)
5	8.0 (H-6), 1.8 (H-7)	12e	13.0 (H-12a), 4.0 (H-11e), 3.0 (H-11a)
6	8.0 (H-5), 7.5 (H-7), 1.0 (H-8)	12a	13.0 (H-12e), 11.5 (H-11a), 3.5 (H-11e)
7	1.8 (H-5), 7.5 (H-6), 8.0 (H-8)		

The coupling partner is indicated in parentheses next to the SSCC.

The structure of **5** was established by an x-ray structure analysis (XSA) in addition to IR and PMR spectra. Figure 3 and Table 2 give the molecular structure of **5** and its experimentally determined geometric parameters (bond lengths and angles), respectively. Figure 3 shows that the aromatic ring, like in other quinazolines, is planar (within ±0.014 Å) whereas the cyclohexane ring adopts an ideal chair conformation. This is consistent with the conformation proposed on the basis of the PMR data for **3**. The pyrimidine ring with the acetyl group is slightly distorted and has the twist—boat conformation (a two-fold symmetry axis passes through the middle of the C4–C4a and N1–C2 bonds). The planar acetyl group (±0.006 Å) is slightly rotated (16.3°) relative to the plane of the N1 bonds (±0.022 Å). This indicates that the π-electrons of the carbonyl may be conjugated with the unshared pair on N1 with sp^2-hybridization (like in amides).

We showed that acylation of **3** by benzoylchloride in $CHCl_3$ occurred at N1 and gave 1-benzoyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (**6**). Under similar conditions, **3** was acylated by 4-nitrobenzoylchloride to give 1-(4-nitrobenzoyl)-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (**7**).

The structures of **5**-**7** were confirmed by spectral methods. Thus, the IR spectrum of **5** contained an absorption band for carbonyl at 1646 cm^{-1}; of **6**, at 1647 cm^{-1}.

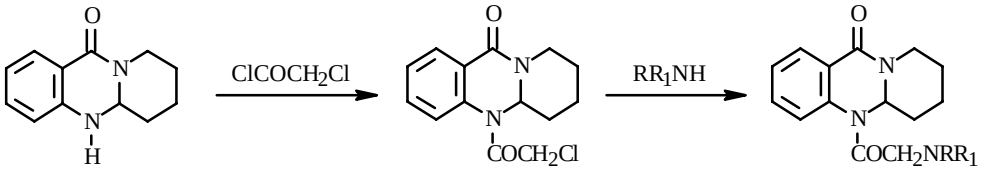
The PMR spectra of **6**, **7**, and the product from reaction of **3** and 4-tolylisocyanate (**17**, see below) were typical of quinazolones. Of the aromatic protons, H-5 was particularly noteworthy because of its weak-field shift and appearance at 7.85 ppm. In **6** and **7**, the aromatic protons formed a symmetric structure that could be recognized as AB_2C. The chemical shifts of H-6 and H-7 were the same whereas that of H-8 was almost a mirror reflection of the H-5 resonance relative to the combined resonance of H-6 and H-7. In general, these resonances gave a typical symmetric structure with doublets ($J \approx 8.0$ Hz) at the edges and a 2H triplet in the middle. In **17**, H-6 and H-8 formed an asymmetric structure that was more typical of **3** near 7.2 ppm. For **6**, the aromatic protons of the benzene ring formed a single slightly broadened singlet at 7.35 ppm. In **7** and **17**, the aromatic ring of the substituent appeared as two characteristic 2H doublets with an *o*-constant of about 8.0 Hz. The most significant difference in the spectra of **6**, **7**, and **17** from that of **3** was the weak-field shift of H-8 (by ~0.5 ppm) due to the effect of the acyl group on N1.

The cyclohexane part of the spectra of **6**, **7**, and **17** showed three isolated resonances (H-2, H_e-12, and H_a-12) and a common 6H multiplet at 1.10-1.90 ppm (Table 3).

Table 4 gives the indirect SSCC for all three compounds and shows that they are rather well repeated.

We recently showed that the Cl of 1-chloroacetyl-1,2-dihydrodeoxyvasicinone is labile and susceptible to nucleophilic substitution [6]. This compound was prepared by chloroacetylation of **4**. We decided to study the reaction of **3** with chloroacetylchloride in order to expand this reaction to 2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one derivatives.

Acylation in benzene solution in the presence of Et_3N to bind released HCl produced 1-chloroacetyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (**8**).



3 **8** **9 - 12**

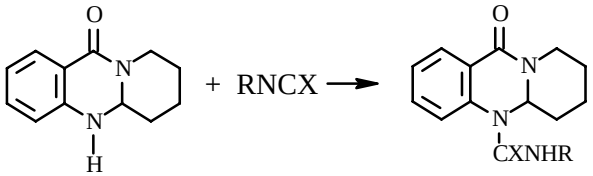
9: R = R_1 = CH_3; **10:** R = R_1 = C_2H_5; **11:** R + R_1 = $(CH_2)_2O(CH_2)_2$; **12:** R + R_1 = $(CH_2)_5$

Nucleophilic sustitution of the Cl in **8** was studied using its reaction with aliphatic and heterocyclic amines. This reaction went smoothly to form 1-dimethyl-, -diethylamino-, -morpholino-, and -piperidinoacetyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-ones (**9-12**) in good yields.

The possible substitution of Cl by other nucleophilic reagents was studied by reacting 1-chloroacetyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one with metal alkoxides, phenoxide, cyanide, selenide, and anions of compounds with an activated methylene (acetoacetic, cyanacetic, and malonic esters and acetylacetone). However, like for 1-chloroacetyl-1,2-dihydrodeoxyvasicinone [6], this produced 2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one. Because reactions with nucleophilic reagents can involve the Cl (substitution) or the amide (transamidation or cleavage of acetyl), the reaction for these nucleophilic reagents occurred with cleavage of the chloroacetyl and formation of **3**.

Next we investigated the reaction of **3** with isocyanates and isothiocyanates.

Compound **3** reacted with isocyanates and isothiocyanates to form the corresponding quinazoline ureas and thioureas (**13-17**).



3 **13 - 17**

13: R = C_6H_5, X = S; **14:** R = *o*-NO_2-C_6H_4, X = O
15: R = *o*-Cl-C_6H_4, X = O; **16:** R = *m*-Cl-C_6H_4, X = O
17: R = *p*-CH_3-C_6H_4, X = O

We used 2-nitro-, 2-, 3-chlorophenyl-, and 4-tolylisocyanates and phenylisothiocyanate as the isocyanates and isothiocyanate. Compound **3** reacted with phenylisothiocyanate to form the corresponding thiourea **13**.

The reaction proceeded smoothly with heating of a 1:2 ratio of reagents in benzene without a catalyst. The ability to perform this reaction without catalyst, in particular Et_3N that is often used for these purposes, was indicative of the rather high basicity of the N atom in **3**.

The structures of **13-17** were confirmed by IR and PMR spectra. The IR spectra of **14-17** had absorption bands at 1681-1648, 1628-1647, and 3434-3390 cm^{-1}. The absorption band of the 4-carbonyl in **13** appeared at 1694 cm^{-1}; of NH, at 3185 cm^{-1}.

The structures of **13-17** were established using **16** as an example by x-ray structure analysis (XSA). Figure 4 and Table 5 give the molecular structure of **16** projected along the N1 bond (the same projection as in Fig. 4) and the experimentally determined geometric parameters, respectively.

TABLE 5. Crystallographic and X-ray Structure Data for **5** and **16**

Structure	**5**	**16**
Molecular formula	$C_{14}H_{16}N_2O_2$	$C_{19}H_{18}N_3O_2Cl$
MW/g·mol	244.29	355.81
System	Monoclinic	Triclinic
Space group	$P2_1/n$	P-1
Z	4	2
a, Å	12.512 (3)	9.229 (2)
b, Å	7.4160 (15)	9.334 (2)
c, Å	13.919 (3)	11.787 (2)
α	90	111.93 (3)
β	104.55 (3)	91.75 (3)
γ	90	111.35 (3)
V, Å^3	1250.1 (4)	860.8 (3)
ρ, g/cm^3	1.298	1.373
Crystal size, mm	0.70×0.55×0.25	0.85×0.20×0.20
2θ scan range	2.0≤θ≤25.0°	1.9≤θ≤25.0°
μ_{exp}, cm^{-1}	0.088	0.240
Number of reflections	2200	3028
Number of reflections with I > 2σ(I)	1635	2204
R_1 (I>2σ (I) and total)	0.0485 (0.0759)	0.0520 (0.0810)
wR_2	0.1056 (0.1255)	0.0974 (0.1129)
S	1.005	1.144
Electron density difference peaks	0.16 and -0.15 e.Å^3	0.19 and -0.21 e. Å^{-3}

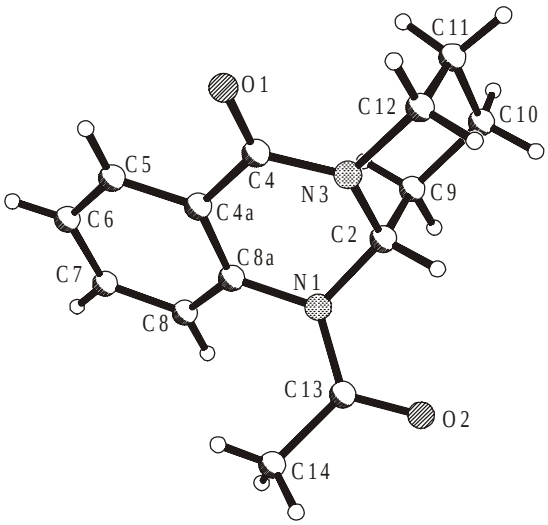


Fig. 3. Molecular structure and atomic numbering of **5**.

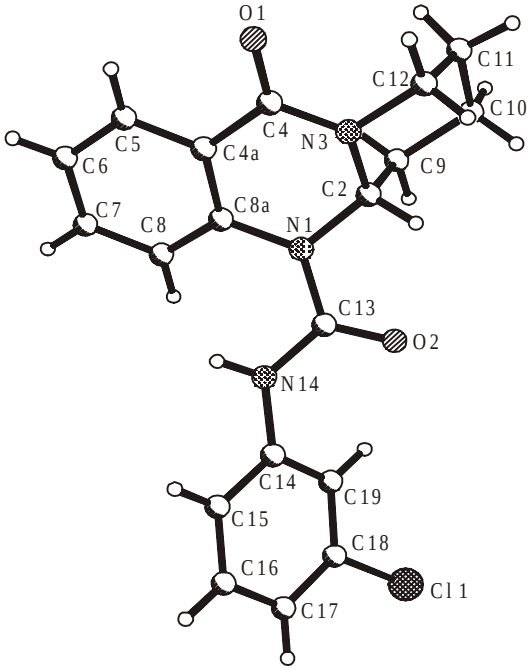


Fig. 4. Molecular structure and atomic numbering of **16**.

The conformation of the quinazoline ring and the location of the carbonyl relative to this ring in **16** are identical to those observed in **5**. The planar aminoacyl group (±0.042 Å) is rotated by 18.1° relative to the plane of the N1 bonds (±0.003 Å) whereas the 2-chlorobenzene ring (±0.008 Å) is rotated relative to the plane of the aminoacyl group by 25.9°. Comparison of equivalent bond lengths and angles in **16** and **5** (Table 2) did not reveal significant differences in their values with the exception of the bond angles of N1, which was probably due to steric differences in the substituents on it.

EXPERIMENTAL

IR spectra were recorded on a Model 2000 Fourier IR spectrometer (Perkin—Elmer) in pressed KBr disks. Mass spectra were recorded in MX-1310 and MS25,30RS spectrometers (Kratos) at ionizing potential 70 eV, source temperatures 250 and 210°C, direct injection of probe temperature 120°C, and accelerating potential 4 kV. NMR spectra were recorded on a UNITY-400+ spectrometer at operating frequency 400 MHz for ^{1}H and 100 MHz for ^{13}C. Samples were prepared in CD_3OD and DMSO-d_6 with TMS (0 ppm) internal standard. Spectra were recorded at room temperature.

X-ray Structure Analysis. Unit-cell constants of crystals of **5** and **16** were determined and refined on a Stoe Stadi-4 diffractometer (T = 300 K, graphite monochromator). Table 5 gives the main parameters of the XSA and the calculations. A three-dimensional set of reflections was obtained on the same diffractometer by ω/2θ-scanning using MoKα-radiation. Absorption corrections were not applied.

The structures of **5** and **16** were solved by direct methods using the SHELXS-97 programs and refined using the SHELXL-97 programs. All nonhydrogen atoms were refined by full-matrix anisotropic least-squares methods (over F^2). Positions of H atoms were found geometrically and refined using fixed isotropic thermal parameters $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} is the equivalent isotropic thermal parameter of the corresponding C atoms. Methyl H atoms in **5** were found in a difference electron density synthesis.

Data from the XSA were deposited as CIF files in the Cambridge Crystallographic Data Centre (CCDC 635629 and 635630).

2,3-Tetramethylene-3,4-dihydroquinazol-4-one (1) was prepared by the literature method [4].

2,3-Tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (3). A solution of **1** (1 g, 5 mmol) in alcohol (20 mL) was treated with $NaBH_4$ (1 g, 26 mmol) and heated on a water bath for 6 h. Solvent was distilled off. The solid was treated with water until it dissolved and was extracted with $CHCl_3$ (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4. The $CHCl_3$ was distilled off. The solid was recrystallized to afford **3** (0.89 g, 89%), mp 135°C (water), R_f 0.65 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm $^{-1}$): 1629 (CO).

1-Acetyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (5). Compound **3** (1 g, 4.9 mmol) was dissolved in acetic anhydride (10 mL), heated on a water bath for 3 h, treated with water, neutralized with aqueous $NaHCO_3$ (20%), and extracted with $CHCl_3$ (3 × 50 mL). The $CHCl_3$ was distilled off. The solid was recrystallized to afford **5** (1.06 g, 87%), mp 130°C (hexane), R_f 0.68 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm $^{-1}$): 1672 (CO). Mass spectrum (*m*/*z*, %): 244 (20) $[M]^+$, 201 (45) $[M - 1]^+$, 200 (100) $[M - 2]^+$, 185 (25), 173 (25), 160 (23), 147 (19), 146 (40), 119 (30).

1-Benzoyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (6). A solution of **3** (1 g, 4.9 mmol) in $CHCl_3$ (50 mL) was treated with benzoylchloride (1 mL, 9 mmol), heated and stirred on a water bath for 3 h, and treated with aqueous NaOH (10%). The organic layer was separated, washed with water (3 times), and dried over $MgSO_4$. The $CHCl_3$ was distilled off. The solid was recrystallized to afford **6** (1.14 g, 78%), mp 181°C (Et_2O), R_f 0.68 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm $^{-1}$): 1647 (CO).

1-(4-Nitrobenzoyl)-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (7) was prepared analogously as above from **3** (1 g, 4.9 mmol) and 4-nitrobenzoylchloride (1.67 g, 9 mmol) to afford **7** (1.35 g, 80%), mp 184°C, R_f 0.77 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm $^{-1}$): 1647 (CO).

1-Chloroacetyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (8). A solution of **3** (2.4 g, 12 mmol) and Et_3N (1.2 mL, 8.6 mmol) in benzene (30 mL) was stirred, treated dropwise with chloroacetylchloride (1.81 mL, 24 mmol) in benzene (5 mL), and heated on a water bath for 3 h. The resulting precipitate was filtered off. Solvent was distilled off. The solid was washed with water, dried, and recrystallized from hexane to afford **8** (2.6 g, 79%), mp 158-160°C, R_f 0.73 (Silufol, $CHCl_3$:CH_3OH, 10:1). IR spectrum (ν, cm $^{-1}$): 1645 (CO). Mass spectrum (*m*/*z*, %): 278/280 (8) $[M]^+$, 277/279 (5) $[M - 1]^+$, 244 (22), 243 (60), 201 (26), 200 (13), 174 (25), 160 (100), 119 (23).

1-Dimethylaminoacetyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (9). A mixture of **7** (0.4 g, 1.4 mmol) in alcohol (10 mL) and aqueous dimethylamine (0.5 mL, 8.4 mmol, 33%) was heated on a water bath for 4 h, cooled, diluted with water, and extracted with $CHCl_3$ (3×). The extract was dried over Na_2SO_4. Solvent was distilled off. The solid was reprecipitated from hexane to afford **9** (0.3 g, 70%), R_f 0.73 (Silufol, $CHCl_3$:CH_3OH, 10:1). IR spectrum (ν, cm $^{-1}$): 1645 (CO), 2995 (CH_{Ar}). Mass spectrum (*m*/*z*, %): 287 (22) $[M]^+$, 286 (10) $[M - 1]^+$, 285 (13) $[M - 2]^+$, 243 (21), 229 (7), 228 (13), 202 (100), 201 (23), 200 (19), 175 (89), 161 (48), 119 (26).

1-Diethylaminoacetyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (10). A mixture of **7** (0.4 g, 1.4 mmol) and diethylamine (0.44 mL, 4.2 mmol) in benzene (10 mL) was boiled on a water bath for 3.5 h, cooled, and washed with water (3×). The organic layer was dried over Na_2SO_4. Solvent was distilled off. The solid was reprecipitated from hexane to afford **10** (0.32 g, 72%), R_f 0.64 (Silufol, $CHCl_3$:CH_3OH, 10:1). IR spectrum (ν, cm^{-1}): 1645 (CO), 2995 (CH_{Ar}).

1-Morpholinoacetyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (11) was prepared analogously to that above from **7** (0.4 g, 1.4 mmol) and morpholine (0.34 mL, 4.2 mmol) to afford **11** (0.35 g, 73%), mp 135-137°C (hexane), R_f 0.62 (Silufol, $CHCl_3$:CH_3OH, 10:1). IR spectrum (ν, cm^{-1}): 1615 (CO), 2995 (CH_{Ar}). Mass spectrum (*m*/*z*, %): 329 (15) $[M]^+$, 328 (4) $[M - 1]^+$, 327 (6) $[M - 2]^+$, 299 (70), 259 (81), 243 (55), 229 (19), 201 (83), 200 (75), 199 (64), 174 (71), 160 (100), 119 (42).

1-Piperidinoacetyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (12) was prepared analogously from **7** (0.4 g, 1.4 mmol) and piperidine (0.37 mL, 4.2 mmol) to afford **12** (0.35 g, 70%) as an oil, R_f 0.53 (Silufol, $CHCl_3$:CH_3OH, 5:1). Mass spectrum (*m*/*z*, %): 327 (18) $[M]^+$, 326 (22) $[M - 1]^+$, 325 (17) $[M - 2]^+$, 243 (48), 229 (9), 228 (17), 202 (89), 201 (83), 200 (75), 160 (100).

1-(2-Chlorophenylaminocarbonyl)-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (15). A solution of **3** (0.25 g, 1.2 mmol) in benzene (25 mL) was treated with *o*-chlorophenylisocyanate (0.37 g, 2.5 mmol), boiled on a water bath for 3 h, and left for 1 d. The resulting precipitate was filtered off to afford **15** (0.29 g, 68%), mp 214°C (alcohol), R_f 0.67 (Silufol, benzene:acetone, 5:2). Compounds **13**, **14**, **16**, and **17** were prepared analogously.

1-Phenylaminothiocarbonyl-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (13) was prepared from **3** (0.25 g, 1.2 mmol) and phenylisothiocyanate (0.33 g, 2.5 mmol). Yield 0.12 g (29%), mp 212-214°C (acetone), R_f 0.68 (Silufol, benzene:acetone, 5:2).

1-(2-Nitrophenylaminocarbonyl)-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (14) was prepared from **3** (0.25 g, 1.2 mmol) and *o*-nitrophenylisocyanate (0.4 g, 2.5 mmol). Yield 0.32 g (71%), mp 195°C (benzene), R_f 0.68 (Silufol, benzene:acetone, 5:2).

1-(3-Chlorophenylaminocarbonyl)-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (16) was prepared from **3** (0.25 g, 1.2 mmol) and *m*-chlorophenylisocyanate (0.37 g, 2.5 mmol). Yield 0.31 g (70%), mp 245°C (alcohol), R_f 0.68 (Silufol, benzene:acetone, 5:2).

1-(4-Tolylaminocarbonyl)-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (17) was prepared from **3** (0.25 g, 1.2 mmol) and *p*-tolylisocyanate (0.34 g, 2.5 mmol). Yield 0.25 g (60%), mp 273°C (alcohol), R_f 0.68 (Silufol, benzene:acetone, 5:2). Mass spectrum (*m*/*z*, %): 335 (14) $[M]^+$, 252 (15) $[M - 1]^+$, 202 (50) $[M - 2]^+$, 201 (100), 185 (19), 174 (30), 173 (50), 147 (33), 146 (58).

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