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REACTIONS OF QUINAZOLINE ALKALOIDS AND THEIR DERIVATIVES WITH ELECTROPHILIC REAGENTS

Z. U. Samarov,* Z. M. Khakimova, R. Okmanov, B. Tashkhodzhaev, and Kh. M. Shakhidoyatov

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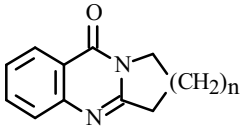
Nitration of deoxypeganine (DOP), deoxyvasicinone (DOV), 2,3-tetramethylene-, 2,3-pentamethylene-, and 3,4-dihydroquinazol-4-ones and their 1,2-dihydro derivatives was studied. It was shown that the reaction pathway changed depending on the presence of a carbonyl on C-4 and an N=C bond in these compounds. Only the H atom on C-6 was subject to nitration if both functional groups were present, for example DOV and its homologs. Substitution of the H atom of either the 6-position (DOP, 1,2-dihydro-DOV, and their homologs) or the 6- and 8-positions simultaneously (DOP and its homologs) was enhanced if one of these functional groups was missing depending on the substrate:nitrating agent ratio. The bromination and nitration reactions of 1,2-dihydro-DOV and its analogs in a 1:2 ratio were accompanied by oxidation of the N^1H–CH bond with formation of 6,8-dibromo- and 6,8-nitro-DOV and their homologs. The difference in the behavior of these compounds was due to the different nucleophilicity of the benzene rings in them. The reaction of 1,2-dihydro-DOV and its homologs with isocyanates and p-*nitro- and* p-*methylbenzoic acid chlorides was studied. 6-Nitro- and 6,8-dinitro-DOP and 6,8-dibromo- and 6,8-dinitro-DOV and their homologs and 6-bromo- and 6-nitro-1,2,3,4-tetrahydro-2,3-polymethylenequinazol-4-ones and their 1-alkyl(aryl)-carbamoyl and* p-*nitro(methyl)-benzoyl derivatives were synthesized. The molecular structures of 1-ethyl- and 1-(*o-*chlorophenyl)-carbamoyl-1,2-dihydrodeoxyvasicinones and 6,8-dinitro-2,3-pentamethylene-3,4-dihydroquinazol-4-one were established.*

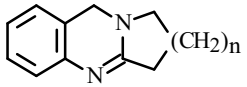
Key words: deoxypeganine, deoxyvasicinone, 2,3-tetramethylene-, 2,3-pentamethylene-3,4-dihydroquinazol-4-ones, 1,2,3,4-tetrahydro-2,3-polymethylenequinazol-4-ones, isocyanates, electrophilic substitution, alkaloids, x-ray diffraction analysis, carbamoylation, acylation.

The alkaloids deoxyvasicinone (**1**) and deoxypeganine (**2**) were isolated from the plant *Peganum harmala* [1, 2]; 2,3-tetramethylene-3,4-dihydroquinazol-4-one (**3**) and -quinazoline (**4**), from *Mackinlaya subulata* and *M. makrosciadia* [3]. These alkaloids and their seven-membered ring synthetic homolog **5** have been synthesized. A simple and convenient preparation method has been developed [4, 5].



1, 3, 5

1: n = 1; **3:** n = 2; **5:** n = 3



2, 4

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

We have previously studied the reaction of **1** with various electrophilic reagents (nitration, sulfochlorination, bromination with potassium bromate and conc. H_2SO_4) to give 6-substituted **1** [4-6].

S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (99871) 120 64 75, e-mail: Zarif1980@rambler.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 387-393, July-August, 2008. Original article submitted May 5, 2008.

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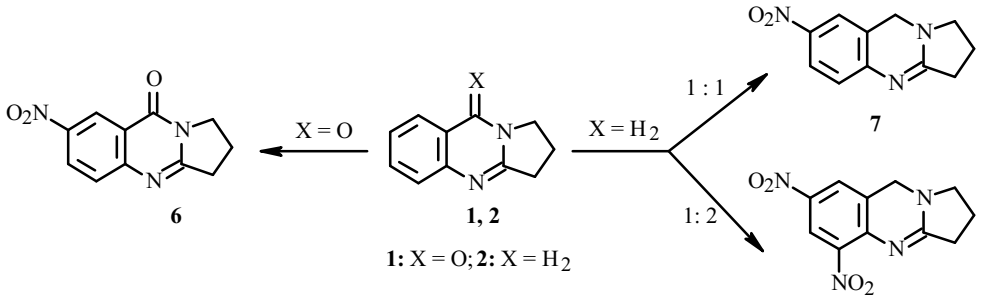
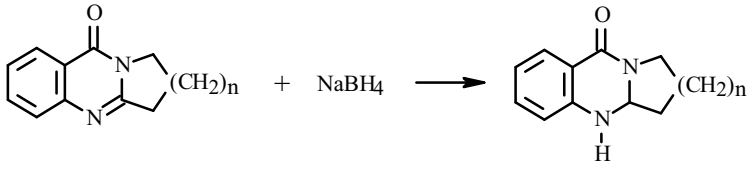
In continuation of our research on the search for biologically active compounds among tricyclic quinazolone alkaloids and on the introduction of a second electrophilic substituent in the 8-position to produce 6,8-disubstituted **1**, we reacted **1** with an excess of a nitrating mixture under various conditions, in contrast with the literature [4]. However, we produced only 6-nitrodeoxyvasicinone (**6**) despite using a 1:2 ratio of **1**:nitrating mixture and increasing the reaction temperature to 0-5°C. In contrast with this, nitration of **2** followed various pathways and depended on the ratio of reagents. Thus, using a 1:1 ratio of **2**:nitrating mixture formed 6-nitrodeoxypeganine (**7**); using a 1:2 ratio of reagents, 6,8-dinitrodeoxypeganine (**8**).



Such a difference in the behavior of **1** and **2** in the nitration reaction is explained by the relatively low nucleophilicity of the benzene ring in **1** after introducing one nitro group. Thus, **6** contains such electronegative groups as NO_2, C=O, and C=N, which withdraw electrons from the benzene ring and create a deficiency of electron density in it. Without the carbonyl on C-4, i.e., in **7**, the nucleophilicity of the aromatic ring is relatively higher than in **6** [6]. Therefore, the intermediate 6-nitrodeoxypeganine (**7**) undergoes a second electrophilic substitution by the nitrating agent at the 8-position and forms **8**.

It can be assumed that the lack of a N=C double bond increases the nucleophilicity of the benzene ring compared with **6**. In order to confirm this hypothesis, we reduced the N=C bond in **1** with sodium borohydride [7, 8] to give 1,2-dihydrodeoxyvasicinone (**9**) and its homologs **10** and **11**.

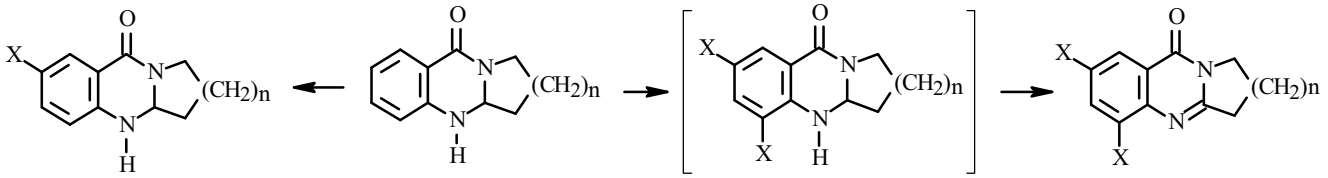


1: n = 1; **3:** n = 2; **5:** n = 3

9: n = 1; **10:** n = 2; **11:** n = 3

A study of the nitration of **9** showed, as hypothesized, 6-nitro-1,2-dihydrodeoxyvasicinone (**12**) was formed with a 1:1 ratio of **9**:nitrating agent. Using a 1:2 ratio of reagents led to the formation of 6,8-dinitrodeoxyvasicinone (**18**) instead of the expected 6,8-dinitro-1,2-dihydrodeoxyvasicinone (**15**).

Nitration of 2,3-tetramethylene- and 2,3-pentamethylene-1,2,3,4-tetrahydroquinazol-4-ones (**10**, **11**) occurred analogously to produce 6,8-dinitro-2,3-tetramethylene- and 2,3-pentamethylene-3,4-dihydroquinazol-4-ones (**19**, **20**), respectively.



12 - 20: X = NO_2; **21 - 29:** X = Br

12, 15, 18, 21, 24, 27: n = 1; **13, 16, 19, 22, 25, 28:** n = 2; **14, 17, 20, 23, 26, 29:** n = 3

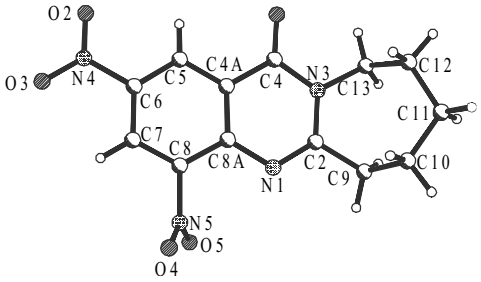


Fig. 1. Molecular structure of **20**.

Thus, we developed a method for preparing 6,8-dinitrodeoxyvasicinone and its six- and seven-membered ring homologs, which are difficultly available by other methods.

It seemed interesting to investigate the behavior of **9**-**11** in bromination reactions because they might behave similarly as for nitration.

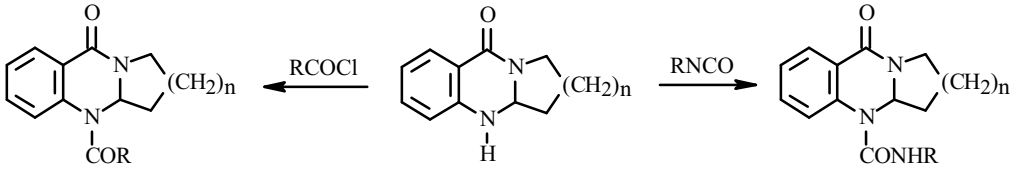
Bromination of **9** in 70% acetic acid formed 6-bromo-1,2-dihydrodeoxyvasicinone (**21**, **9**:bromine ratio 1:1). Using a 1:2 ratio of reagents gave 6,8-dibromodeoxyvasicinone (**27**), i.e., bromination of **9** occurred anlaogously to nitration with simultaneous oxidation of the NH–CH bond to an N=C bond. According to the literature, bromination of DOV (**1**) with bromine in acetic acid occurred exclusively at the α-C atom [4-6]. Electrophilic substitution of the H atoms in the 6- or 8-positions did not occur although it is known that the hydrochloride of **2** reacted with *N*-bromosuccinimide (NBS) in dry $CHCl_3$ to give a mixture of 6-bromopeganol (6-bromo-4-hydroxy-**2**) and 8-bromo-DOV in a 1:1.7 ratio. The main product was 6-bromopeganol [9]. We showed recently that bromination of **2** with NBS in $CHCl_3$ and subsequent treatment with NaOH (10%) gave a mixture of peganol (4-hydroxy-**2**) and 6-bromopeganol, which formed mixed crystals upon crystallization [10, 11].

Bromination of 2,3-tetramethylene- and 2,3-pentamethylene-1,2,3,4-tetrahydroquinazol-4-ones (**10** and **11**) by bromine in a 1:1 ratio gave monobromo-2,3-tetramethylene- and -pentamethylene-1,2,3,4-tetrahydroquinazol-4-ones (**22** and **23**). A 1:2 ratio of reagents formed, like for bromination of 1,2-DOV, 6,8-dibromo-2,3-tetramethylene- and -pentamethylene-3,4-dihydroquinazol-4-ones (**28** and **29**).

The structures of 6,8-dinitro-2,3-polymethylene-3,4-dihydroquinazol-4-ones **18**-**20** were confirmed by spectral data and for **20**, also by an x-ray diffraction analysis. Figure 1 shows the molecular structure of **20**. It can be seen that the quinazolone core with the adjoining atoms and the nitro group in the C6-position are planar within 0.037 Å. The seven-membered heterocycle adopted the chair conformation. The planar nitro group in the C8-position is situated practically perpendicular (73.3°) to the plane of the aromatic ring. This is unusual in conjugated systems. An analogous placement of the nitro group was observed in the structure of 2-(3′,5′-dinitro-2′-methoxyphenyl)-6,8-dinitroquinazolin-4-one [12]. The molecules in the crystal are located at Van-der-Waals distances from each other.

It is known that **9** reacts with acid chlorides, adds to phenylacetylene, and is alkylated by allylchloride [7, 8, 13]. The analog of **9** with a six-membered ring instead of the five-membered one, the 1,2-dihydro derivative of the alkaloid 2,3-tetramethylene-3,4-dihydroquinazol-4-one, is also acylated and carbamoylated upon reaction with acid chlorides and isocyanates [14]. Herein we report on an investigation of the reaction of **9** and its homolog **11** with *p*-nitro- and *p*-methylbenzoylchlorides and isocyanates.

A study of the acylation of **9** and **11** by *p*-nitrobenzoylchloride and *p*-toluylchloride showed that the reaction occurs in $CHCl_3$ solution at the N-1 nitrogen and gives 1-*p*-nitrobenzoyl- and 1-*p*-methylbenzoyl-1,2-dihydrodeoxyvasicinones and their homologs (**30**-**33**).



30 - 33 **9, 11** **34 - 42**

9: n = 1; **11:** n = 3

30, 32: R = *p*-NO_2-C_6H_4; **31, 33, 37, 42:** R = *p*-CH_3-C_6H_4; **34, 39:** R = *o*-NO_2-C_6H_4; **35, 40:** R = *o*-Cl-C_6H_4
36, 41: R = *m*-Cl-C_6H_4; **38:** R = C_2H_5 **30, 31, 34 - 38:** n = 1; **32, 33, 39 - 42:** n = 3

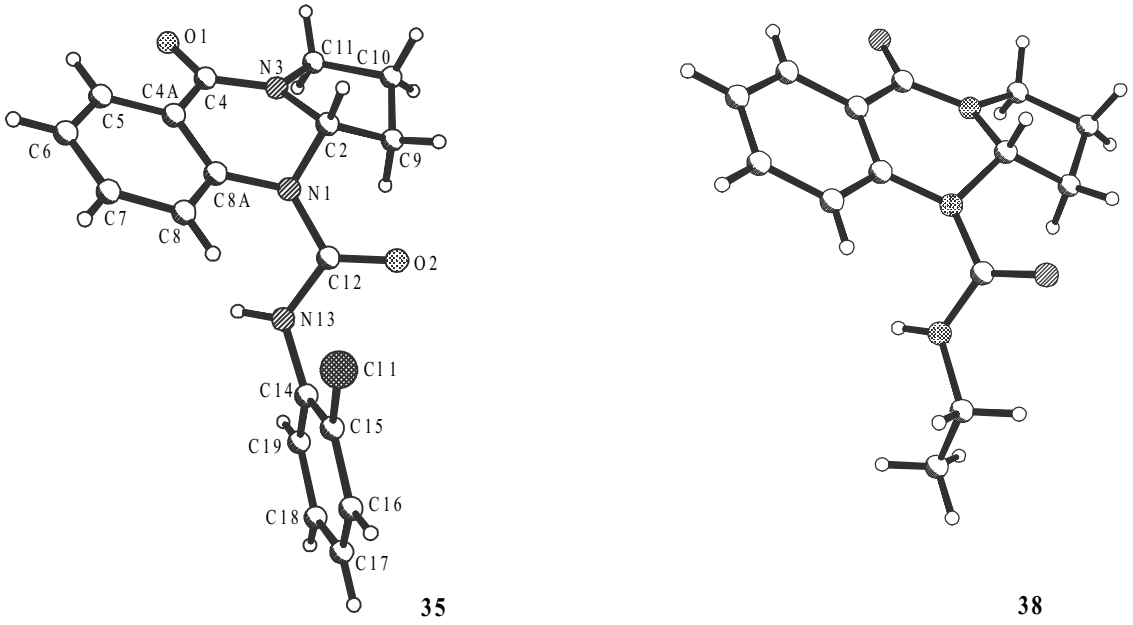


Fig. 2. Molecular structures of **35** and **38**.

Compounds **9** and **11** reacted with isocyanates to form the corresponding quinazoline ureas (**34**-**42**). We used the isocyanates *o*-nitro-, *o*- and *m*-chloro-, and *p*-methylphenylisocyanates and ethylisocyanate. The reaction occurred smoothly with heating of a 1:2 mixture of the reagents in benzene solution without a catalyst.

The structures of **34**-**42** were established by spectral properties and for **35** and **38**, also by x-ray diffraction analyses.

The crystal structures of **35** and **38** showed that the crystals were racemic. Both crystals had antipodes related by a center of symmetry that formed dimers through intermolecular H-bonds between the quinazolone carbonyl O atom and the aminoacetyl NH group with N13...O1, 2.88; N13–H...O1, 1.94 Å; 160.9°. These values for **35** were 2.86 and 2.03 Å and 175.2°, respectively.

Figure 2 shows the molecular structures of **35** and **38**. The quinazolone benzene ring (including N1 and C4) was planar within 0.008 Å. Atoms C2 and N3 in the six-membered ring in **35** and **38** deviated from the plane of the remaining four atoms by -0.76 and 0.28 Å and -0.74 and 0.26 Å, respectively. These values indicated that the six-membered ring adopted an intermediate conformation between a chair and half-chair. The five-membered rings in **35** and **38** adopted the envelope conformation with C9 deviating from the plane of the remaining four atoms by 0.55 and 0.57 Å, respectively. The aminoacyl group (including N1 and C14) in **35** and **38** were planar within 0.024 and 0.009 Å and was twisted relative to the mean-square plane of the quinazolone benzene ring (including N1 and C4) by 57.2 and 63.3°, respectively. The *o*-chlorophenyl group in **35** is twisted relative to the plane of the amino group by 63.3°.

The methyl group in **38** was disordered. This moiety was found in two positions with different occupancies (degree of occupying positions in the unit cell) of 0.7 and 0.3. This was evident in the large thermal parameters of C15 and the anomalous shortening of the length of the C14–C15 single bond [distances of 1.331(8) and 1.393(8) Å, respectively] compared with the normal value (1.54 Å).

A comparison of equivalent bonds in **35** and **38** showed that they differed significantly in the aminoacetyl group. The C12–N13 amide bond length in **35** [1.358(4) Å] was longer whereas the N1–C12 bond [1.407(4) Å] was shorter than that observed in **38** [1.294(3) and 1.421(2) Å, respectively]. This indicated that the π-electron system of –C(O)–NH bonds was conjugated with the analogous system of the chloro-substituted benzene ring, which is impossible in **38**.

TABLE 1. Principal Crystallographic Parameters and X-ray Structure Properties for **20**, **35**, and **38**

Structure	**20**	**35**	**38**
Molecular formula	$C_{13}H_{12}N_4O_5$	$C_{18}H_{16}N_3O_2Cl$	$C_{14}H_{17}N_3O_2$
MW	304.27	341.79	259.31
System	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/c$	$P2_1/n$	P-1
Z	4	4	2
a, Å	6.383 (3)	11.701 (6)	8.138 (1)
b, Å	22.556 (11)	11.103 (4)	8.414 (2)
c, Å	9.310 (5)	12.730 (5)	10.966 (2)
α	89.99 (4)	90	82.82 (3)
β	92.16 (4)	110.93 (3)	70.73 (3)
γ	90.00 (4)	90	64.93 (3)
V, Å^3	1339.6 (11)	1544.7 (12)	641.9 (2)
Dx, g/cm^3	1.508	1.470	1.342
Crystal size, mm	0.60×0.50×0.25	0.45×0.35×0.15	0.70×0.60×0.20
θ-Scanning range	1.96≤θ≤58.0°	1.71≤θ≤25.0°	1.97≤θ≤26.0°
μ_{exp}, mm^{-1}	1.012	0.264	0.092
Number of reflections	1857	2714	2290
Number of reflections with I>2σ (I)	1710	1829	1896
R_1 (I>2σ (I) and total)	0.04 (0.043)	0.07 (0.111)	0.05 (0.062)
WR_2	0.11 (0.112)	0.10 (0.120)	0.12 (0.135)
S	1.09	1.17	1.10
Difference electron-density peaks	0.17 and -0.19 eÅ^{-3}	0.26 and -0.23 eÅ^{-3}	0.22 and -0.32 eÅ^{-3}

EXPERIMENTAL

IR spectra in mineral oil were recorded on a Perkin—Elmer Model 2000 Fourier-IR spectrometer. PMR spectra in TFA and $CDCl_3$ were recorded on a UNITY 400$^+$ plus spectrometer (Varian). Mass spectra were obtained in a MS 25-RF (Kratos) instrument with direct sample introduction into the ion source, ionizing electron energy 70 eV, ion source temperature 250°C, and sample introduction temperature 200°C. The course of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using benzene:acetone (5:2) and UV light developer.

X-ray Diffraction Analyses. Unit-cell constants of crystals of **20**, **35**, and **38** were determined and refined on a Stoe Stadi-4 diffractometer (T = 298 K, graphite monochromator). Intensities of reflections were measured on the same diffractometer by ω/2θ-scanning using Cu (**20**) and Mo (**35** and **38**) Kα-radiation. Absorption corrections for **20** were applied by ψ-scanning and were not applied for the other structures. Table 1 lists the principal parameters of the x-ray diffraction analyses and the calculations. The structures were solved by direct methods using the SHELXS-97 programs. Structures were refined using the SHELXL-97 program. All nonhydrogen atoms were refined by a full-matrix anisotropic least-squares method (over F^2). Positions of H atoms were found geometrically and refined with fixed isotropic thermal parameters $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} are the equivalent isotropic thermal parameters of the corresponding C atoms. The positions of the NH H atoms in **35** and **38** were found in difference electron-density syntheses and refined isotropically. Data from the x-ray diffraction analyses were deposited as CIF-files in the Cambridge Crystallographic Database [CCDC-685459 (**20**), 685460 (**35**), 685461 (**38**)].

Deoxyvasicinone (**1**), deoxypeganine (**2**), and 2,3-tetramethylene-3,4-dihydroquinazol-4-one (**5**) were prepared as before [3]. 1,2-Dihydrodeoxyvasicinone (**9**), 2,3-tetramethylene- (**10**), and 2,3-pentamethylene-1,2,3,4-tetrahydroquinazol-4-ones (**11**) were synthesized by the literature method [7].

Elemental analyses for newly synthesized compounds agreed with those calculated.

6-Nitrodeoxypeganine (7). Compound **2** (0.33 g, 2 mmol) was dissolved with stirring and cooled to -5°C in conc. H_2SO_4 (3 mL), stirred vigorously, treated in portions with a nitrating mixture consisting of HNO_3 (0.09 mL, 2.1 mmol, d = 1.5) and H_2SO_4 (0.2 mL, d = 1.84) at a rate such that the temperature remained below 0°C, stirred at this temperature for 30 min,

at 5-10°C for 1 h, at 20°C for 1 h, poured into ice, and basicified with ammonia solution until the pH was 8-9. The resulting solid was filtered off, washed with water, and dried. Yield of **7**, 0.33 g (82%), mp 187-189°C, R_f 0.46 (Al_2O_3, $CHCl_3$:ether, 1:1). IR spectrum (ν, cm^{-1}): 1620 (C=N), 1508 (NO_2).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 6.80 (1H, d, J = 8.0, H-8), 7.78 (1H, d, J_{ortho} = 12, J_{meta} = 2, H-7), 8.70 (1H, d, J_{meta} = 2.5, H-5), 2.80 (2H, t, α-CH_2), 2.10 (2H, m, β-CH_2), 3.63 (2H, t, γ-CH_2), 4.55 (2H, s, H_2-4).

Mass spectrum (*m*/*z*, %): 262 (100) $[M]^+$, 215 (25) $[M - 47]^+$, 182 (12) $[M - 80]^+$, 169 (54) $[M - 93]^+$, 149 (10) $[M - 113]^+$, 103 (9) $[M - 159]^+$.

6,8-Dinitrodeoxypeganine (8) was prepared analogously as above from **2** (0.5 g, 3 mmol) and a nitrating mixture consisting of HNO_3 (0.25 mL, d = 1.5) and H_2SO_4 (0.36 mL, d = 1.84) to afford **8**. Yield 0.56 g (76%), mp 214-216°C, R_f 0.46 (Al_2O_3, $CHCl_3$:ether, 1:1). IR spectrum (ν, cm^{-1}): 1625 (C=N), 1520 (NO_2).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 8.68 (1H, d, J_{meta} = 2.5, H-5), 7.98 (1H, d, J_{meta} = 2, H-7), 2.98 (2H, t, α-CH_2), 2.10 (2H, m, β-CH_2), 3.63 (2H, t, γ-CH_2), 4.73 (2H, s, H_2-4).

Mass spectrum (*m*/*z*, %): 217 (100) $[M]^+$, 201, 187, 170 (57), 158, 149.

6-Nitro-1,2-dihydrodeoxyvasicinone (12). Compound **9** (0.541 g, 2.87 mmol) was dissolved with stirring and cooled to 0°C in conc. H_2SO_4 (21 mL), stirred vigorously, treated in portions with a nitrating mixture (0.25 mL HNO_3, d = 1.34; 0.3 mL H_2SO_4, d = 1.84) at such a rate that the temperature remained at 0-2°C, stirred for 1 h at 5-10°C, and poured onto ice. The solid was filtered off, washed with water, and dried. Recrystallization afforded **12**, 0.54 g (80%), mp 210°C (methanol), R_f 0.49 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1630 (C=N), 1522 (NO_2), 1645 (C=O).

6-Nitro-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (13). Compound **10** (0.58 g, 2.87 mmol) was dissolved with stirring and cooled to 0°C in conc. H_2SO_4 (21 mL), stirred vigorously, treated in portions with a nitrating mixture (0.25 mL HNO_3, d = 1.34; 0.3 mL H_2SO_4, d = 1.84) at such a rate that the temperature remained at 0-2°C, stirred for 1 h at 5-10°C, and poured onto ice. The solid was filtered off, washed with water, and dried. Recrystallization afforded **13**, 0.55 g (78%), mp 224-226°C (methanol), R_f 0.56 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1630 (C=N), 1522 (NO_2), 1645 (C=O).

6-Nitro-2,3-pentamethylene-1,2,3,4-tetrahydroquinazol-4-one (14) was prepared analogously as above from **11** (0.62 g, 2.87 mmol), conc. H_2SO_4 (21 mL), and HNO_3 (0.25 mL, d = 1.34) and H_2SO_4 (0.3 mL, d = 1.84) to afford **14** (0.61 g, 82%), mp 175-177°C (methanol), R_f 0.55 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1630 (C=N), 1522 (NO_2), 1640 (C=O).

Reaction of 9 and Nitrating Mixture. Synthesis of 6,8-Dinitrodeoxyvasicinone (18). Compound **9** (0.6 g, 3.91 mmol) was dissolved with stirring and cooled to 0°C in conc. H_2SO_4 (21 mL), stirred vigorously, treated in portions with a nitrating mixture (0.56 mL HNO_3, d = 1.34; H_2SO_4, 0.3 mL, d = 1.84) at a rate such that the temperature remained below 2°C, stirred at room temperature for 1 h, and poured onto ice. The resulting precipitate was filtered off, washed with water, and dried. Recrystallization afforded **18** (0.8 g, 90%), mp 216-218°C (methanol), R_f 0.69 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1628 (C=N), 1640 (C=O), 1526 (NO_2).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 9.23 (1H, d, J_{meta} = 2.7, H-5), 8.77 (1H, d, J_{meta} = 2.7, H-7), 3.23 (2H, t, α-CH_2), 2.25 (2H, m, β-CH_2), 4.22 (2H, t, γ-CH_2).

Nitration of 2,3-Tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (1:2 10:nitrating mixture ratio). Synthesis of 6,8-Dinitro-2,3-tetramethylene-3,4-dihydroquinazol-4-one (19). Compound **10** (0.79 g, 3.91 mmol) was dissolved with stirring and cooled to 0°C in conc. H_2SO_4 (21 mL), stirred vigorously, treated in portions with a nitrating mixture (0.56 mL HNO_3, d = 1.34; 0.3 mL H_2SO_4, d = 1.84) at such a rate that the temperature remained below 2°C, stirred for 1 h at 5-10°C, and poured onto ice. The resulting precipitate was filtered off, washed with water, and dried. Recrystallization afforded **19** (0.97 g, 85%), mp 220-222°C (methanol), R_f 0.7 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1628 (C=N), 1526 (NO_2), 1635 (C=O).

Reaction of 2,3-Pentamethylene-1,2,3,4-tetrahydroquinazol-4-one with Nitrating Mixture. Synthesis of 6,8-Dinitro-2,3-pentamethylene-3,4-dihydroquinazol-4-one (20). Compound **20** was prepared analogously as above from **11** (0.85 g, 3.91 mmol), conc. H_2SO_4 (21 mL), and nitrating mixture (0.56 mL HNO_3, d = 1.34; 0.3 mL H_2SO_4, d = 1.84), 1.1 g (90%), mp 239-241°C (methanol), R_f 0.75 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1628 (C=N), 1526 (NO_2), 1645 (C=O).

Mass spectrum (*m*/*z*, %): 304 (38) $[M]^+$, 55 (88), 43 (100). Table 1 and Fig. 1 list the principal crystallographic parameters and characteristics of the x-ray diffraction analysis.

6-Bromo-1,2-dihydrodeoxyvasicinone (21). Compound **9** (1 g, 5.32 mmol) was dissolved in acetic acid (20 mL, 70%), stirred vigorously, treated in portions with bromine (0.3 mL, d = 3.1), stirred for 3 h at 5-10°C, and poured onto ice. The resulting precipitate was filtered off, washed with water, and dried. Recrystallization afforded **21** (0.51 g, 36%), mp 218-220°C (acetone). IR spectrum (ν, cm^{-1}): 1645 (C=O), 1628 (C=N), 855 (Br).

Reaction of 1,2-Dihydrodeoxyvasicinone with Bromine (1:2 ratio). Synthesis of 6,8-Dibromodeoxyvasicinone (27). A solution of **9** (1 g, 5.32 mmol) in acetic acid (20 mL, 70%) was stirred vigorously, treated dropwise over 30 min with bromine (0.55 mL, d = 3.1), stirred for 2 h at 5-10°C, and poured onto ice. The resulting precipitate was filtered off, washed with water, and dried to afford **27** (1.6 g, 87%), mp 255-257°C (acetone). IR spectrum (ν, cm^{-1}): 1643 (C=O), 1628 (C=N), 850 (Br).

PMR spectrum (TFA, δ, ppm, J/Hz): 8.10 (1H, d, J_{meta} = 2.04, H-5), 7.95 (1H, d, J_{meta} = 2.04, H-7), 3.38 (2H, t, α-CH_2), 2.20 (2H, m, β-CH_2), 4.10 (2H, t, γ-CH_2).

Mass spectrum (*m*/*z*, %): 346 (30) $[M]^+$, 344 (100), 77 (51) $[M]^+$.

6-Bromo-2,3-tetramethylene-1,2,3,4-tetrahydroquinazol-4-one (22). Compound **10** (1.1 g, 5.32 mmol) and bromine (0.3 mL, d = 3.1) in acetic acid (20 mL, 70%) analogously as above afforded **22** (0.6 g, 40%), mp 214-216°C (acetone), R_f 0.52 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1645 (C=O), 1626 (C=N), 855 (Br).

Conversion of 2,3-Tetramethylene-1,2,3,4-tetrahydroquinazol-4-one into 6,8-Dibromo-2,3-tetramethylene-3,4-dihydroquinazol-4-one (28). Compound **10** (1.1 g, 5.32 mmol) and bromine (0.55 mL, d = 3.1) in acetic acid (20 mL, 70%) analogously as above afforded **28** (1.7 g, 85%), mp 217-218°C (acetone), R_f 0.75 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1643 (C=O), 1628 (C=N), 850 (Br).

6-Bromo-2,3-pentamethylene-1,2,3,4-dihydroquinazol-4-one (23). Compound **11** (1.15 g, 5.32 mmol) and bromine (0.3 mL, d = 3.1) in acetic acid (20 mL, 70%) analogously as above afforded **23** (0.6 g, 38%), mp 245-247°C (acetone), R_f 0.72 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1640 (C=O), 1624 (C=N), 850 (Br).

Reaction of 2,3-Pentamethylene-1,2,3,4-tetrahydroquinazol-4-one with Bromine (1:2 ratio). Synthesis of 6,8-Dibromo-2,3-pentamethylene-3,4-dihydroquinazol-4-one (29). Compound **11** (1.15 g, 5.32 mmol) and bromine (0.55 mL, d = 3.1) in acetic acid (20 mL, 70%) analogously as above afforded **29** (1.75 g, 87%), mp 166-168°C (acetone), R_f 0.83 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1643 (C=O), 1628 (C=N), 850 (Br).

Mass spectrum (*m*/*z*, %): 372 (100) $[M]^+$, 318 (72), 343 (62).

1-(*p*-Nitrobenzoyl)-1,2-dihydrodeoxyvasicinone (30). A solution of **9** (1 g, 4.9 mmol) in $CHCl_3$ (50 mL) was treated with 4-nitrobenzoylchloride (1.36 g, 7.35 mmol), heated on a water bath at 50-60°C with sitrring for 2 h, and treated with aqueous NaOH (10%). The organic layer was separated, washed with water (3×), and dried over $MgSO_4$. The $CHCl_3$ was distilled off. Recrystallization afforded **30** (1.15 g, 70%), mp 158°C (hexane), R_f 0.7 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1651 (C=O), 1351-1333 (NO_2).

1-(*p*-Methylbenzoyl)-1,2-dihydrodeoxyvasicinone (31). A solution of **9** (1 g, 4.9 mmol) in $CHCl_3$ (50 mL) was treated with toluylchloride (0.2 mL, 7.35 mmol), refluxed for 3 h, and treated with aqueous NaOH (10%). The organic layer was separated, washed with water (3×), and dried over Na_2SO_4. The solvent was distilled off. Recrystallization afforded **31** (1.15 g, 70%), mp 146°C (hexane), R_f 0.6 (Silufol, benzene:acetone, 5:2), IR spectrum (ν, cm^{-1}): 1651 (C=O), 1351-1333 (NO_2).

1-(*p*-Nitrobenzoyl)-2,3-pentamethylene-1,2,3,4-tetrahydroquinazol-4-one (32). A solution of **11** (1.1 g, 5 mmol) in absolute benzene (30 mL) was treated with 4-nitrobenzoylchloride (1.36 g, 7.35 mmol), refluxed on a water bath with stirring for 4 h, and treated with aqueous NaOH (10%). The organic layer was separated, washed with water (3×), and dried over Na_2SO_4. The solvent was distilled off. Recrystallization afforded **32** (1.48 g, 80%), mp 149-151°C (hexane), R_f 0.8 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1651 (C=O), 1351-1333 (NO_2).

1-(*p*-Methylbenzoyl)-2,3-pentamethylene-1,2,3,4-tetrahydroquinazol-4-one (33). Compound **11** (1.1 g, 5 mmol) was dissolved in $CHCl_3$ (30 mL), treated with toluylchloride (0.2 mL, 7.35 mmol), heated on a water bath at 60-70°C for 2 h, and worked up analogously as above to afford **33** (1.2 g, 70%), mp 139°C (hexane), R_f 0.65 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1651 (C=O), 1351-1333 (NO_2).

1-(*o*-Chlorophenylcarbamoyl)-1,2-dihydrodeoxyvasicinone (35). A solution of **9** (0.225 g, 1.2 mmol) in benzene (25 mL) was treated with *o*-chlorophenylisocyanate (0.37 g, 2.5 mmol), refluxed on a water bath for 3 h, and left for 1 d. The resulting precipitate was filtered off to afford **35** (0.17 g, 41%), mp 210°C (alcohol), R_f 0.48 (Silufol, benzene:acetone, 5:2). IR spectrum (ν, cm^{-1}): 1644 (C=O), 739 (Cl). Table 1 and Fig. 2 list the principal crystallographic parameters and the characteristics of the x-ray diffraction analysis.

1-(*o*-Nitrophenylcarbamoyl)-1,2-dihydrodeoxyvasicinone (34) was prepared analogously from **9** (0.225 g, 1.2 mmol) and *o*-nitrophenylisocyanate (0.4 g, 2.5 mmol) to afford **34** (0.31 g, 73%), mp 205°C (benzene), R_f 0.57 (Silufol, benzene:acetone, 5:2), IR spectrum (ν, cm^{-1}): 1643 (C=O), 1362 (NO_2).

1-(*m*-Chlorophenylcarbamoyl)-1,2-dihydrodeoxyvasicinone (36) was prepared analogously as above from **9** (0.225 g, 1.2 mmol) and *m*-chlorophenylisocyanate (0.37 g, 2.5 mmol) to afford **36** (0.2 g, 48%), mp 258-259°C (alcohol), R_f 0.48 (Silufol, benzene:acetone, 5:2), IR spectrum (ν, cm^{-1}): 1697 (C=O), 777 (Cl).

1-(*p*-Methylphenylcarbamoyl)-1,2-dihydrodeoxyvasicinone (37) was prepared analogously as above from **9** (0.225 g, 1.2 mmol) and *p*-tolylisocyanate (0.34 g, 2.5 mmol) to afford **37** (0.27 g, 70%), mp 253°C (alcohol), R_f 0.61 (Silufol, benzene:acetone, 5:2), IR spectrum (ν, cm^{-1}): 1645 (C=O).

Mass spectrum (*m*/*z*, %): 321 (2.8) $[M]^+$, 187 (76), 133 (96), 132 (100), 146 (73), 160 (47), 104 (50).

1-(Ethylcarbamoyl)-1,2-dihydrodeoxyvasicinone (38) was prepared analogously as above from **9** (0.225 g, 1.2 mmol) and ethylisocyanate (0.177 g, 2.5 mmol) to afford **38** (0.186 g, 60%), mp 208°C (alcohol), R_f 0.49 (Silufol, benzene:acetone, 5:2), IR spectrum (ν, cm^{-1}): 1645 (C=O). Table 1 and Fig. 2 list the principal crystallographic parameters and characteristics of the x-ray diffraction analysis.

1-(*o*-Nitrophenylcarbamoyl)-3,4-pentamethylene-1,2,3,4-tetrahydroquinazol-4-one (39) was prepared analogously as above from **11** (0.257 g, 1.2 mmol) and *o*-nitrophenylisocyanate (0.4 g, 2.5 mmol) to afford **39** (0.31 g, 68%), mp 210-212°C (benzene), R_f 0.85 (Silufol, benzene:acetone, 5:2), IR spectrum (ν, cm^{-1}): 1626 (C=O), 1362 (NO_2).

Mass spectrum (*m*/*z*, %): 380 (2.4) $[M]^+$, 216 (56), 187 (60), 173 (100), 160 (68).

1-(*o*-Chlorophenylcarbamoyl)-3,4-pentamethylene-1,2,3,4-tetrahydroquinazol-4-one (40). A mixture of **11** (0.257 g, 1.2 mmol) and *o*-chlorophenylisocyanate (0.37 g, 2.5 mmol) in aboslute benzene (20 mL) was heated for 2 h and worked up analogously as above to afford **40** (0.21 g, 48%), mp 248°C (alcohol), R_f 0.74 (Silufol, benzene:acetone, 5:2), IR spectrum (ν, cm^{-1}): 1644 (C=O), 739 (Cl).

1-(*m*-Chlorophenylcarbamoyl)-3,4-pentamethylene-1,2,3,4-tetrahydroquinazol-4-one (41) was prepared analogously as above from **11** (0.257 g, 1.2 mmol) and *m*-chlorophenylisocyanate (0.37 g, 2.5 mmol) to afford **41** (0.215 g, 49%), mp 255°C (alcohol), R_f 0.69 (Silufol, benzene:acetone, 5:2), IR spectrum (ν, cm^{-1}): 1697 (C=O), 777 (Cl).

1-(*p*-Methylphenylcarbamoyl)-3,4-pentamethylene-1,2,3,4-tetrahydroquinazol-4-one (42) was prepared analogously as above from **11** (0.257 g, 1.2 mmol) and *p*-tolylisocyanate (0.34 g, 2.5 mmol) to afford **42** (0.25 g, 60%), mp 242°C (alcohol), R_f 0.65 (Silufol, benzene:acetone, 5:2), IR spectrum (ν, cm^{-1}): 1645 (C=O).

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