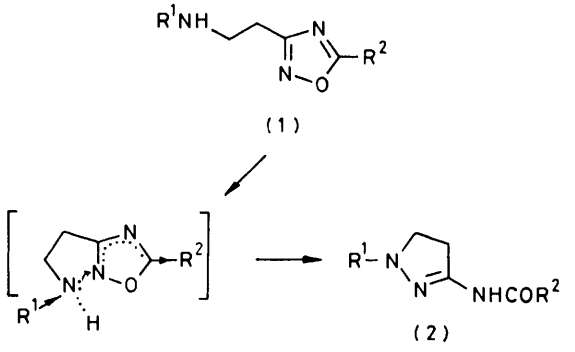
Ring Transformation of 3-(2-Aminoaryl)-1,2,4-oxadiazoles into 3-Acylaminoindazoles; [1] Extension of the Boulton–Katritzky Scheme

By **Dezsö Korbonits,* Ida Kanzel-Szvoboda,** and **Károly Horváth,** Chinoin Pharmaceutical and Chemical Works, P.O.B. 110, H-1325 Budapest, Hungary

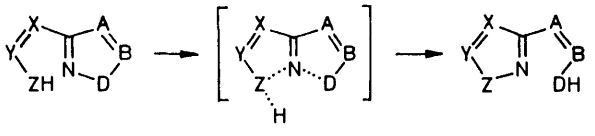
The ring transformation of 3-(2-aminoethyl)-1,2,4-oxadiazoles (1) into acylaminopyrazolines (2) reported earlier has been extended to 5-substituted 3-(2-aminoaryl)-1,2,4-oxadiazoles (3), (5), (7), and (9). Depending on the reaction conditions and the substitution at the amino-group, the isomerization of 3-(2-aminophenyl)oxadiazoles (3) to 3-acylaminoindazoles (4) follows two different mechanisms (A and B), but is invariably promoted by electron-attracting substituents at C-5. Mechanism A differs from those proposed earlier for azole–azole rearrangements, and resembles the transformation (1) ⟶ (2). An extended general scheme is suggested.

EARLIER we reported that 3-(2-aminoethyl)-1,2,4-oxadiazoles (1), readily accessible from primary amines, isomerize spontaneously or on heating in excellent yield to pyrazolines (2).[2]



SCHEME 1

This ring transformation is general and provides an easy access to 3-amino-Δ^2-pyrazolines. Kinetic and thermodynamic studies permitted the conclusion that this azole–azoline-type ring transformation involved a special bicyclic transition state (Scheme 1) which was different from those proposed earlier for related azole–azole-type transformations.[3] It was previously [3] assumed that in the absence of external base, ABD–XYZ †-type transformations are concerted and involve a bicyclic transition state in which a continuous π-electron system surrounding the reaction centre plays a decisive role (Scheme 2). With transformations (1) ⟶ (2) such a delocalization is excluded by the saturation of the side chain.



SCHEME 2

We now report the extension of this isomerization to oxadiazoles in which the saturated 2-aminoethyl side chain is replaced by 2-aminophenyl [(3.1)—(3.34)] ‡ and 2-aminoheteroaryl groups [(5.1)—(5.4), (7.1), (7.2), and (9)] (see Scheme 3). Since the starting materials (3) can be conveniently prepared, this rearrangement provides a practical and general method for the synthesis of 3-acylaminoindazoles and hetero-analogues.

2-Aminophenyl- or 2-benzylaminophenyl-oxadiazoles [(3.2—3.5), (3.7—3.18)] were prepared in one step, as were compounds (1),[2] from 2-amino- and 2-benzylaminobenzamide oxime and the corresponding carboxylic esters. This method is more convenient than that reported earlier.[6,7]

Compounds (3.1) and (3.6) were obtained by ethylation, (3.19)—(3.31) by acylation, and (3.32)—(3.34) from the corresponding (primary amino)phenyl oxadiazoles using 1-fluoro-2,4-dinitrobenzene. The heteroaryl derivatives (5), (7), and (9) were prepared by similar methods.

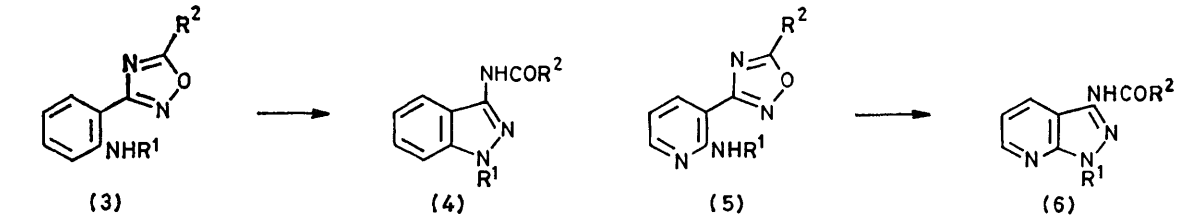
Depending on the substitution, our oxadiazoles exhibited a wide range of reactivity, and their behaviour was rather similar to that of the aminoethyl compounds (1). Thus the *N*-alkyl derivatives (3.1)—(3.10), when heated in various solvents or kept neat at 150 °C, rearrange in excellent yield to the 3-acylaminoindazoles (4.1)—(4.10). The rate of ring transformation increases with the polarity of the solvent (DMF > cyclohexanol > tetralin). The use of solvents is however not essential: *e.g.* (3.2) is transformed at nearly the same rate to (4.2) at 150 °C in dimethylformamide (DMF) or when melted. As with the isomerizations (1) ⟶ (2), base catalysis was not observed. In order to determine the effect of substituents R^1 and R^2, rate constants for 24 substrates were measured at 150 °C for reactions in DMF (Table 1).

The most important conclusion was that, as with the transformations (1) ⟶ (2), replacement of a 5-alkyl group with phenyl invariably increased the rate of rearrangement.§ The electronic nature of this effect is

† Rearrangements corresponding to the scheme ABD–XYZ, as proposed originally by Boulton and Katritzky,[4] have been termed in the recent literature 'mononuclear heterocyclic rearrangements '(m.h.r.s).[5]

‡ Shortly after our paper had been submitted [1] a publication appeared in which three examples of a similar transformation were reported.[7]

§ Vivona *et al.* have found that in equilibrium ring transformations of acylamino-oxadiazoles the 4-aryl substituent produces a greater stability enhancement than a methyl group, and this finding has been attributed to a biaryl-type resonance stabilisation.[8] This factor seems in our case to play no decisive role.



R¹		R²	
(3.1)	Et	Ph	(4.1)
(3.2)	$PhCH_2$	Ph	(4.2)
(3.3)	$PhCH_2$	p-MeC_6H_4	(4.3)
(3.4)	$PhCH_2$	p-ClC_6H_4	(4.4)
(3.5)	$PhCH_2$	p-$O_2N{\cdot}C_6H_4$	(4.5)
(3.6)	Et	Me	(4.6)
(3.7)	$PhCH_2$	Me	(4.7)
(3.8)	$PhCH_2$	Pr^n	(4.8)
(3.9)	$PhCH_2$	$PhCH_2$	(4.9)
(3.10)	$PhCH_2$	Ph_2CHCH_2	(4.10)
(3.11)	H	Ph	(4.11)
(3.12)	H	p-MeC_6H_4	(4.12)
(3.13)	H	p-ClC_6H_4	(4.13)
(3.14)	H	p-$O_2N{\cdot}C_6H_4$	(4.14)
(3.15)	H	Me	(4.15)
(3.16)	H	Pr^n	(4.16)
(3.17)	H	$PhCH_2$	(4.17)
(3.18)	H	Ph_2CHCH_2	(4.18)
(3.19)	MeCO	Ph	(4.19)
(3.20)	PhCO	Ph	(4.20)
(3.21)	p-$O_2N{\cdot}C_6H_4CO$	Ph	(4.21)
(3.22)	MeCO	p-MeC_6H_4	(4.22)

R¹		R²	
(3.23)	PhCO	p-MeC_6H_4	(4.23)
(3.24)	MeCO	p-ClC_6H_4	(4.24)
(3.25)	PhCO	p-ClC_6H_4	(4.25)
(3.26)	MeCO	Me	(4.26)
(3.27)	PhCO	Me	(4.27)
(3.28)	p-$O_2N{\cdot}C_6H_4CO$	Me	(4.28)
(3.29)	MeCO	Pr^n	(4.29)
(3.30)	PhCO	Pr^n	(4.30)
(3.31)	MeCO	Ph_2CHCH_2	(4.31)
(3.32)	2,4-$(O_2N)_2C_6H_3$	Ph	(4.32)
(3.33)	2,4-$(O_2N)_2C_6H_3$	Me	(4.33)
(3.34)	2,4-$(O_2N)_2C_6H_3$	$PhCH_2$	(4.34)
(5.1)	H	Ph	(6.1)
(5.2)	H	Me	(6.2)
(5.3)	MeCO	Ph	(6.3)
(5.4)	MeCO	Me	(6.4)
(7.1)		Ph	(8.1)
(7.2)		4-pyridyl	(8.2)
(7.3)		Me	

SCHEME 3

TABLE 1

Rate constants for rearrangements of 3-(2-aminoaryl)-1,2,4-oxadiazoles at 150 °C in DMF

Compound no.	k/s^{-1}	R¹	R²
(3.1)	8.08×10^{-4}	Et	Ph
(3.6)	2.56×10^{-4}	Et	Me
(3.2)	6.42×10^{-4}	$PhCH_2$	Ph
(3.3)	4.47×10^{-4}	$PhCH_2$	p-MeC_6H_4
(3.4)	1.44×10^{-3}	$PhCH_2$	p-ClC_6H_4
(3.5)	3.25×10^{-3}	$PhCH_2$	p-$O_2N{\cdot}C_6H_4$
(3.7)	1.40×10^{-4}	$PhCH_2$	Me
(3.9)	3.85×10^{-4}	$PhCH_2$	$PhCH_2$
(3.11)	2.44×10^{-5}	H	Ph
(3.12)	1.73×10^{-5}	H	p-MeC_6H_4
(3.13)	3.13×10^{-5}	H	p-ClC_6H_4
(3.14)	9.71×10^{-5}	H	p-$O_2N{\cdot}C_6H$
(3.20)	2.93×10^{-3}	PhCO	Ph
(3.27)	1.95×10^{-3}	PhCO	Me
(3.19)	3.85×10^{-4}	MeCO	Ph
(3.26)	1.92×10^{-4}	MeCO	Me
(3.32)	3.52×10^{-2}	2,4-$(O_2N)_2C_6H_3$	Ph
(3.34)	2.12×10^{-2}	2,4-$(O_2N)_2C_6H_3$	$PhCH_2$
(3.33)	1.00×10^{-2}	2,4-$(O_2N)_2C_6H_3$	Me
(3.32) [a]	4.62×10^{-3}	2,4-$(O_2N)_2C_6H_3$	Ph
(3.34) [a]	8.45×10^{-4}	2,4-$(O_2N)_2C_6H_3$	$PhCH_2$
(3.33) [a]	3.85×10^{-4}	2,4-$(O_2N)_2C_6H_3$	Me
(5.3)	1.15×10^{-3}	MeCO	Ph
(5.4)	6.45×10^{-4}	MeCO	Me

[a] Neat at 240 °C.

indicated by the nearly linear Hammett correlation of the rate with the σ values of the *para*-substituents on the 5-phenyl group of the benzylamino-derivatives (3.2)—(3.5). The ρ value was 0.89 in this case, whereas with compound (1; R^1 = Ph, R^2 = p-XC_6H_4) it was 0.78. In view of this small difference and our earlier results,[2] it can be concluded that transmission of the effect of the 5-substituent by the π-electron system of the oxadiazole ring is both important and of nearly the same effectiveness in the two series. Decreasing basicity of the amino-group retards the rearrangement, as with the transformation (1) ⟶ (2). Thus with 5-phenyl derivatives containing a primary amino-group (3.11)—(3.14), the transformation is slower by a factor of 10 than with the alkylamino-derivatives (3.1)—(3.5). The corresponding 5-alkyl compounds (3.15)—(3.18) do not rearrange under standard conditions (150 °C in DMF), and isomerization requires melting at much higher temperature.* No base catalysis was observed in the latter case either.

The ring transformation is exothermic: the differential

* We disagree with the interpretation of Vivona *et al.*,[7] who ascribed also to steric effects the difference in rates of transformation in the case of (3.15) and its methylated derivative.

scanning calorimetry (d.s.c.) curve of (3.1) is similar to that of its analogue having a saturated side-chain (1; $R^1 = R^2 = Ph$) (see Figure). The driving force of the

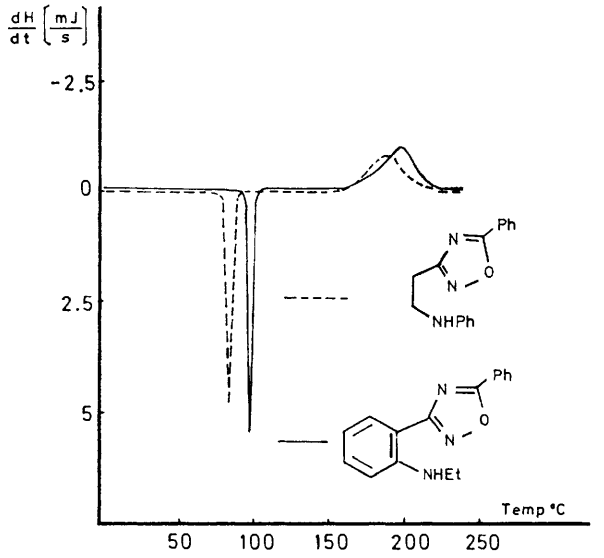
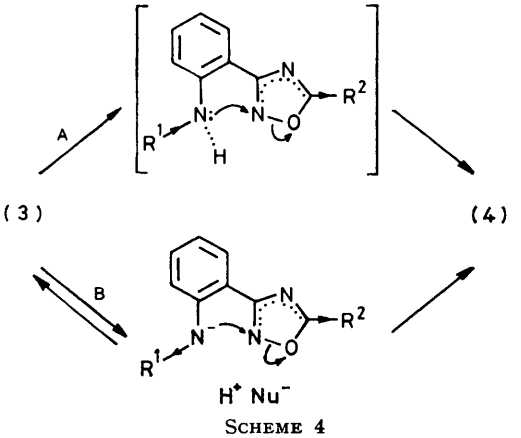


FIGURE Differential scanning calorimetry diagram of compounds (1; $R^1 = R^2 = Ph$) and (3.1); program 5 °C min^{-1}; $\Delta H_{93\,°C}$ 32.75 kJ mol^{-1} [melting (1)]; $\Delta H_{190\,°C}$ −56.61 kJ mol^{-1} [isomerization (1)]; $\Delta H_{98\,°C}$ 27.32 kJ mol^{-1} [melting (3.1)]; $\Delta H_{200\,°C}$ −82.77 kJ mol^{-1} [isomerization (3.1)]

reaction may in both cases be the higher thermodynamic stability of the amide group appearing in the product.

The present ring isomerizations are clearly of the azole–azole type and satisfy the condition that the reacting centres should be joined by a continuous π-electron system.[3b,5,7] Nevertheless the similarity of substituent effects of the transformations (1) ⟶ (2) and (3) ⟶ (4) suggests that both involve the same special S_Ni mechanism, namely pathway A in Scheme 4. In this the essential step is an attack of the non-bonding amino-nitrogen pair of electrons on the delocalized π-electron system of the oxadiazole ring. There was no indication of participation of the π-system of the aniline phenyl ring.

Mechanism A bears a resemblance to one of the three



SCHEME 4

pathways proposed originally[3a] for azole rearrangements. However it is wider in scope in that the side-chain need not be unsaturated.

A significant reduction in the basicity of the amino-group, as compared with the primary amino-group in compounds (3.11)—(3.18), again promotes isomerization, but in this case route A is not followed. Thus, when strongly electron-attracting substituents such as acyl or 2,4-dinitrophenyl were attached to the nitrogen [(3.19)—(3.31) and (3.32)—(3.34) respectively], the corresponding N^1-acyl- (4.19)—(4.31) and N^1-(2,4-dinitrophenyl)-3-acylaminoindazoles (4.32)—(4.34) were obtained in excellent yield.

Owing to the acidic character of the NH function, solvent effects become prominent in this group and base catalysis can be observed. In non-polar solvents (tetralin, xylene) isomerization is insignificant at 150 °C; reaction is still slow in boiling cyclohexanol, but it proceeds readily in boiling DMF.* For example, the dinitrophenylamino-derivative (3.32), which remained unchanged in refluxing xylene or in tetralin at 150 °C, was completely transformed within a few hours after addition of piperidine or triethylamine. The reaction was over in a few minutes in hot DMF and proceeded at room temperature in dimethyl sulphoxide. Note that substitution at C-5 with an electron-attracting group again promotes ring transformation. These facts suggested an ionic mechanism, as has often been suggested for models with an unsaturated side-chain (Scheme 4; route B).[3,5,9]

Finally, the transformations of the *N*-dinitrophenyl derivatives (3.32)—(3.34) ⟶ (4.32)—(4.34) can also be accomplished without catalyst by melting at 240 °C. This indicates an electrocyclic concerted transition state mechanism,[3,4] but the significant influence of the C-5 substituent on the rate of isomerization (*cf.* Table 1) supports the highly polar character of the transition state.

The switch between mechanism A and B as a consequence of the character of the amino-group can best be observed with the rather unreactive 5-alkyl derivatives. Accordingly if R^1 was H (3.15)—(3.18) no reaction took place in DMF at 150 °C, but both with electron-donating (3.6)—(3.10) and electron-attracting *N*-substituents [(3.26)—(3.31), (3.33), and (3.34)] ring isomerization was successful under the same conditions. The relative stability of compounds (3.15)—(3.18) is further evidence for the relative unimportance of the electronic structure of the aminophenyl group.

The experience that electron-attracting groups R^2 accelerate the isomerization of compounds (3) was exploited with the heteroaryl-oxadiazoles of types (5), (7), and (9). Except for (7.3), these could be isomerized in excellent yield to compounds (6), (8), and (10), respectively. It was remarkable that in these cases, owing to the enhanced mobility of the hydrogen atoms in

* As reported,[7] compound (3.26) isomerized with partial hydrolysis in the presence of KOH.

comparison with the aminophenyl derivatives, significant base catalysis could be observed even with the primary amines. Thus the 5-methyloxadiazole derivative (5.2) remained unchanged in DMF at 150 °C,[10] but was transformed into (6.2) in the presence of added NaOH within a few hours. Isomerization took place also on heating to 200 °C, but extremely slowly (40—50 h). The 5-phenyl analogue (5.1) isomerized to (6.1) on prolonged heating in DMF, while in the presence of NaOH reaction was complete within about 21 min. *N*-Acylation [(5.3), 5.4)] substantially accelerated isomerization in DMF. The 5-methyl derivative (7.3) could not be isomerized at all, while the 5-phenyl (7.1) and 4-pyridyl analogues (7.2), as well as the aminopyrazole (9) gave in DMF with NaOH catalysis within a few minutes nearly quantitative yields of the isomerized products (8.1), (8.2), and (10).

Conclusions.—Depending on substitution, the 3-(2-aminoaryl)-1,2,4-oxadiazoles (3), (5), (7), and (9) are transformed into the isomeric condensed acylaminopyrazoles (4), (6), (8), and (10) by mechanisms A and B. Mechanism A is similar to that suggested in the case of 3-(aminoethyl)-1,2,4-oxadiazoles (1). With both these mechanisms ring transformation is promoted by electron-attracting substituents at C-5 (R^2). It is probable that the π-electron system of the oxadiazole ring is of primary importance for the success of isomerization, while the character of the side-chain (saturated or unsaturated) is only one of several contributing factors determining the mechanism of ring isomerization.

Therefore it seems to be reasonable to suggest the extension of the m.h.r. scheme [4] to that outlined below (Scheme 5) in which the A–B link may symbolize a single *or* a double bond.

R = H, or RR = a single bond

SCHEME 5

EXPERIMENTAL

Instruments used were: u.v. (EtOH) Unicam SP 8-100; i.r. (KBr) Nicolet 7199 Fourier transform mass spectrometry A.E.I. MS 902; ^{1}H n.m.r. ($CDCl_3$) Bruker WP 80; d.s.c. 990 DuPont; t.l.c. Macherey–Nagel Polygram Sil G/UV 254. Evaporations were carried out *in vacuo*. 2-Aminobenzamide oxime,[6] 2-aminopyridine-3-carboxamide oxime,[10] and 3-amino-2-phenylpyrazole-4-carboxamide oxime [11] are known compounds. M.p.s, solvents of crystallization, yields, and analytical and spectral data for the oxadiazole derivatives are shown in Table 2; m.p.s, solvents of crystallization, reaction times, and analytical and spectral data for the isomerization products are shown in Table 3.

2-Benzylaminobenzamide Oxime.—A hot solution of 2-benzylaminobenzonitrile [12] (20.8 g, 0.10 mol) in 96% ethanol (250 ml) was added to a solution of hydroxylamine hydrochloride (13.9 g, 0.20 mol) and sodium hydrogen carbonate (16.8 g, 0.20 mol) in water (65 ml). After refluxing for 6 h, the mixture was evaporated and the residue

TABLE 2

Yields, m.p.s, recrystallization solvents (r.s.), and spectral and analytical data of oxadiazoles (3), (5), (7) and (9).

Compd. no.	Yield (%)	M.p. (°C) r.s. [a]	λ nm	ν cm^{-1} (CO,NH)	δ_H [b]	Formula	Found (%) (Required) C	H	N
(3.1)	72	101 E	350, 255	3 200	1.40 (t, 3 H), 3.35 (m, 2 H)	$C_{16}H_{15}N_3O$	72.7 (72.4	6.1 5.7	15.9 15.8)
(3.2)	86	110 E	344, 254	3 370	4.50 (d, 2 H)	$C_{21}H_{17}N_3O$	77.1 (77.8	5.2 5.2	12.6 12.8)
(3.3)	90	125 E	343, 258	3 379	2.45 (s, 3 H), 4.56 (d, 2 H)	$C_{22}H_{19}N_3O$	77.5 (77.4	5.6 5.6	12.6 12.3)
(3.4)	79	122 E	350, 263	3 395	4.58 (d, 2 H)	$C_{21}H_{16}ClN_3O$	70.1 (69.7	4.2 4.4	11.6 11.6)
(3.5)	44	188 B	341 [i]	3 380	4.60 (d, 2 H)	$C_{21}H_{16}N_4O_3$	67.7 (67.9	4.6 4.1	14.8 15.1)
(3.6)	69	42 LP	344, (260)	3 250	1.35 (t, 3 H), 2.63 (s, 3 H) 3.31 (m, 2 H)	$C_{11}H_{13}N_3O$	64.8 (65.0	6.3 6.4	20.4 20.7)
(3.7)	90	83 E	340, (309)	3 390	2.65 (s, 3 H), 4.60 (s, 2 H)	$C_{16}H_{15}N_3O$	72.4 (72.4	5.7 5.7	16.0 15.8)
(3.8)	65	65 E	342, (260)	3 250	1.08 (t, 3 H), 1.93 (m, 2 H) 2.93 (t, 2 H), 4.55 (s, 2 H)	$C_{18}H_{19}N_3O$	73.3 (73.7	6.2 6.5	14.8 14.3)
(3.9)	53	85 E	343, 310	3 360	4.28 (s, 2 H), 4.51 (d, 2 H)	$C_{22}H_{19}N_3O$	77.4 (77.4	5.5 5.6	12.3 12.3)
(3.10)	62	119 E	342, (260)	3 370	3.65 (d, 2 H), 4.60 (d, 2 H) 4.73 (t, 1 H)	$C_{28}H_{25}N_3O$	80.9 (80.7	5.8 5.8	9.8 9.7)
(3.11)	91	139 [c] B–EA	330, 250	3 402, 3 320	5.50 (br, 2 H)				
(3.12)	86	127 E	330, 256	3 410, 3 320	2.42 (s, 3 H), 5.50 (br, 2 H)	$C_{15}H_{13}N_3O$	72.0 (71.7	5.1 5.2	17.0 16.7)
(3.13)	86	145 E	320, 256	3 460, 3 420, 3 350	5.50 (br, 2 H)	$C_{14}H_{10}ClN_3O$	62.2 (62.0	3.7 3.5	15.2 15.9)
(3.14)	87	213 A	324, 268	3 495, 3 380	6.40 (br, 2 H) [h]	$C_{14}H_{10}N_4O_3$	59.9 (59.6	3.6 3.6	20.2 19.9)

TABLE 2 (*continued*)

Compd. no.	Yield (%)	M.p. (°C) r.s.[a]	λ nm	ν cm⁻¹ (CO,NH)	δ_H [b]	Formula	Found (%) (Required) C	H	N
(3.15)	65	87 [d]	331,	3 461,	2.61 (s, 3 H), 5.30 (br, 2 H)				
		E aq.	293	3 360					
(3.16)	87	53	330,	3 430,	2.05 (t, 3 H), 1.88 (m, 2 H)	$C_{11}H_{13}N_3O$	65.2	6.5	20.7
		LP	293	3 330	2.90 (t, 2 H), 5.30 (br, 2 H)		(65.0	6.4	20.7)
(3.17)	73	85	332	3 450,	4.30 (s, 2 H), 5.25 (br, 2 H)	$C_{15}H_{13}N_3O$	71.5	5.1	16.5
		E		3 350			(71.7	5.2	16.7)
(3.18)	91	100	330,	3 475,	3.65 (d, 2 H), 4.75 (t, 1 H)	$C_{22}H_{19}N_3O$	77.8	5.9	12.3
		E	294	3 379	5.25 (br, 2 H)		(77.4	5.6	12.3)
(3.19)	93	152	302,	3 335,	2.30 (s, 3 H), 10.3 (br, 1 H)	$C_{16}H_{13}N_3O_2$	68.5	4.5	15.2
		E	256	1 682			(68.8	4.7	15.0)
(3.20)	92	151 [c]	307,	3 320	11.2 (br, 1 H)				
		B	243						
(3.21)	75	183	(304),	3 390,	9.5 (br, 1 H)	$C_{21}H_{14}N_4O_4$	65.3	3.9	14.3
		B	253	1 690			(65.3	3.6	14.5)
(3.22)	92	151	(310),	3 330,	2.28 (s, 3 H), 2.47 (s, 3 H)	$C_{17}H_{15}N_3O_2$	69.7	5.0	14.4
		E	262	3 300,	10.3 (br, 1 H)		(69.6	5.1	14.3)
				1 705					
(3.23)	88	147		3 300	2.44 (s, 3 H), 11.3 (br, 1 H)	$C_{22}H_{17}N_3O_2$	73.9	4.8	11.9
		E					(74.3	4.8	11.8)
(3.24)	70	162	310,	3 330,	2.28 (s, 3 H), 10.2 (br, 1 H)	$C_{16}H_{12}ClN_3O_2$	61.4	3.6	13.3
		E	261	1 680			(61.2	3.8	13.4)
(3.25)	91	168		3 350	11.2 (br, 1 H)	$C_{21}H_{14}ClN_3O_2$	66.6	3.4	11.3
		EA					(67.1	3.7	11.2)
(3.26)	74	98 [f]	302,	3 339,	2.25 (s, 3 H), 2.65 (s, 3 H)				
		C	257	3 310,					
				1 710					
(3.27)	61	141	307,	3 200	2.65 (s, 3 H), 11.0 (br, 1 H)	$C_{16}H_{13}N_3O_2$	69.1	4.5	15.1
		E	272				(68.8	4.7	15.0)
(3.28)	53	175	304,	3 330,	2.73 (s, 3 H), 11.2 (br, 1 H)	$C_{16}H_{12}N_4O_4$	59.6	3.9	17.7
		B	252	3 290,			(59.3	3.7	17.3)
				1 690					
(3.29)	90	84	301,	3 250	1.10 (t, 3 H), 1.95 (m, 2 H)	$C_{13}H_{15}N_3O_2$	63.5	6.2	17.0
		E	257		3.0 (t, 2 H), 10.2 (br, 1 H)		(63.6	6.2	17.1)
(3.30)	94	90	307,	3 200	1.08 (t, 3 H), 1.95 (m, 2 H)	$C_{18}H_{17}N_3O_2$	70.1	5.6	13.6
		E	272		2.98 (t, 2 H), 11.2 (br, 1 H)		(70.3	5.6	13.7)
(3.31)	93	102	301,	3 440,	2.20 (s, 3 H), 3.70 (d, 2 H)	$C_{24}H_{21}N_3O_2$	75.1	5.1	11.4
		E	251	1 680	4.75 (t, 1 H), 10.1 (br, 1 H)		(75.2	5.5	11.0)
(3.32)	71	245	357,	3 260	10.85 (br, 1 H) [h]	$C_{20}H_{13}N_5O_5$	59.1	3.2	17.3
		T	248				(59.5	3.2	17.4)
(3.33)	76	182	358	3 330	2.66 (s, 3 H) [h]	$C_{16}H_{11}N_5O_5$	52.7	3.1	20.3
		T			10.75 (br, 1 H)		(52.8	3.2	20.5)
(3.34)	20	173	357,	3 150	4.35 (s, 2 H)	$C_{21}H_{15}N_5O_5$	60.4	3.5	16.9
		A	(260)				(60.4	3.6	16.8)
(5.1)	50	177		3 410,	6.30 (br, 2 H)	$C_{13}H_{10}N_4O$	65.7	4.0	23.5
		E		3 330,			(65.5	4.2	23.5)
				3 150					
(5.2)	52	148 [g]	327	3 460,	2.67 (s, 3 H), 6.15 (br, 2 H)				
		E	253	3 330,					
				3 270					
(5.3)	73	125	254	3 315,	2.55 (s, 3 H)	$C_{15}H_{12}N_4O_2$	63.9	4.8	19.6
		C		1 695	10.25 (br, 1 H)		(64.3	4.3	20.0)
(5.4)	30	111	290	3 355,	2.50 (s, 3 H), 2.73 (s, 3 H)	$C_{10}H_{10}N_4O$	54.9	4.3	25.8
		T	255	3 320,	10.1 (br, 1 H)		(55.0	4.6	25.7)
				1 732					
(7.1)	81	185	(296)	3 425,	1.03 (t, 3 H), 1.85 (m, 2 H)	$C_{15}H_{15}N_5O$	63.9	5.2	24.5
		E. aq.	289	3 310	2.83 (t, 2 H), 6.50 (br, 2 H)		(64.0	5.4	24.9)
(7.2)	78	220	294	3 440,	1.05 (t, 3 H), 1.90 (m, 2 H)	$C_{14}H_{14}N_6O$	59.3	5.0	29.6
		E	244	3 420,	2.85 (t, 2 H), 6.50 (br, 1 H)		(59.6	5.0	29.8)
				3 305					
(7.3)	70	126	296	3 390,	1.00 (t, 3 H), 1.85 (m, 2 H)	$C_{10}H_{13}N_5O$	59.3	6.1	34.2
		E	249	3 280	2.70 (m, 5 H), 6.50 (br, 5 H)		(59.1	6.4	34.5)
(9)	69	156	250	3 429,	5.2 (br, 1 H)	$C_{17}H_{13}N_5O$	67.6	4.4	23.2
		P		3 334			(67.3	4.3	23.1)

[a] Recrystallization solvents: E = EtOH, A = acetone, LP = light petroleum, EA = EtOAc, C = cyclohexane, B = benzene, T = toluene, P = propan-2-ol. [b] Aromatic protons and NH (if obscured by the aromatic protons) not included. [c] Lit. 135—136 °C (ref. 6). [d] Lit. 79—80 °C (ref. 6). [e] Lit. 153—154 °C (ref. 6). [f] Lit. 91—92 °C (ref. 6). [g] Lit. 145 °C (ref. 10). [h] In $(CD_3)_2SO$. [i] In DMF.

* U.v. values in parentheses are inflections.

TABLE 3

Times of isomerisations in DMF at 150 °C; m.p.s, recrystallization solvents (r.s.), and spectral and analytical data of the products (4), (6), (8), and (10)

Compd. no.	Time (h)	M.p. (°C) r.s.[a]	λ nm	ν cm⁻¹ (CO,NH)	δ_H [b]	Formula	Found (%) (Required) C	H	N
(4.1)	1.5	152 E	308, 258	3 250, 1 659	1.48 (t, 3 H), 4.35 (q, 2 H), 8.43 (br, 1 H)	$C_{16}H_{15}N_3O$	72.0 (72.4	5.5 5.7	15.9 15.8)
(4.2)	2	154 E	306	3 300, 1 655	5.45 (s, 2 H), 8.65 (br, 1 H)	$C_{21}H_{17}N_3O$	76.9 (77.1	5.2 5.2	12.7 12.8)
(4.3)	3	160 E	306	3 260, 1 660	2.45 (s, 3 H), 5.50 (s, 2 H), 8.55 (br, 1 H)	$C_{22}H_{19}N_3O$	77.2 (77.4	5.4 5.6	12.5 12.3)
(4.4)	1	144 E	308, (260)	3 250	5.49 (s, 2 H), 8.70 (br, 1 H)	$C_{21}H_{16}ClN_3O$	70.1 (69.7	4.0 4.4	11.6 11.6)
(4.5)	0.5	203 E	300, 256	3 230, 1 662	5.63 (s, 2 H), 11.1 (br, 1 H) [h]	$C_{21}H_{16}N_4O_3$	67.9 (67.9	4.4 4.1	15.1 15.1)
(4.6)	5	122 LP–C	305	3 150, 1 659	1.46 (t, 3 H), 2.22 (s, 3 H), 4.35 (q, 2 H)	$C_{11}H_{13}N_3O$	64.7 (65.0	6.2 6.4	20.3 20.7)
(4.7)	9	143 B–LP	345, 305	3 449, 3 390, 3 220, 1 660	2.25 (s, 3 H), 5.50 (s, 2 H)	$C_{16}H_{15}N_3O$	72.6 (72.4	5.6 5.7	15.5 15.8)
(4.8)	9	81 C	305	3 230, 1 660	1.05 (t, 3 H), 1.85 (m, 2 H), 2.45 (t, 2 H), 5.48 (s, 2 H)	$C_{18}H_{19}N_3O$	73.2 (73.7	6.4 6.5	13.8 14.3)
(4.9)	3.5	141 E	305	3 290, 1 663	3.85 (s, 2 H), 5.45 (s, 2 H)	$C_{22}H_{19}N_3O$	76.6 (77.4	5.4 5.6	12.2 12.3)
(4.10)	3	128 E	304, 258	3 200, 1 662	3.2 (d, 2 H), 4.75 (t, 1 H), 5.44 (s, 2 H)	$C_{28}H_{25}N_3O$	81.2 (80.7	5.8 5.8	9.7 9.7)
(4.11)	50	161 B	297	3 280, 1 659	10.3 (br, 1 H), 12.2 (br, 1 H) [h]	$C_{14}H_{11}N_3O$	70.9 (70.9	4.4 4.7	17.8 17.7)
(4.12)	70	197 E	297, 236	3 250, 1 660	2.44 (s, 3 H), 10.8 (br, 1 H) [h] 12.8 (br, 1 H)	$C_{15}H_{13}N_3O$	71.7 (71.7	5.3 5.2	16.7 16.7)
(4.13)	40	211 E	299	3 250, 1 658	10.9 (br, 1 H), 12.8 (br, 1 H) [h]	$C_{14}H_{10}ClN_3O$	61.8 (62.0	3.7 3.6	15.5 15.9)
(4.14)	13	272 A	(290), 258	3 250, 3 150, 1 650	11.2 (br, 1 H), 12.9 (br, 1 H) [h]	$C_{14}H_{10}N_4O_3$	59.7 (59.6	3.7 3.6	20.0 19.9)
(4.15)	15 [d]	196 [e] E–EA	308, 272	3 250, 1 680	2.14 (s, 3 H), 10.3 (br, 1 H),[h] 12.8 (br, 1 H)				
(4.16)	15 [d]	157 EA	298, 260	3 250, 3 150, 1 660	1.05 (t, 3 H), 1.85 (m, 2 H), 2.48 (t, 2 H), 9.75 (br, 1 H)	$C_{11}H_{13}N_3O$	64.9 (65.0	6.4 6.4	20.4 20.7)
(4.17)	12 [d]	230 E	298, 258	3 210, 1 658	3.78 (s, 2 H), 10.4 (br, 1 H) [h]	$C_{15}H_{13}N_3O$	71.2 (71.7	5.1 5.2	16.6 16.7)
(4.18)	12 [d]	191 E	298, 258	3 330, 1 664	3.25 (d, 2 H), 4.75 (t, 1 H), 9.75 (br, 1 H), 11.9 (br, 1 H)	$C_{22}H_{19}N_3O$	78.0 (77.4	5.8 5.6	12.3 12.3)
(4.19)	3	168 B	303, 237	3 280, 1 720 1 660	2.66 (s, 3 H), 8.70 (br, 1 H)	$C_{16}H_{13}N_3O_2$	69.1 (68.8	4.7 4.7	14.8 15.0)
(4.20)	0.5	185 [e] E	313, 240	3 295, 1 690, 1 660	7.0—8.8 (m, 15 H)				
(4.21)	0.4	228 EA	313, 254	3 280, 1 680, 1 662	11.25 (br, 1 H) [h]	$C_{21}H_{14}N_4O_4$	65.0 (65.3	3.7 3.6	14.0 14.5)
(4.22)	4	180 E	300, 238	3 250, 1 720, 1 658	2.45 (s, 3 H), 2.70 (s, 3 H), 9.4 (br, 1 H)	$C_{17}H_{15}N_3O_2$	69.3 (69.6	5.1 5.1	14.2 14.3)
(4.23)	1	166 B		3 300, 1 682, 1 650	2.42 (s, 3 H), 11.3 (br, 1 H) [h]	$C_{22}H_{17}N_3O_2$	74.0 (74.3	4.5 4.8	11.7 11.8)
(4.24)	2.5	211 E	304, 242	3 250, 1 720, 1 660	2.55 (s, 3 H), 8.5 (br, 1 H)	$C_{16}H_{12}ClN_3O_2$	61.0 (61.2	3.7 3.8	13.2 13.5)
(4.25)	0.5	180 E		3 200, 1 680, 1 650	8.6 (br, 1 H)	$C_{21}H_{14}ClN_3O_2$	67.7 (67.1	3.7 3.7	11.1 11.2)
(4.26)	7	179 [f] E	310, 299	3 205, 1 730, 1 662	2.22 (s, 3 H), 2.68 (s, 3 H) [h] 10.9 (br, 1 H)				
(4.27)	1	201 E	313, 244	3 200, 1 681, 1 660	2.19 (s, 3 H), 10.9 (br, 1 H) [h]	$C_{16}H_{13}N_3O_2$	69.2 (68.8	4.5 4.7	15.1 15.0)
(4.28)	0.6	240 E	314, 251	3 260, 1 690, 1 685	2.18 (s, 3 H)	$C_{13}H_{12}N_4O_4$	58.9 (59.3	3.6 3.7	17.3 17.3)
(4.29)	7	163 E	310, 299	3 286, 1 720, 1 672	1.10 (t, 3 H), 1.85 (m, 2 H), 2.60 (t, 2 H), 2.73 (s, 3 H)	$C_{13}H_{15}N_3O_2$	63.7 (63.6	6.1 6.2	17.1 17.1)

TABLE 3 (*continued*)

Compd. no.	Time (h)	M.p. (°C) r.s.[a]	λ nm	ν cm⁻¹ (CO,NH)	δ_H [b]	Formula	Found (%) (Required) C	H	N
(4.30)	1	174 E	313, 243	3 230, 1 690 1 675	1.05 (t, 3 H), 1.85 (m, 2 H), 2.52 (t, 2 H)	$C_{18}H_{17}N_3O_2$	70.0 (70.3	5.4 5.6	13.6 13.7)
(4.31)	5	221 B		3 300, 1 739, 1 680	2.63 (s, 3 H), 3.20 (d, 2 H), 4.75 (t, 1 H)	$C_{24}H_{21}N_3O_2$	75.8 (75.2	5.2 5.5	10.8 11.0)
(4.32)	0.1	198 E	377, 304	3 400, 1 682	11.2 (br, 1 H)	$C_{20}H_{13}N_5O_5$	59.2 (59.5	3.2 3.2	17.1 17.4)
(4.33)	0.3	251 E	377, 300	3 300— 3 600, 1 682	2.22 (s, 3 H), 10.8 (br, 1 H) [h]	$C_{16}H_{11}N_5O_5$	52.3 (52.8	3.1 3.2	20.4 20.5)
(4.34)	0.1	177 E	378 298	3 300, 1 650	4.40 (s, 2 H), 10.6 (br, 1 H) [h]	$C_{21}H_{15}N_5O_5$	60.2 (60.4	3.8 3.6	16.9 16.8)
(6.1)	0.4 [g]	217 E		3 260, 3 150, 1 675	10.7 (br, 1 H), 13.0 (br, 1 H)	$C_{13}H_{10}N_4O$	65.3 (65.5	4.0 4.2	23.7 23.5)
(6.2)	5 [g]	238 E		3 400, 3 130, 1 675	2.13 (s, 3 H), 10.6 (br, 1 H) [h]	$C_8H_8N_4O$	54.7 (54.4	4.6 4.6	31.9 31.8)
(6.3)	1	179 E aq.	303 240	3 450, 1 735, 1 695	2.9 (s, 3 H)	$C_{15}H_{12}N_4O_2$	64.1 (64.3	4.5 4.3	20.1 20.0)
(6.4)	2	203 E	302 245	3 300, 3 100, 1 725, 1 655	2.35 (s, 3 H), 2.93 (s, 3 H)	$C_{10}H_{10}N_4O$	54.9 (55.0	4.6 4.6	25.8 25.7)
(8.1)	0.3 [g]	256 E	(300) 262	3 280, 1 655	0.95 (t, 3 H), 1.85 (m, 2 H), [h] 2.95 (t, 2 H), 9.48 (s, 1 H)	$C_{15}H_{15}N_5O$	64.0 (64.0	5.8 5.4	25.3 24.9)
(8.2)	0.3 [g]	270 E	270 (300)	2 400— 3 400, 3 285, 1 668	1.03 (t, 3 H), 1.93 (m, 2 H) 3.03 (t, 2 H), 11.2 (br, 1 H), 12.9 (br, 1 H)	$C_{14}H_{14}N_6O$	60.1 (59.6	5.2 5.0	29.8 29.8)
(10)	0.2 [g]	190 E	276 230	2 400— 3 400, 3 321, 1 665	10.25 (br, 1 H), 11.2 (br, 1 H)	$C_{17}H_{13}N_5O$	67.3 (67.3	4.3 4.3	23.0 23.1)

[a] Recrystallization solvents: E = EtOH, A = acetone, B = benzene, EA = EtOAc, LP = light petroleum (b.p. 60—80 °C), C = cyclohexane. [b] Aromatic protons and NH (if obscured by the aromatic protons) not included. [c] Lit. 204 °C (ref. 7). [d] In melting at 200 °C. [e] Lit. 183—184 °C (ref. 13). [f] Lit. 181 °C (ref. 13). [g] In DMF with NaOH catalysis. [h] In $(CD_3)_2SO$.

triturated with water; the product was filtered off and dried to yield the oxime (23.5 g, 97.5%), m.p. 100 °C (EtOH); δ($CDCl_3$) 4.40 (s, 2 H), 4.90 (br, 1 H, NH), and 6.50—7.75 (m, 10 ArO, OH).

4-Amino-2-propylpyrimidine-5-carboxamide Oxime.—3-Amino-4-cyano-2-propylpyrimidine,[11] when treated as above, gave the oxime (88%), m.p. 214 °C (EtOH); δ[$(CD_3)_2SO$] 0.88 (t, 3 H), 1.63 (s, 2 H), 5.93 (br, 2 H, NH_2), 7.63 (br, 2 H, NH_2), 8.45 (s, 1 H, ArH), and 9.85 (s, 1 H, OH).

General Method for Preparation of 5-Substituted 1,2,4-Oxadiazoles from Amide Oximes and Esters [(3.2)—(3.5), (3.7)—(3.18), (5.1), (5.2), (7.1)—(7.3), *and* (9)].—The amide oxime (0.01 mol) and the appropriate ethyl carboxylate (0.02 mol) in ethanol (200 ml) were added to a freshly prepared solution of sodium ethoxide [from sodium (2.3 g, 0.10 mol)] in ethanol (40 ml). After refluxing for 8 h the mixture was evaporated, the residue triturated with water, and product separated, dried, and recrystallized.

3-(2-Ethylaminophenyl)-5-phenyl-1,2,4-oxadiazole (3.1).—The oxadiazole (3.11) (7.11 g, 0.03 mol) and diethyl sulphate (7.35 g, 0.056 mol) were refluxed in 2N-sodium hydroxide (26 ml) for 5 h. The product was recovered by extraction and chromatography on silica (eluant hexane–chloroform, 1 : 1).

3-(2-Ethylaminophenyl)-5-methyl-1,2,4-oxadiazole (3.6).—The oxadiazole (3.15) was treated as described for (3.1). The crude product was purified, as the hydrochloride, by recrystallization from acetone, and converted into the base with aqueous sodium hydrogen carbonate.

General Procedure for Preparation of Acetamido 5-Substituted 1,2,4-Oxadiazole Derivatives [(3.19), (3.22), (3.24), (3.26), (3.29), (3.31), (5.3), *and* (5.4)].—The amine (0.01 mol) was dissolved in acetic anhydride (20 ml) with slight warming. On cooling the product crystallized. Next day it was filtered off, washed with ether, dried, and recrystallized.

General Procedure for Preparation of 5-Substituted 3-(2-Benzoylaminophenyl)-1,2,4-oxadiazoles [(3.20, (3.21), (3.23), (3.25), (3.27), (3.28), *and* (3.30)].—To a solution of the amine (0.01 mol) and triethylamine (1.01 g, 0.01 mol) in dry acetone (50 ml), benzoyl chloride (1.40 g, 0.01 mol) or 4-nitrobenzoyl chloride (1.85 g, 0.01 mol) was added dropwise with stirring over 10 min. Next day triethylamine hydrochloride was filtered off and washed with acetone, and the combined filtrates were evaporated. The residue was triturated with water (50 ml), filtered off, dried, and recrystallized.

3-[2-(2,4-Dinitrophenyl)aminophenyl]-5-phenyl-1,2,4-oxadiazole (3.32).—The oxadiazole (3.11) (4.74 g, 0.02 mol), triethylamine (2.02 g, 0.02 mol), and 1-fluoro-2,4-dinitrobenzene (3.72 g, 0.02 mol) were refluxed in ethanol (70 ml) for 12 h. Evaporation and several recrystallizations from toluene gave the pure product.

3-[2-(2,4-*Dinitrophenyl*)*aminophenyl*]-5-*methyl*-1,2,4-*oxadiazole* (3.33).—The oxadiazole (3.15) was treated as described for (3.32) but in acetone (40 ml) for 2 days at room temperature. Addition of water (130 ml) precipitated the product, which was separated and recrystallized.

The 5-benzyl derivative (3.34) was obtained from (3.17) by the same method.

General Procedure for Ring Transformation of Oxadiazoles (3) *into Acylaminoindazoles* (4).—(*a*) *In dimethylformamide at* 150 °C. A solution of the oxadiazole (3) in 10 times its weight of dry dimethylformamide was kept at 150 °C until t.l.c. indicated complete transformation. The cooled solution was poured into 4 times its volume of water, and the product was separated and crystallized. Yields were almost quantitative. Except for (3.15)—(3.18), all oxadiazoles (3) can be isomerized by this method.

Kinetic measurements were carried out as described earlier [2] by u.v. spectrophotometry and checked by hydrogenolysis.

(b) *Isomerization by melting.* The oxadiazoles (3) were heated at 150 °C or, when the m.p. was higher [(3.5) and (3.14)] at the m.p. in sealed vials until t.l.c. indicated complete transformation. Compounds (3.15)—(3.18) required heating at 200 °C, and the dinitrophenylamino-derivatives were transformed at 240 °C. By this method the oxadiazoles (3.1)—(3.18) and (3.32)—(3.34) could be isomerized. Owing to decomposition the acylamino-derivatives (3.19)—(3.31) gave only poor yields of the products (4.19)—(4.31).

3-*Benzoylamino*-1H-*pyrazolo*[3,4-b]*pyridine* (6.1).—Compound (5.1) (2.38 g, 0.01 mol) and sodium hydroxide (0.2 g, 5 mmol) were refluxed in dimethylformamide (24 ml) for 0.5 h. Dilution with water gave the product, which was separated and recrystallized from ethanol to give (6.1) (2.2 g, 92%). When melted at 200 °C compound (5.1) was isomerized completely in 1 h.

3-*Acetamido*-1H-*pyrazolo*[3,4-b]*pyridine* (6.2) was prepared from (5.2) in 91% yield as described for (6.1).

1-*Acetyl*-3-*benzoylamino*-1H-*pyrazolo*[3,4-b]*pyridine* (6.3) was obtained from (5.3), and 1-*acetyl*-3-*acetylamino*-1H-*pyrazolo*[3,4-b]*pyridine* (6.4) from (5.4) by boiling in dimethylformamide in 88 and 87% yield, respectively.

6-*Propyl*-3-*benzoylamino*-1H-*pyrazolo*[3,4-d]*pyrimidine* was obtained from (7.1), and 6-*propyl*-3-*isonicotinoylamino*-1H-*pyrazolo*[3,4-d]*pyrimidine* (8.2) from (7.2) in nearly quantitative yield as described for (6.1).

3-*Benzoylamino*-6-*phenyl*-1H-*pyrazolo*[3,4-c]*pyrazole* (10) was obtained from (9) as described for (6.1) in 97% yield.

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