Synthesis of 4-Aminopyrimidines from 1,2,4-Oxadiazoles. Part 4.[1] A Novel Heterocyclic Rearrangement: Formation of 4-Hydroximinohexahydropyrimidines from 3-(2-Aminoethyl)-4,5-dihydro-1,2,4-oxadiazoles

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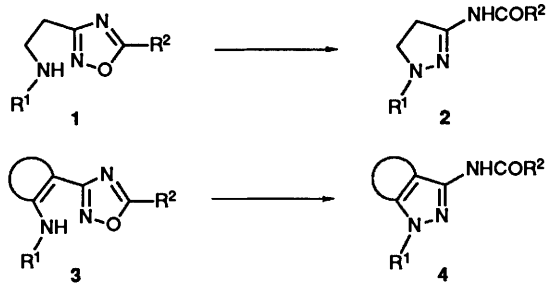
The 4,5-dihydro derivatives of 3-(2-aminoethyl)-5-substituted-1,2,4-oxadiazoles **1** have been prepared. These derivatives **8a–d** rearrange readily, but in contrast to compounds **1**, not to pyrazoles, but to 2-aryl-1-benzyl-4-hydroximinohexahydropyrimidines **9a–d**. Studies on the mechanism of the **1** ⟶ **2** azole–azole, and the novel **8** ⟶ **9** azole–azine, rearrangements revealed that the site of the side chain nitrogen attack is controlled by the presence or absence of a delocalized π-electron system in the starting azole ring. Compound **9a** and benzaldehyde gave *cis*- and *trans*-6-benzyl-3,5-diphenyl-5,6,7,8-tetrahydro-3*H*-[1,2,4]-oxadiazolo[4,3-*c*]pyrimidines **16** and **17**, respectively. The structures of **9a**, **16** and **17** were confirmed by X-ray crystallography.

We have previously reported the rearrangement of oxadiazoles of types **1** and **3**, and their congeners, to the pyrazoles **2** and **4** (Scheme 1). For compounds **1** (R^1 = alkyl or arylalkyl) this ring transformation proceeds spontaneously in solution at room temperature.[2]



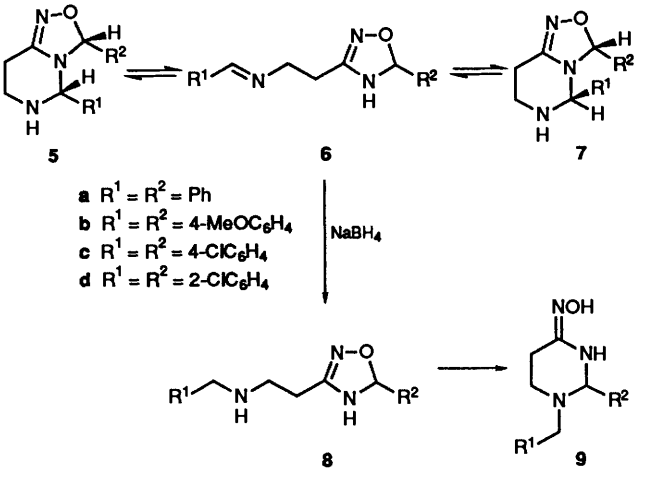
Scheme 1

While the rearrangement **3** ⟶ **4** is in accord with the second scheme suggested by Boulton and Katritzky,[3] ring transformation **1** ⟶ **2** is in conflict with this concept due to the saturation of the side chain. We found that in the latter case the length of the side chain is crucial,[4] whereas its saturation or unsaturation is not of basic importance for the success of the transformation† and we therefore proposed an extension of the scheme to azoles bearing a saturated side chain.[2b–d]

In contrast to a π-bond in the side chain, delocalization of the π-electron system of the azole ring plays an important role, as shown by kinetic and computational studies.[2a–d] In order to give more support to this proposition we set out to prepare the 4,5-dihydro-derivatives of oxadiazoles **1** with side chains containing substituents of high nucleophilicity, *e.g.* alkylamino or arylalkylamino groups, and to examine their tendency to rearrange.

In this paper we describe these studies, including a novel azole–azine rearrangement, which is basically different from the Boulton–Katritzky scheme.

For the preparation of model compounds, reductive transformation of the recently recognized[6] triple ring-chain tautomeric system (**5** ⇌ **6** ⇌ **7**) seemed to be promising (Scheme 2).



Scheme 2

The N–O bond in 1,2,4-oxadiazoles is prone to reductive cleavage,[7] but we hoped that applying the selective method used previously for the azomethine bond in iminoethyloxadiazoles[2a,b] would also enable selective saturation of the C=N bond in iminoethyloxadiazolines. Although from solutions containing the above mentioned triple equilibrium mixture the readily crystallizing *cis*-oxadiazolo[4,3-*c*]pyrimidines **5a–d**[6] could be isolated when R = phenyl derivative, it could be anticipated that on reduction the equilibrium would be shifted towards the imines **6** and thus the target aminoethyloxadiazoles **8** could be obtained. In fact on treating the oxadiazolopyrimidine **5a** in methanol at 10–15 °C with sodium borohydride and working up the reaction mixture immediately, we obtained the required oxadiazoline **8a**, formed evidently by reduction of the side chain of the open-chain tautomer **6a**.

In contrast, when the reducing agent was added at 20–25 °C and stirring was continued for an additional hour the isomeric 1-benzyl-4-hydroximino-2-phenylhexahydropyrimidine **9a** was isolated in 92% yield. There is compelling evidence that this unexpected transformation involves a ring transformation of oxadiazoline **8a**, the primary product of the reaction. For example in methanolic solution **8a** rearranges at room temperature to **9a** within one day. Although basic catalysts, *e.g.* sodium

† The role of the side chain in similar rearrangements is discussed from a different point of view by Frenna and co-workers.[5]

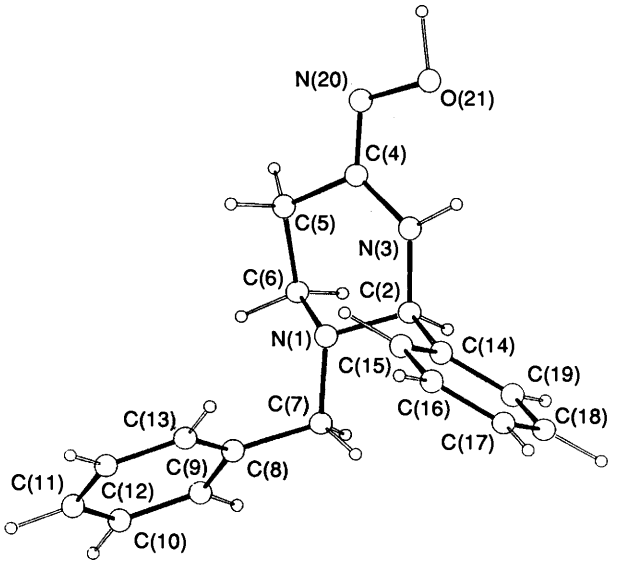


Fig. 1 PLUTO diagram of **9a**

Table 1 CNDO/2 net charges for the oxadiazole ring of 1 (R^1 = Me, R^2 = Ph) and **8** (R^1 = H, R^2 = Ph)

Ring atom labels	Charges in a.u. for 1	Charges in a.u. for **8**
O(1)	−0.173	−0.209
N(2)	−0.128	−0.114
C(3)	0.212	0.207
N(4)	−0.262	−0.191
C(5)	0.283	0.254

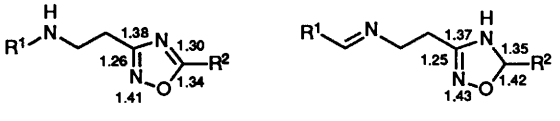


Fig. 2 Bond lengths (Å) of the 3,5-disubstituted-1,2,4-oxadiazole ring 1 (R^1 = R^2 = Ph) taken from ref. 2*d*, bond lengths of the 3,5-disubstituted-4,5-dihydro-1,2,4-oxadiazole ring **6** (R^1 = R^2 = PhCH=CH) taken from ref. 6

methoxide or the reducing agent itself highly accelerate the reaction, they are not indispensable. Isomerization also proceeds albeit at a slower rate in aprotic media, such as chloroform, or in the melt.

Structures **8a** and **9a** are fully supported by analytical data and by comparison of their spectra with those of known analogues.[8]

Apart from NH bands there are no characteristic features in the IR spectrum of **8a** (recorded in KBr), however the spectrum of **9a** exhibits a strong band at 1658 cm^{-1} characteristic for cyclic amide oximes and strong absorption at 900 cm^{-1} for the =N–O-bond.

The ^1H NMR spectrum of a freshly prepared solution of **8a** in $CDCl_3$ is in accord with the dihydro-oxadiazole structure, however after a few minutes peaks for the hydroximinopyrimidine **9a** start to emerge.

Transformation of the N–CH–O group in **8a** into N–CH–N in **9a** results in a substantial upfield shift of the corresponding proton signal (6.34 ⟶ 4.79 ppm). In addition the benzyl-CH_2 singlet in **8a** becomes an AB quartet owing to the diastereotopic nature of these protons in **9a**. After 2 h in $CDCl_3$ the **8a**:**9a** ratio was 2:1. The structure of **9a** was confirmed by X-ray diffraction (Fig. 1).

By changing the conditions, oxadiazolines **8b–d** or the hydroximinopyrimidines **9b–d** can be selectively prepared from the oxadiazolo[4,3-*c*]pyrimidines **5b–d**, but phenyl substituents greatly influence the rate of the process. The electron-releasing methoxy group accelerates the rearrangement **8** ⟶ **9**, and the electronegative chlorine atom retards it. Accordingly transformation of **5b** into **8b** required a much lower (3–5 °C) reduction temperature than did the transformation **5a** ⟶ **8a**, otherwise the main product was the pyrimidine **9b**. While the 4-chlorophenyl derivative **5c** behaved almost as the phenyl analogue, the 2-chlorophenyl compound required both higher temperature and more reducing agent for reduction to **8d**. Transformation into the pyrimidine **9d** took 24 h.

Substituent effects can be observed in the broad spread of isomerization rates in $CDCl_3$ at 20 °C. Signals of the starting materials vanished in 12 days for **8a**, in 4 days for **8b**, in 30 days for **8c**, while for **8d** the signals were only reduced to 10% after 42 days.*

As is apparent from Scheme 3, the azole–azine rearrangement **8** ⟶ **9** is basically different from the azole–azole ring transformation depicted in Scheme 1. According to our earlier findings,[2a,d] in the case of azoles **1**, due to participation of the delocalized π-electron system, the effect of the C(5) substituent is realized on the N(2) atom. Therefore, although C(5) is the most positive in the ring (Table 1), nucleophilic attack of the side chain nitrogen occurs at the N(2). However, attack against the C(5) atom and formation of the hypothetical 4-hydroximinopyridimidine **10** cannot be totally precluded.†

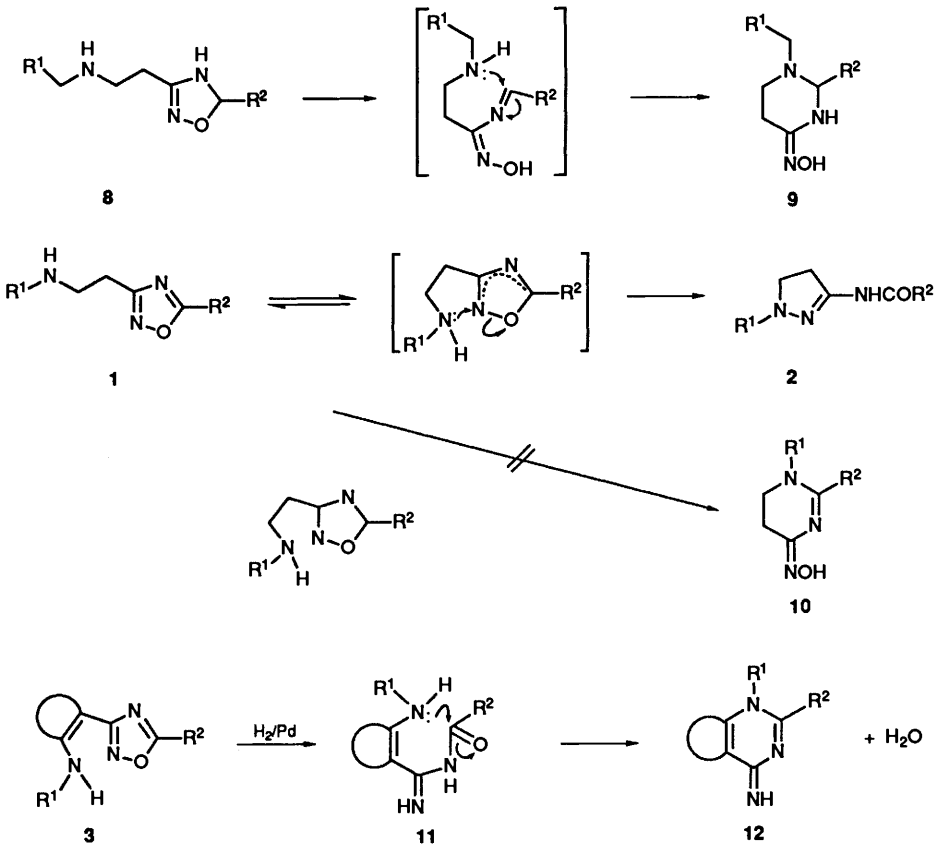
In the competition between the N(2) and C(5) atom, an important decisive factor is on one hand the fact that in the 1,2,4-oxadiazole ring the O(1)–N(2) bond is the longest (Fig. 2), so the opening of the N–O bond is understandable, and on the other hand formation of the very stable amide group favours formation of acylaminopyrazoles **2**. In the case of compounds **8** lacking the delocalized π-electron system it is indeed the most positive C(5) atom which is involved in bond formation with the amino nitrogen of the side chain giving, with concomitant cleavage of the C–O bond, a relatively stable semicyclic amide oxime **9**. Note that in the 4,5-dihydro-1,2,4-oxadiazole ring the O(1)–C(5) bond (1.42 Å) is significantly longer than that in the 1,2,4-oxadiazole ring (1.34 Å) (Fig. 2).

Formation of compounds **9** permits another interesting comparison. With iminoethyloxadiazolines **6** it is the C=N bond of the side chain which is reduced by sodium borohydride to give **8** (Scheme 2), while the oxadiazoline ring remains unchanged, whereas, as we have already reported,[7] with oxadiazoles of type **3** the N–O bond of the ring is cleaved on catalytic hydrogenolysis and acylamidines **11** are obtained which can be readily converted into pyrimidines **12** (Scheme 3). A common feature of both methods of forming a pyrimidine ring (**8** ⟶ **9** and **11** ⟶ **12**) is that the nitrogen atom of the side chain is establishing a bond with C(5) of the original oxadiazole ring in such a way that a C–O bond is cleaved.

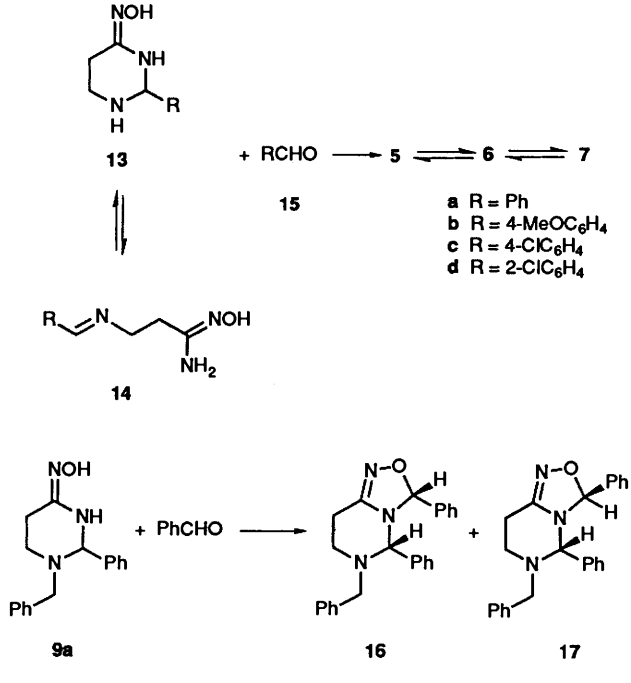
Synthesis of compounds **9** was helpful in clearing up an interesting problem concerning the direction of a reaction. The parent compounds **5a–d** of oxadiazolines **8a–d** were prepared[6] by heating **13** and the tautomers **14**, respectively, with aldehydes **15** (Scheme 4). In all four instances only *cis*-oxadiazolo[4,3-*c*]-pyrimidines **5** could be isolated from the reaction mixture but as mentioned earlier, according to NMR spectroscopy, in

* The importance of substituents is reflected by the fact that the dihydro-1,2,4-oxadiazoles with the less nucleophilic anilinoethyl side chain failed to rearrange under the conditions applied in our experiments.[8a]

† Earlier, in the case of the hydrolytic acyl migration of 3-(1-aminopropyl)-5-substituted-1,2,4-oxadiazoles, we suggested that it proceeded *via* an attack of the amino nitrogen at C(5).[10]



Scheme 3



Scheme 4

solution a triple tautomeric equilibrium (**5** ⇌ **6** ⇌ **7**) is established. Here the question arises whether, in the reaction of **15** with the tautomers **13** and **14**, formation of *cis*-**5** is a primary event or whether the other tautomers are also formed and the exclusive isolation of **5** is due to its higher thermodynamic stability in the solid state.

Since in compounds **9** no mobile hydrogen is attached to N(1) we expected that its reaction with aldehydes would give

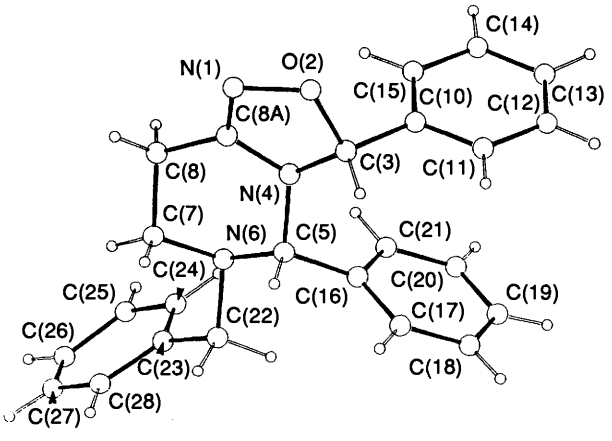


Fig. 3 PLUTO diagram of **16**

oxadiazolo[4,3-*c*]pyrimidines in which tautomerization is impossible. In fact the NMR spectrum of the reaction product of **9a** and benzaldehyde indicated the presence of the bicyclic products **16** and **17** in a 1 : 1 ratio. These were then separated by chromatography and identified by X-ray crystallography as the *cis* and *trans* stereoisomers (Figs. 3, 4). These results suggested that exclusive isolation of the *cis* compounds **5** is the result of equilibration.

Conclusions.—Our earlier[2] and present results concerning the ring transformations of amino-1,2,4-oxadiazoles indicate that with the Boulton–Katritzky second type scheme[3] it is not the saturation or unsaturation of the side chain but the delocalized π-electron system of the parent ring which is important for the success of these ring transformations. With oxadiazoles the nucleophilic attack of the side chain nitrogen is

Table 2 Analytical and spectral data for the oxadiazolines **8b–d** and for the pyrimidines **9b–d**

Compound (Formula)	Yield (%)	M.p./°C	Found (%) (Required) C	H	N	ν_{max}(KBr)/ cm^{-1}	δ_H(100 MHz; $CDCl_3$)	δ_C(25 MHz; $CDCl_3$)
8b	73	106–108	66.5	6.6	11.9	3405,	3.69 (2 H, s, benzyl)	92.59 (C-5)
($C_{19}H_{23}N_3O_3$)			(66.8)	(6.8)	(12.3)	3395	6.28 (1 H, s, 5-H)	157.17 (C-3)
8c	64	80–83	58.1	4.6	12.3	3415,	3.70 (2 H, s, benzyl)	91.94 (C-5)
($C_{17}H_{17}Cl_2N_3O$)			(58.3)	(4.9)	(12.0)	3400	6.28 (1 H, s, 5-H)	156.52 (C-3)
8d	58	95–97	57.95	4.8	12.1	3403,	3.79 (2 H, s, benzyl)	89.16 (C-5)
($C_{17}H_{17}Cl_2N_3O$)			(58.3)	(4.9)	(12.0)	3390	6.68 (1 H, s, 5-H)	156.44 (C-3)
9b	74	85–88	66.9	6.9	12.0	3395,	3.17 (1 H, d, benzyl)	74.99 (C-2)
($C_{19}H_{23}N_3O_3$)			(66.8)	(6.8)	(12.3)	1663,	3.70 (1 H, d, benzyl)	150.45 (C-4)
						910	4.69 (1 H, s, 2-H)	
9c	84	69–72	58.4	4.8	11.9	3410,	3.31 (1 H, d, benzyl)	74.56 (C-2)
($C_{17}H_{17}Cl_2N_3O$)			(58.3)	(4.9)	(12.0)	1670,	3.75 (1 H, d, benzyl)	150.21 (C-4)
						918	4.76 (1 H, s, 2-H)	
9d	80	144–146	57.8	4.7	11.9	3400,	3.76 (1 H, d, benzyl)	72.05 (C-2)
($C_{17}H_{17}Cl_2N_3O$)			(58.3)	(4.9)	(12.0)	1640,	3.85 (1 H, d, benzyl)	150.50 (C-4)
						900	5.44 (1 H, s, 2-H)	

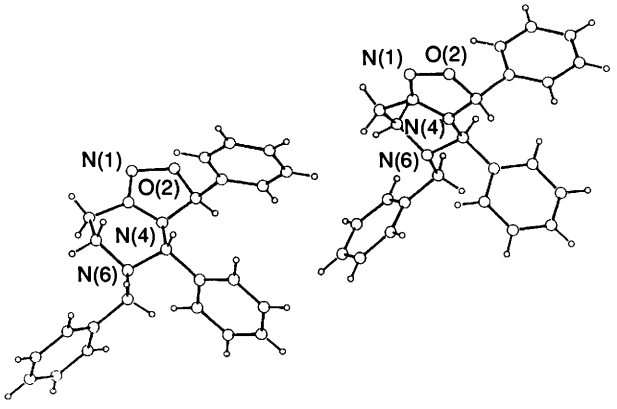


Fig. 4 PLUTO diagram of the two independent molecules A and B of **17**

directed against N(2) of the ring resulting in an azole–azole rearrangement, while with dihydro-oxadiazoles this attack is directed against the most positive atom *i.e.* C(5) and a novel azole–azine ring transformation takes place. This work is a continuation of our studies in the chemistry of amino–amide oximes.[1,2,4,6–9]

Experimental

IR Spectra were recorded on a Zeiss Specord M-80. ^1H, ^{13}C and ^{15}N NMR spectroscopy was performed using a JEOL FX-100 instrument, *J* values are given in Hz.

3-(2-*Benzylaminoethyl*)-5-*phenyl*-4,5-*dihydro*-1,2,4-*oxadiazole* **8a**.—To the solution of **5a**[6] (1.40 g, 5 mmol) in methanol (60 cm^3) was added sodium borohydride (0.19 g, 5 mmol) at 12–15 °C over 10 min. After 30 min stirring at 12–15 °C the mixture was poured into ice–water (60 cm^3) and extracted with cold chloroform (60 cm^3). The extract was dried and evaporated under reduced pressure at 20–25 °C. The residue was dissolved in ether (15 cm^3) and after refrigerating it for one day the white crystals were separated (0.72 g, 51%), m.p. 61–63 °C (Found: C, 72.85; H, 6.8; N, 15.0. $C_{17}H_{19}N_3O$ requires C, 72.6; H, 6.8; N, 14.9%); ν_{max}(KBr)/cm^{-1} 3310 and 3300 (NH); δ_H(100 MHz; $CDCl_3$) 2.50 (2 H, t, *J* 6, CH_2), 2.90 (2 H, t, *J* 6, CH_2), 3.76 (2 H, s, CH_2 benzyl), 6.34 (1 H, s, 5-H) and 7.1–7.6 (11 H, m, NH + 10 Ar); δ_C(25 MHz; $CDCl_3$) 24.54 (CH_2), 46.04 (CH_2), 53.71 (CH_2 benzyl), 92.73 (C-5), 126.45 (–C=), 127.30 (–CH=), 127.86 (–CH=), 128.18 (–CH=), 128.65 (–CH=), 129.35 (–CH=), 139.47 (C-1′, phenyl), 139.97 (C-1″, phenyl) and 156.64 (C-3).

Table 3 Crystal data

Parameter	Compound **9a**	**16**	**17**
Formulae	$C_{17}H_{19}N_3O \cdot CH_2Cl_2$	$C_{24}H_{23}N_3O$	$C_{24}H_{23}N_3O$
M_w	336.29	369.47	369.47
a/Å	32.312(4)	17.630(1)	5.947(1)
b/Å	5.757(1)	9.124(1)	10.193(1)
c/Å	18.677(2)	12.742(1)	17.533(2)
α/°			96.14(1)
β/°	90.47(2)	100.51(1)	99.77(1)
γ/°			107.00(1)
V/Å^3	3479.6	2015.2	987.8
Space group	*C*2/*c*	*Cc*	*P*1
Z	8	4	2
D_x/g cm^{-3}	1.40	1.22	1.24
N_{tot}	3778	2014	4084
N_{obs}	1739 [$I > 3\sigma(I)$]	1402 [$I > 3\sigma(I)$]	3675 [$I > 3\sigma(I)$]
R	0.064	0.069	0.050
R_w	0.072	0.060	0.046
p	0.001	0.01	0.01
$2\theta_{max}$/°	54	150	150
λ/Å	0.7107	1.5418	1.5418
μ/cm^{-1}	0.54	5.4	5.6

3,5-*Disubstituted*-4,5-*dihydro*-1,2,4-*oxadiazoles* **8b–d**.—Reduction of oxadiazolo[4,3-*c*]pyrimidines **5b–d**[6] was carried out as described for **5a**, however, at 3–8 °C in the case of **5b**, and with twice the amount of sodium borohydride at 20–22 °C for **5d**. Yields, melting points, analytical and spectral data for **8b–d** are given in Table 2.

1-*Benzyl*-4-*hydroxyimino*-2-*phenylhexahydropyrimidine* **9a**.—(*a*) To a solution of **5a**[6] (2.79 g, 10 mmol) in methanol (80 cm^3) was added sodium borohydride (0.38 g, 10 mmol) at 20–25 °C over 30 min. After stirring for 1 h, ice–water (80 cm^3) was added and the crystals were separated (2.6 g, 92%), m.p. 140–142 °C (from EtOH).

(*b*) Compound **8a** (280 mg, 1 mmol) was heated in a glass tube at 80 °C for 2 h. The product was crystallized from ethanol (250 mg, 89%), m.p. 140–142 °C (Found: C, 72.6; H, 6.7; N, 14.85. $C_{17}H_{19}N_3O$ requires C, 72.6; H, 6.8; N, 14.9%); ν_{max}(KBr)/cm^{-1} 3380 (NH), 1658 (amide) and 900 (=N–O); δ_H(100 MHz; $CDCl_3$) 2.44 (3 H, m, 5-, 6-, 6-H), 3.0 (1 H, m, 5-H), 3.30 (1 H, d, *J* 13, CH_2 benzyl), 3.81 (1 H, d, *J* 13, CH_2 benzyl), 4.79 (1 H, s, 2-H), 5.67 (1 H, br s, NH), 7.1–7.6 (10 H, m, Ar) and 7.5 (1 H, v br, =N–OH); δ_C(25 MHz; $CDCl_3$) 23.46 (C-5), 45.49 (C-6), 55.84 (CH_2 benzyl), 127.16 (–CH=), 127.80 (–CH=), 128.30

Table 4 Positional parameters and their esds (in parentheses) for compound **9a**. Atoms with asterisks have a multiplicity of 0.5

Atom	*x*	*y*	*z*
N(1)	0.8753(1)	0.3622(6)	0.0003(2)
C(2)	0.9030(1)	0.3456(9)	0.0619(2)
N(3)	0.9325(1)	0.5364(8)	0.0578(2)
C(4)	0.9442(1)	0.6407(9)	−0.0024(2)
C(5)	0.9227(2)	0.583(1)	−0.0714(3)
C(6)	0.8996(1)	0.3530(9)	−0.0656(2)
C(7)	0.8445(1)	0.1750(8)	0.0003(2)
C(8)	0.8092(1)	0.2291(8)	−0.0514(2)
C(9)	0.7978(2)	0.067(1)	−0.1034(3)
C(10)	0.7646(2)	0.118(1)	−0.1492(3)
C(11)	0.7429(2)	0.323(1)	−0.1434(3)
C(12)	0.7541(2)	0.477(1)	−0.0916(3)
C(13)	0.7869(1)	0.4323(9)	−0.0459(3)
C(14)	0.8804(1)	0.3697(8)	0.1320(2)
C(15)	0.8565(1)	0.5633(9)	0.1467(3)
C(16)	0.8370(2)	0.589(1)	0.2121(3)
C(17)	0.8417(2)	0.419(1)	0.2637(3)
C(18)	0.8651(2)	0.229(1)	0.2502(3)
C(19)	0.8848(1)	0.2027(9)	0.1842(3)
N(20)	0.9716(1)	0.7984(8)	−0.0041(2)
O(21)	0.9871(1)	0.8467(8)	0.0665(2)
Cl(1)	−0.0445(1)	−0.3093(3)	0.2499(1)
Cl(2)*	−0.0049(2)	0.1180(9)	0.2692(3)
C(25)*	−0.0002(6)	−0.162(2)	0.2741(6)
C(26)*	0.014(1)	0.101(4)	0.195(1)

Table 5 Positional parameters and their esds (in parentheses) for compound **16**

Atom	*x*	*y*	*z*
N(1)	−0.0819(3)	−0.5962(7)	−0.0830(5)
O(2)	−0.1560	−0.6108(5)	−0.1536
C(3)	−0.2050(4)	−0.4866(8)	−0.1351(5)
N(4)	−0.1513(3)	−0.3923(6)	−0.0653(4)
C(5)	−0.1803(3)	−0.3067(7)	0.0170(5)
N(6)	−0.1153(3)	−0.2225(6)	0.0746(4)
C(7)	−0.0549(4)	−0.3242(8)	0.1268(5)
C(8)	−0.0206(4)	−0.4060(9)	0.0417(5)
C(8A)	−0.0847(4)	−0.4721(8)	−0.0373(5)
C(10)	−0.2384(4)	−0.4186(7)	−0.2406(5)
C(11)	−0.3175(4)	−0.4265(9)	−0.2774(6)
C(12)	−0.3492(4)	−0.362(1)	−0.3735(7)
C(13)	−0.3041(5)	−0.289(1)	−0.4327(6)
C(14)	−0.2248(5)	−0.281(1)	−0.3977(6)
C(15)	−0.1926(4)	−0.3468(8)	−0.3015(6)
C(16)	−0.2466(3)	−0.2118(7)	−0.0375(5)
C(17)	−0.3210(4)	−0.2428(8)	−0.0220(6)
C(18)	−0.3824(4)	−0.165(1)	−0.0764(7)
C(19)	−0.3709(4)	−0.061(1)	−0.1487(7)
C(20)	−0.2978(5)	−0.026(1)	−0.1635(7)
C(21)	−0.2355(4)	−0.1037(8)	−0.1089(6)
C(22)	−0.1420(4)	−0.1272(8)	0.1561(5)
C(23)	−0.0773(4)	−0.0232(7)	0.2015(5)
C(24)	−0.0485(4)	0.0784(8(	0.1382(6)
C(25)	0.0086(5)	0.176(1)	0.1846(8)
C(26)	0.0357(5)	0.1705(9)	0.2938(8)
C(27)	0.0088(5)	0.071(1)	0.3520(7)
C(28)	−0.0479(5)	−0.0265(9)	0.3109(6)

(–CH=), 128.56 (–CH=), 128.68 (–CH=), 138.39 (C-1′, phenyl), 141.11 (C-1″, phenyl) and 150.32 (C-4); δ_N(10 MHz; [$^2H_6$]-DMSO) 52.1 (s, N-1), 79.4 (d, N-2) and 280.3 (s, =N–OH).

1,2-Disubstituted-4-hydroximinohexahydropyrimidines **9b–d**.—Compounds **5b–d** [6] were reduced, as described for **9a** [method (*a*)], however, with twice the amount of sodium borohydride for **9d** and the solution was left standing for one day at 20–25 °C before work-up. Yields, melting points, analytical and spectral data for **9b–d** are compiled in Table 2.

Table 6 Positional parameters and their esds (in parentheses) for compound **17**

Atom	*x*	*y*	*z*
N(1)	−0.1735(5)	0.6528(3)	0.0763(2)
O(2)	−0.2219(0)	0.7542(0)	0.0293(0)
C(3)	−0.0185(6)	0.8805(4)	0.0493(2)
N(4)	0.1251(5)	0.8542(3)	0.1189(1)
C(5)	0.3823(5)	0.9313(3)	0.1472(2)
N(6)	0.4611(5)	0.8794(3)	0.2197(1)
C(7)	0.4152(6)	0.7281(3)	0.2018(2)
C(8)	0.1468(7)	0.6548(3)	0.1843(2)
C(8a)	0.0267(6)	0.7171(3)	0.1239(2)
C(10)	0.1080(6)	0.9062(3)	−0.0187(2)
C(11)	0.2183(8)	0.8145(4)	−0.0469(2)
C(12)	0.3463(9)	0.8463(5)	−0.1054(3)
C(13)	0.3634(9)	0.9681(5)	−0.1352(2)
C(14)	0.2518(9)	1.0575(5)	−0.1087(2)
C(15)	0.1232(8)	1.0262(4)	−0.0497(2)
C(16)	0.4199(6)	1.0853(3)	0.1632(2)
C(17)	0.3233(7)	1.1394(4)	0.2203(3)
C(18)	0.3635(8)	1.2823(4)	0.2352(3)
C(19)	0.4968(9)	1.3675(4)	0.1912(3)
C(20)	0.5909(9)	1.3130(4)	0.1353(3)
C(21)	0.5528(7)	1.1728(4)	0.1201(2)
C(22)	0.7179(6)	0.9511(4)	0.2538(2)
C(23)	0.7798(6)	0.9275(3)	0.3369(2)
C(24)	0.6576(6)	0.9643(4)	0.3921(2)
C(25)	0.7145(7)	0.9445(4)	0.4686(2)
C(26)	0.8918(8)	0.8863(5)	0.4921(2)
C(27)	1.0165(8)	0.8516(5)	0.4373(3)
C(28)	0.9611(7)	0.8730(4)	0.3611(2)
N(1′)	0.4793(5)	0.1526(3)	0.5763(2)
O(2′)	0.5842(5)	0.2553(3)	0.5304(1)
C(3′)	0.5233(6)	0.3802(4)	0.5491(2)
N(4′)	0.4255(5)	0.3545(3)	0.6192(1)
C(5′)	0.2709(6)	0.4302(3)	0.6475(2)
N(6′)	0.2148(5)	0.3795(2)	0.7194(1)
C(7′)	0.0915(6)	0.2288(3)	0.7023(2)
C(8′)	0.2681(7)	0.1547(3)	0.6847(2)
C(8a′)	0.3897(6)	0.2175(3)	0.6234(2)
C(10′)	0.3557(6)	0.4059(3)	0.4817(2)
C(11′)	0.4303(7)	0.5264(4)	0.4501(2)
C(12′)	0.2737(9)	0.5577(4)	0.3925(2)
C(13′)	0.0451(9)	0.4666(5)	0.3655(3)
C(14′)	−0.0306(9)	0.3464(5)	0.3938(3)
C(15′)	0.1261(8)	0.3150(4)	0.4532(2)
C(16′)	0.4045(6)	0.5848(3)	0.6635(2)
C(17′)	0.6127(7)	0.6398(4)	0.7206(3)
C(18′)	0.7303(8)	0.7819(5)	0.7354(3)
C(19′)	0.6389(9)	0.8673(4)	0.6918(3)
C(20′)	0.4364(9)	0.8142(4)	0.6354(3)
C(21′)	0.3156(7)	0.6733(4)	0.6201(2)
C(22′)	0.0619(6)	0.4497(3)	0.7541(2)
C(23′)	0.0594(6)	0.4267(3)	0.8364(2)
C(24′)	−0.1517(7)	0.3714(5)	0.8602(2)
C(25′)	−0.1525(8)	0.3501(5)	0.9373(2)
C(26′)	0.0613(8)	0.3855(5)	0.9915(2)
C(27′)	0.2754(7)	0.4436(4)	0.9691(2)
C(28′)	0.2744(6)	0.4638(4)	0.8919(2)

cis- and trans-6-Benzyl-3,5-diphenyl-5,6,7,8-tetrahydro-3H-[1,2,4]oxadiazolo[4,3-c]pyrimidines **16** *and* **17**.—Compound **9a** (2.8 g, 10 mmol), benzaldehyde (1.28 g, 12 mmol) and toluene (40 cm^3) were heated with stirring in a sealed vessel at 98 °C for 4 h. The toluene was evaporated under reduced pressure to give a 1:1 mixture of **16** and **17** in nearly quantitative yield. Chromatography on silica gel with diethyl ether as eluent yielded **16** (1.03 g, 28%) and **17** (0.81 g, 22%).

16: m.p. 126–129 °C (diethyl ether) (Found: C, 78.1; H, 6.3; N, 11.5. $C_{24}H_{23}N_3O$ requires C, 78.0; H, 6.3; N, 11.4%); ν_{max}(KBr)/cm^{-1} 1638 (C=N); δ_H(100 MHz; $CDCl_3$) 2.2–2.8 (3 H, m, 7-, 7-, 8-H), 3.01 (1 H, d, *J* 13.5, CH_2 benzyl), 3.0–3.2 (1 H, m, 8-H), 3.61 (1 H, d, *J* 13.5, CH_2 benzyl), 4.31 (1 H, s, 5-H),

5.78 (1 H, s, 3-H) and 6.9–7.2 (15 H, m, Ar); δ_C(25 MHz; $CDCl_3$) 21.41 (C-8), 47.53 (C-7), 55.37 (CH_2 benzyl), 84.16 (C-5), 98.02 (C-3), 127.10 (–CH=), 127.51 (–CH=), 127.65 (–CH=), 127.92 (–CH=), 128.24 (–CH=), 128.35 (–CH=), 128.47 (–CH=), 128.76 (–CH=), 128.97 (–CH=), 136.60 (C-1′, phenyl), 137.66 (C-1″, phenyl), 138.04 (C-1‴, phenyl) and 154.07 (C-8a).

17: m.p. 107–109 °C (EtOH) (Found: C, 77.9; H, 6.2; N, 11.5. $C_{24}H_{23}N_3O$ requires C, 78.0; H, 6.3; N, 11.4%); ν_{max}(KBr)/cm^{-1} 1638 (C=N); δ_H(100 MHz; $CDCl_3$) 2.4–3.2 (4 H, m, 7-, 8-CH_2), 3.49 (1 H, d, *J* 13.5, CH_2 benzyl), 3.68 (1 H, d, *J* 13.5, CH_2 benzyl), 4.51 (1 H, s, 5-H), 5.93 (1 H, s, 3-H) and 7.0–7.5 (15 H, m, Ar); δ_C(25 MHz; $CDCl_3$) 18.22 (C-8), 42.09 (C-7), 55.81 (CH_2 benzyl), 93.40 (C-3), 127.16 (–CH=), 127.36 (–CH=), 128.21 (–CH=), 128.33 (–CH=), 128.56 (–CH=), 128.71 (–CH=), 129.61 (–CH=), 136.78 (C-1′, phenyl), 137.54 (C-1″, phenyl), 137.77 (C-1‴, phenyl) and 151.05 (C-8a).

X-Ray Crystal Structure Analyses.—Crystals of **9a**, **16** and **17** were grown from dichloromethane, diethyl ether, and ethanol respectively. Crystal data are listed in Table 3. Data were collected on an Enraf–Nonius CAD-4 diffractometer at the Central Research Institute for Chemistry of the Hungarian Academy of Sciences, Budapest.

The structures were solved through the application of the MULTAN 84 program. An empirical absorption correction was applied to all reflections, using the DIFABS[11] program. Hydrogen atoms with known positions were generated except for N–H and O–H atoms which were taken from difference Fourier calculations. The fractional coordinates with their esd values are given in Tables 4, 5 and 6, respectively. A partially disordered dichloromethane group was found in structure **9a**. Full lists of bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.*

Structure determinations were carried out on a PDP 11/34 minicomputer by means of the Enraf–Nonius SDP program package with local modifications. The weighting scheme was $w = 1/[\sigma^2(F_o) + pF^2{}_o]$.

Calculations of electronic charges for oxadiazole **1** *and dihydro-oxadiazole* **6**. All calculations have been made by the CNDO[9] program, QCPE No. 240 for IBM-PC (Modified by J. D. Bowden and G. S. Owen, Atlanta, Georgia). The geometries used for the calculations are based on the X-ray measurements of molecule **1** ($R^1 = R^2 = Ph$),[2d] and **6** ($R^1 = R^2 = PhCH{=}CH$).[6] Hydrogen atoms were generated with standard bond distances and angles.

* For details of the Cambridge Crystallographic Data Centre deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

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