HETEROCYCLES, Vol. 57, No. 11, 2002, pp. 2045 - 2064, Received, 12th July, 2002

SYNTHESIS AND REACTIVITY OF (*Z*)-3-BENZOYLAMINO-4-DIMETHYLAMINO-2-OXO-3-BUTENE. PREPARATION OF 1-ARYL- AND 1-HETEROARYL-SUBSTITUTED 4-BENZOYLAMINO-5-METHYL-1*H*-PYRAZOLES

Urška Bratušek, Simon Rečnik, Jurij Svete*, Ljubo Golič, and Branko Stanovnik*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia

Abstract – (*Z*)-3-Benzoylamino-4-dimethylamino-2-oxo-3-butene (**4**), prepared from 1-benzoylamino-2-propanone (**3**) and *N*,*N*-dimethylformamide dimethyl acetal, was converted regioselectively by reaction with a series of hydrazines (**5**) into 1-substituted 4-benzoylamino-5-methyl-1*H*-pyrazoles (**8**). Reactions of **4** with primary amines (**10**) and with dimethylbarbituric acid (**12**) afforded the dimethylamine substitution products (**11**) and (**13**), respectively. Treatment of the butenone (**13**) with ammonia furnished tetrahydropyrido[2,3–*d*]pyrimidine derivative (**14**).

Pyrazoles are important class of heterocyclic compounds as constituents of natural and synthetic products.[1–3] Pyrazoles and their derivatives found a widespread use in various applications in last decades.[1b,4] They exhibit biological activity, and are applicable for industrial and synthetic purposes, such as devolops in photographic applications[6–8] as inhibitors of cyclooxygenase, lipooxygenase, and γ-aminobutyrate transferase.[9–14] The standard method of synthesis of pyrazoles consists in the condensation of 1,3-bifunctional compound with hydrazine or its derivatives, and 1,3-dipolar cycloadditions.[1b,5,15,16] The 4-nitrogen substituted 2-pyrazolin-5-ones are usually prepared by modification of already formed pyrazolinones,[17] while the 5-substituted 4-amino-3-hydroxypyrazoles have been synthesized by transformation of β-keto esters, *via* oxime formation, into 2-amino-β-keto esters followed by treatment with hydrazines[18] and from methyl 2-benzoylamino-3-oxobutanoate and hydrazines.[19] Recently, pyrazolidinones have been used for regio- and stereoselective synthesis of *rel*-(2*R*,3*R*)-3-alkylamino-3-phenylalanine amides[20] and alanine esters,[21,22] tetracyclic systems,[23] *rel*-(4'*R*,5'*S*)-3-(5-aryl-3,4-

bis(hydrazinocarbonyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-3-methylbutanohydrazides,[24] and (1*Z*)-1-arylmethylidene-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide azomethine imines.[25] Several synthetic routes have been developed in recent decades for their preparation by ring-switching methodology from (*S*)-3-formylpyroglutamates and hydrazines,[26-28] *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone,[21,22] 5-substituted (*S*)-1-acyl-3-[(*E*)-dimethylaminomethylidene]pyrrolidin-2-ones, (*S*)-3-[(*E*)-dimethylaminomethylidene]tetrahydrofuran-2-ones, and their 3-(*E*)-cyanomethylidene analogs.[29-34]

In this paper we present the synthesis and transformations of (*Z*)-3-benzoylamino-4-dimethylamino-2-oxo-3-butene (**4**), prepared in 3 steps from hippuric acid (**1**). This was first treated with *N*,*N*-dimethylacetamide and $POCl_3$ to give the oxazolone (**2**), which was then transformed into 1-benzoylamino-2-propanone (**3**) by treatment with a mixture of methanol and hydrochloric acid. Heating of **3** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) in dry toluene for 45 min afforded (*Z*)-3-benzoylamino-4-dimethylamino-2-oxo-3-butene (**4**) in 58% overall yield. In order to study the reactivity of compound (**4**) a series of hydrazines (**5a–l**) were selected. Since **4** contains two functional groups, the carbonyl and the enamino groups, which react easily with hydrazines, two intermediates can be formed: a) the enehydrazine (**6**) by substitution of the dimethylamino group and b) the corresponding hydrazone (**7**) by the reaction with the carbonyl group. From these two intermediates two isomeric pyrazole derivatives, either 1-substituted 4-benzoylamino-5-methyl-1*H*-pyrazole (**8**) or 1-substituted 4-benzoylamino-3-methyl-1*H*-pyrazole (**9**) could be formed by cyclization. The isolation of intermediate was not possible, since further cyclization occurs at room temperature to give pyrazole derivatives (Scheme 1).

The X-Ray structure of the product derived from 2-hydrazinopyrimidine (**5j**) was determined showing that compound is 4-benzoylamino-5-methyl-1-(pyrimidin-2-yl)-1*H*-pyrazole (**8j**) (Figure 1).

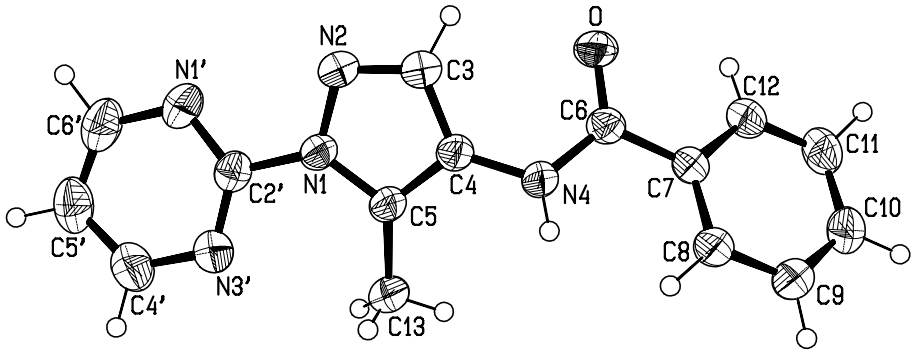
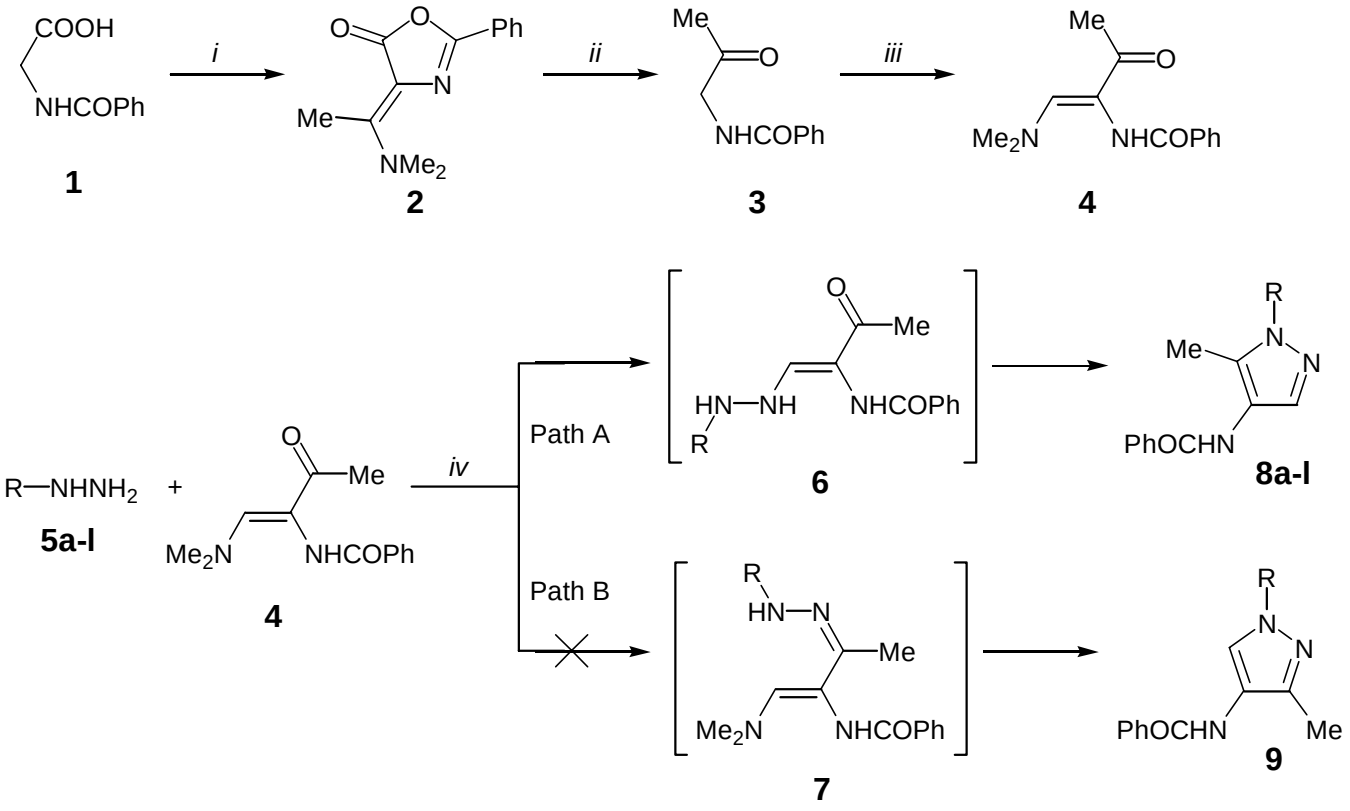


Figure 1. Ortep view at the 50% probability level for compound (**8j**) showing the labeling of the non-hydrogen atoms. H atoms are drawn as circles of arbitrary radii.

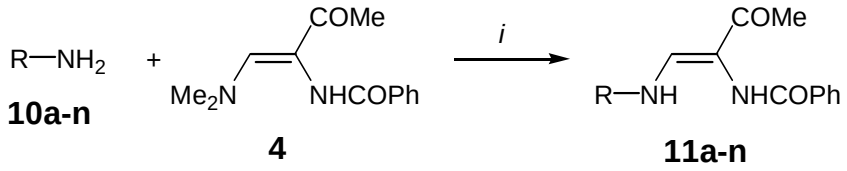


Compound	R
5a, **8a**	H
5b, **8b**	3-hydroxybenzyl
5c, **8c**	Ph
5d, **8d**	4-nitrophenyl
5e, **8e**	4-carboxyphenyl
5f, **8f**	pyridin-2-yl
5g, **8g**	6-methylpyridazin-3-yl
5h, **8h**	6-chloropyridazin-3-yl
5i, **8i**	6-phenylpyridazin-3-yl
5j, **8j**	pyrimidin-2-yl
5k, **8k**	1,2,4-triazolo[4,3–*b*]pyridazin-6-yl
5l, **8l**	3-phenyl-1,2,4-triazolo[4,3–*b*]pyridazin-6-yl

Reagents and Conditions: *i*) $MeCONMe_2$, $POCl_3$, 40–45°C; *ii*) MeOH, 36% HCl, reflux; *iii*) $Me_2NCH(OMe)_2$, toluene, reflux; *iv*) EtOH, 36% HCl (1 equiv), reflux

Scheme 1

In the reactions of **4** with (hetero)aromatic amines (**10a–n**) in acetic acid, in most cases at room temperature, the substitution of dimethylamino group took place to give 3-benzoylamino-4-substituted amino-2-oxo-3-butenes (**11a–n**) (Scheme 2).



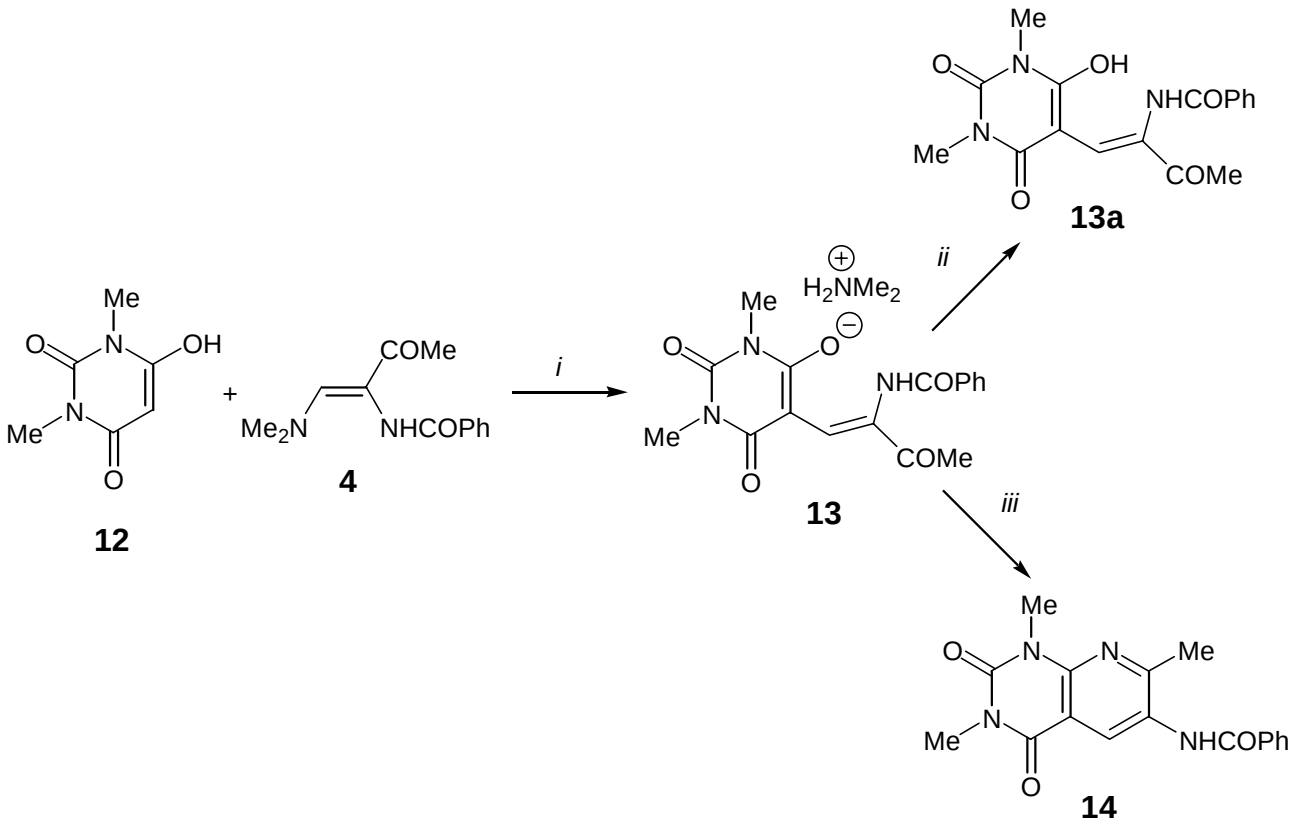
10a-n **4** **11a-n**

Compound	R
10a, **11a**	4-methoxyphenyl
10b, **11b**	3-chloro-4-fluorophenyl
10c, **11c**	phenyl
10d, **11d**	3-bromophenyl
10e, **11e**	2-methylphenyl
10f, **11f**	3-nitrophenyl
10g, **11g**	5-chloropyridin-2-yl
10h, **11h**	4-methylpyridin-2-yl
10i, **11i**	pyridin-2-yl
10j, **11j**	3-hydroxypyridin-2-yl
10k, **11k**	5-nitropyridin-2-yl
10l, **11l**	pyrimidin-2-yl
10m, **11m**	2,6-dimethylpyrimidin-2-yl
10n, **11n**	pyrazinyl

Reagents and Conditions: *i*) AcOH, rt.

Scheme 2

In the reaction of **4** with *C*-nucleophile, 1,3-dimethylbarbituric acid (**12**), in acetic acid at room temperature the product (**13**) was isolated in the form of dimethylamine salt, from which free compound (**13a**) was isolated by treatment with 2% hydrochloric acid. When 25% ammonia was added to the solution of **13** in ethanol and the mixture was stirred at room temperature for three days, 6-benzoylamino-1,3,7-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3–*d*]pyrimidine (**14**) was isolated in 15% yield (Scheme 3).



Reagents and Conditions: *i*) AcOH, rt; *ii*) 2% HCl, rt; *iii*) NH_3, H_2O, EtOH, rt.

Scheme 3

The structures of compounds (**4**, **8a–l**, **11a–n**, **13**, **13a**, and **14**) were determined by spectroscopic methods and by analyses for C, H, and N. The configurations around the C=C double bond in compounds (**4**, **11c**, and **13a**) were determined by NMR spectrometry. Since most of these compounds exist as single isomers, differentiation between (*Z*)- and (*E*)-form is not possible on the basis of chemical shifts or *J* values. However, the two isomeric forms can easily be differentiated on the basis of the magnitude of the long-range heteronuclear $^{13}C–^{1}H$ coupling constants, $^{3}J_{C–H}$, which have been used for determination of conformations and configurations in various systems.[35–37] Several methods for measuring $^{3}J_{C–H}$, such as TOCSY-based methods[38–40] and methods based on HMBC correlation techniques,[41–46] have been described in the literature. Recently, the orientation around the double bond in alkyl 2,3-(diamino)propenoates has been determined using the 2D HMBC method.[47] Generally, the magnitude of coupling constant $^{3}J_{C–H}$ for nuclei with *cis*-configuration around the C=C double bond is smaller (2–6 Hz) than that for *trans*-oriented nuclei (8–12 Hz).[45,47,48] Similar coupling constants have also been observed in some oxazolone derivatives with an analogous structural element.[49] For this reason, HMBC correlation technique was selected as the most suitable for the determination of the configurations around the C=C double bond in this study.[50–52]

Thus, in the case of compounds (**4**, **11c**, and **13a**), the magnitude of heteronuclear coupling constant, $^3J_{C–H}$ = 3.2, 3.8, and 5.1 Hz, respectively, clearly indicates the (*Z*)-orientation. By comparison of the chemical shifts δ_{CH} = 7.40–8.49 ppm and δ_{NH} = 9.69–11.42 ppm for protons of CH–NH structural element and the magnitude of coupling constants, $J_{CH–NH}$ = 10.9 – 12.0 Hz one can conclude that the orientation around the double bond in compounds (**11**) is (*Z*) and that the protons of the CH–NH structural element are *trans*-oriented (Figure 2).

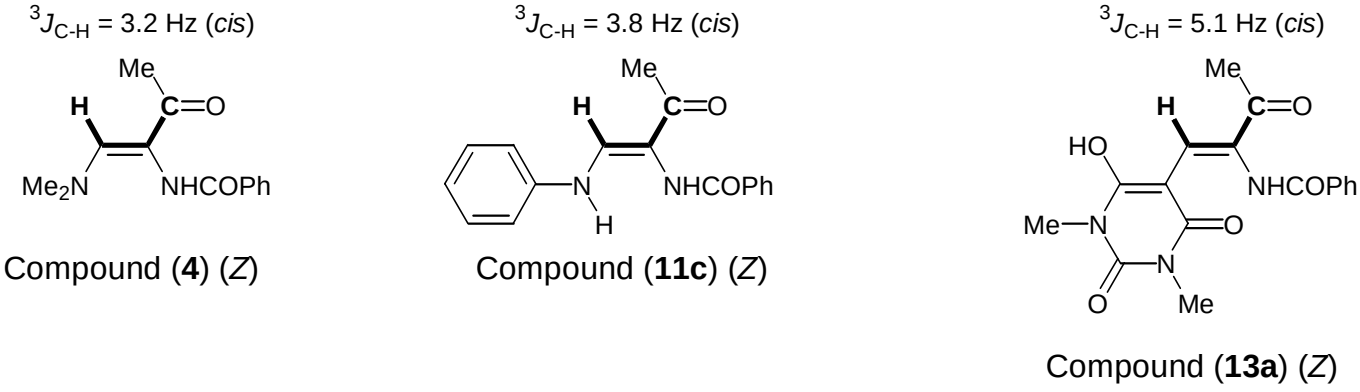


Figure 2

The ^{1}H NMR spectra of pyrazoles (**8a–l**) exhibit, besides the signals characteristic for substituents at position 1 and benzoyl group, a signal for a proton at position 3 in the range of δ = 7.05–8.12 ppm and a signal for a methyl group in the range of δ = 2.14–2.69 ppm. In NOESY spectra only the NOE effect between the methyl protons and proton of the NH part of the benzoylamino group was observed. The structure of pyrazoles (**8**) was unambigously determined by X–Ray analysis of compound (**8j**) (Figure 1).

X-Ray structure determination

Suitable crystals of the compound were obtained by slow evaporation of their solution in **8j**. Structure of compound (**8j**) was solved by direct method using the SIR92[53] program. All hydrogen atoms were located by difference Fourier synthesis and included in refinement with positional parameters and isotropic displacement parameters. Full-matrix least-squares refinement on *F* of all non-hydrogen atoms with anisotropic displacement parameters and an empirical weighting scheme: $w = 14.99*w_f*w_S$, w_f (F_O<2.3) = (F_O/2.3), w_f (F_O>5.5) = $(5.5/F_O)^{0.8}$, w_f (2.3<F_O<5.5)=1.0, w_S(sinθ/λ<0.52) = $((\sin\theta/\lambda)/0.52)^3$, w_S(sinθ/λ>0.64) = $(0.64/(\sin\theta/\lambda))^8$, w_S(0.52<sinθ/λ<0.64) = 1.0 was applied.

Crystal data

$C_{15}H_{13}N_5O$	D_X = 1.340 Mg m^{-3}
M_r = 279.301	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 100
a = 10.8084(9) Å	reflections
b = 13.757(1) Å	θ = 8.39 - 14.86°
c = 10.0279(7) Å	μ = 0.0894 mm^{-1}
β = 111.840(6)°	T = 293(1) K
V = 1384.0(2) Å^3	Colorless prism
Z = 4	0.91 x 0.80 x 0.48 mm

Data collection

Enraf-Nonius CAD-4 diffractometer	θ_{max} = 28°
Profile data from ω-2θ scans	h = -14 → 14
Absorption correction: none	k = -18 → 18
13395 measured reflections	l = -13 → 13
3320 independent reflections	3 standard reflections
2826 reflections with $I > 2.0\sigma(I)$	frequency: 333 min
R_{int} = 0.016	intensity decay -0.42 %

Refinement

Refinement on F	$(\Delta/\sigma)_{max}$ = 0.00082
R = 0.042	$(\Delta/\sigma)_{aver}$ = 0.00006
wR = 0.051	$\Delta\rho_{max}$ = 0.259 e Å^{-3}
S = 0.937	$\Delta\rho_{min}$ = -0.219 e Å^{-3}
2826 reflections	Extinction correction: equation 22
243 parameters	in Larson[54]
w = empirical	Extinction coefficient: 6933(1808)

The asymmetric unit of compound (**8j**) with atom-numbering scheme is shown in Figure 1. Final atomic coordinates and isotropic displacement parameters with their e.s.d.'s are listed in Table 1. Bond lengths and bond angles are presented in Table 2.

The *Xtal3.4*[55] system of crystallographic programs was used for the reduction of data, structure refinement and interpretation. *ORTEPII*[56] was used to produce molecular graphics.

Supplementary data for this structure are available from the IUCr electronic archives with reference number CCDC 188862.

Table 1. Fractional Coordinates and Equivalent Displacement Parameters (Å^2) for Compound (**8j**). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U_{eq}
O	0.09777(11)	0.59510(8)	0.43625(13)	0.0538(4)
N(1)	0.43783(10)	0.82998(7)	0.57054(10)	0.0385(3)
N(2)	0.31822(12)	0.84105(8)	0.58535(13)	0.0473(4)
N(4)	0.27359(11)	0.62275(8)	0.37139(12)	0.0435(4)
N(1')	0.50662(14)	0.96781(10)	0.71121(14)	0.0546(4)
N(3')	0.64330(14)	0.89820(10)	0.59835(16)	0.0579(5)
C(3)	0.24452(14)	0.76824(10)	0.51341(15)	0.0470(4)
C(4)	0.31483(12)	0.70887(8)	0.45093(12)	0.0381(4)
C(5)	0.43986(12)	0.74910(8)	0.49022(12)	0.0382(4)
C(6)	0.16936(12)	0.56832(8)	0.37311(12)	0.0382(3)
C(7)	0.15023(11)	0.47124(8)	0.30049(12)	0.0385(3)
C(8)	0.19997(14)	0.44748(10)	0.19480(16)	0.0484(5)
C(9)	0.18024(16)	0.35469(11)	0.13577(18)	0.0549(5)
C(10)	0.11283(16)	0.28541(11)	0.18228(18)	0.0546(5)
C(11)	0.06310(16)	0.30887(11)	0.28670(18)	0.0558(5)
C(12)	0.08042(13)	0.40124(10)	0.34544(15)	0.0471(4)
C(13)	0.55675(17)	0.71172(14)	0.46190(23)	0.0629(6)
C(2')	0.53572(12)	0.90261(8)	0.63030(11)	0.0396(4)
C(4')	0.73300(19)	0.96895(15)	0.65576(21)	0.0670(6)
C(5')	0.71375(19)	1.04187(13)	0.73896(18)	0.0634(6)
C(6')	0.59754(20)	1.03805(13)	0.76324(19)	0.0643(6)

Table 2. Bond Distances (Å^2) and Bond Angles (°) with e.s.d.'s in Parentheses for Compound (**8j**).

O-C(6)	1.2247(20)	C(4)-C(5)	1.3754(17)
N(1)-N(2)	1.3635(18)	C(5)-C(13)	1.4860(25)
N(1)-C(5)	1.3785(16)	C(6)-C(7)	1.4983(16)
N(1)-C(2')	1.4161(15)	C(7)-C(8)	1.3940(23)
N(2)-C(3)	1.3156(17)	C(7)-C(12)	1.3974(20)
N(4)-C(6)	1.3581(18)	C(8)-C(9)	1.3897(21)
N(4)-C(4)	1.4049(15)	C(9)-C(10)	1.3820(25)
N(1')-C(2')	1.3235(20)	C(10)-C(11)	1.381(3)
N(1')-C(6')	1.3380(22)	C(11)-C(12)	1.3837(21)
N(3')-C(2')	1.3174(23)	C(4')-C(5')	1.369(3)
N(3')-C(4')	1.3429(23)	C(5')-C(6')	1.366(3)
C(3)-C(4)	1.4111(21)		

N(2)-N(1)-C(5)	112.06(10)	N(4)-C(6)-C(7)	116.77(12)
N(2)-N(1)-C(2')	117.68(11)	C(8)-C(7)-C(12)	119.40(12)
C(5)-N(1)-C(2')	130.17(12)	C(8)-C(7)-C(6)	123.78(12)
C(3)-N(2)-N(1)	105.10(12)	C(12)-C(7)-C(6)	116.80(13)
C(6)-N(4)-C(4)	123.17(13)	C(9)-C(8)-C(7)	119.85(15)
C(2')-N(1')-C(6')	114.89(17)	C(10)-C(9)-C(8)	120.43(18)
C(2')-N(3')-C(4')	115.10(16)	C(11)-C(10)-C(9)	119.82(15)
N(2)-C(3)-C(4)	111.59(13)	C(10)-C(11)-C(12)	120.54(16)
C(5)-C(4)-N(4)	124.92(13)	C(11)-C(12)-C(7)	119.95(16)
C(5)-C(4)-C(3)	105.90(11)	N(3')-C(2')-N(1')	127.80(12)
N(4)-C(4)-C(3)	129.09(12)	N(3')-C(2')-N(1)	116.92(12)
C(4)-C(5)-N(1)	105.35(12)	N(1')-C(2')-N(1)	115.28(13)
C(4)-C(5)-C(13)	28.36(12)	N(3')-C(4')-C(5')	122.89(21)
N(1)-C(5)-C(13)	126.19(12)	C(6')-C(5')-C(4')	116.00(17)
O-C(6)-N(4)	121.83(11)	N(1')-C(6')-C(5')	123.29(18)
O-C(6)-C(7)	121.33(12)		

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer with DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard. MS spectra were obtained on an Autospeck Q spectrometer. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN *Analyser* 2400.

The following hydrazino compounds were prepared according to the procedures reported in the literature: 6-chloro-3-hydrazinopyridazine (**5h**),[57] 6-hydrazino-*s*-triazolo[4,3-*b*]pyridazine (**5k**),[58] and 6-hydrazino-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (**5l**).[59]

1-Benzoylamino-2-propanone (3). To a mixture of hippuric acid (**1**) (17.92 g, 0.1 mol) and phosphorus oxychloride (22.9 mL, 0.25 mol) stirred on ice, *N*,*N*-dimethylacetamide (23.1 mL, 0.25 mol) was added dropwise. The mixture was then stirred at 40–45°C for 2 h. The volatile components were evaporated *in vacuo* and the oily residue was poured onto crushed ice (70 g). The precipitate was collected by filtration, washed with cold water and dried at rt. The dried product (**2**) was dissolved in methanol (700 mL), hydrochloric acid (36%, 130 mL) was added, and the mixture was heated under reflux for 4 h. The solvent was evaporated *in vacuo*, water was added and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo*. Ether was added to the oily residue and the precipitate was collected by filtration to give **3** (10.283 g, 58%); mp 78–81°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (3H, s, Me), 4.36 (2H, d, $J_{CH2–NH}$ = 4.1 Hz, CH_2NH), 6.93 (1H, br s, CH_2NH), 7.42–7.55 (3H, m, Ph), 7.80–7.85 (2H, m, Ph). *Anal*. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.76; H, 6.45; N, 7.76.

(*Z*)-3-Benzoylamino-4-dimethylamino-2-oxo-3-butene (4). A mixture of 1-benzoylamino-2-propanone (**3**) (0.709 g, 4 mmol), *N*,*N*-dimethylformamide dimethyl acetal (1.07 mL, 8 mmol), and dry toluene (4 mL) was heated under reflux for 45 minutes. The volatile components were evaporated *in vacuo*, water was added and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo*, the residue was triturated with ethyl acetate, and the precipitate was collected by filtration to give **4** (0.686 g, 74%); mp 120–122°C (from ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00 (3H, s, Me), 3.00 (6H, s, NMe_2), 7.42 (1H, s, CH), 7.45–7.58 (3H, m, Ph), 7.88–7.93 (2H, m, Ph), 9.05 (1H, br s, NHCO). *Anal*. Calcd for $C_{13}H_{16}N_2O_2 \times \cdot H_2O$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.63; H, 7.49; N, 11.52.

General Procedure for the Preparation of 1-Substituted 4-Benzoylamino-5-methyl-1*H*-pyrazoles (8a-l):

A mixture of a hydrazine (**5**) (1 mmol), (*Z*)-3-benzoylamino-4-dimethylamino-2-oxo-3-butene (**4**) (232 mg, 1 mmol), ethanol (5 mL), and catalytic amount of hydrochloric acid (36%, 5 drops) was stirred at rt for several hours. The reaction was followed by TLC (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 5:1 as solvent). The following compounds were prepared in this manner:

4-Benzoylamino-5-methyl-1*H*-pyrazole (8a). This compound was prepared from hydrazine hydrate (**5a**) (100%, 0.05 mL, 50 mg, 1 mmol), stirred for 4 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ether and ethanol, and the precipitate was collected by filtration to give **8a** (120 mg, 60% yield); mp 196–199°C (from methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18 (3H, s, Me), 7.05 (1H, br s, H_3), 7.46–7.59 (3H, m, Ph), 7.92–7.97 (2H, m, Ph), 9.66 (1H, s, NHCO), 12.38 (1H, br s, NH). *Anal*. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.40; H, 5.39; N, 21.04.

4-Benzoylamino-1-(3-hydroxybenzyl)-5-methyl-1*H*-pyrazole (8b). This compound was prepared from 3-hydroxybenzylhydrazine dihydrochloride (**5b**) (211 mg, 1 mmol), stirred for 8 h. Volatile components were evaporated *in vacuo*, the residue was triturated with water, and the precipitate was collected by filtration to give **8b** (201 mg, 65%); mp 198–201°C (from ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.14 (3H, s, Me), 5.21 (2H, s, CH_2), 6.51–6.67 (3H, m, Ar), 7.12 (1H, t, J = 7.8 Hz, Ar), 7.46–7.56 (3H, m, Ph), 7.59 (1H, s, H_3), 7.92–7.95 (2H, m, Ph), 9.40 (1H, s, NHCO), 9.69 (1H, br s, OH). *Anal*. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.57; N, 13.67. Found: C, 70.35; H, 5.57; N, 13.99.

4-Benzoylamino-5-methyl-1-phenyl-1*H*-pyrazole (8c). This compound was prepared from phenylhydrazine (**5c**) (108 mg, 1 mmol), stirred for 4 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ether, and the precipitate was collected by filtration to give **8c** (109 mg, 39%); mp 170–173°C (from ether and ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (3H, s, Me), 7.40–7.62 (8H, m, Ph), 7.82 (1H, s, H_3), 7.96–8.00 (2H, m, Ph), 9.86 (1H, br s, NHCO). *Anal*. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.43; H, 5.25; N, 15.26.

4-Benzoylamino-5-methyl-1-(4-nitrophenyl)-1*H*-pyrazole (8d). This compound was prepared from 4-nitrophenylhydrazine (**5d**) (153 mg, 1 mmol), stirred for 1 h. The precipitate was, after cooling, collected by filtration to give **8d** (273 mg, 85%); mp 252–254°C (from ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.42 (3H, s, Me), 7.50–7.64 (3H, m, Ph), 7.91 (2H, d, J = 9.0 Hz, Ar), 7.95–8.02 (3H, m, Ph, H_3), 8.39 (2H, d, J = 9.0 Hz, Ar), 9.95 (1H, br s, NHCO). *Anal*. Calcd for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.35; H, 4.33; N, 17.19.

4-Benzoylamino-1-(4-carboxyphenyl)-5-methyl-1*H*-pyrazole (8e). This compound was prepared from 4-carboxyphenylhydrazine (**5e**) (152 mg, 1 mmol), stirred for 1.5 h. The precipitate was, after cooling, collected by filtration to give **8e** (100 mg, 31%); mp 248–251°C (from ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.37 (3H, s, Me), 7.50–7.63 (3H, m, Ph), 7.72 (2H, d, *J* = 9.0 Hz, Ar), 7.91 (1H, s, H_3), 7.97–8.01 (2H, m, Ph), 8.10 (2H, d, *J* = 9.0 Hz, Ar), 9.90 (1H, s, NHCO), 13.05 (1H, br s, OH). *Anal*. Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.38; H, 4.86; N, 13.10.

4-Benzoylamino-5-methyl-1-(pyridin-2-yl)-1*H*-pyrazole (8f). This compound was prepared from 2-hydrazinopyridine (**5f**) (109 mg, 1 mmol), stirred for 2 h. Volatile components were evaporated *in vacuo*, the residue was triturated with water, and the precipitate was collected by filtration to give **8f** (172 mg, 62%); mp 168–171°C (from ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.57 (3H, s, Me), 7.38 (1H, ddd, *J* = 1.1, 4.9, 7.3 Hz, $H_{5'}$), 7.50–7.63 (3H, m, Ph), 7.87 (1H, ddd, *J* = 0.9, 1.1, 8.4 Hz, $H_{3'}$), 7.89 (1H, s, H_3), 7.96–8.00 (2H, m, Ph), 8.02 (1H, ddd, *J* = 1.9, 7.3, 8.4 Hz, $H_{4'}$), 8.50 (1H, ddd, *J* = 0.9, 1.9, 4.9 Hz, $H_{6'}$), 9.87 (1H, br s, NHCO). *Anal*. Calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.86; H, 5.03; N, 20.07.

4-Benzoylamino-5-methyl-1-(6-methylpyridazin-3-yl)-1*H*-pyrazole (8g). This compound was prepared from 3-hydrazino-6-methylpyridazine (**5g**) (124 mg, 1 mmol), stirred for 3 h. The precipitate was, after cooling, collected by filtration to give **8g** (182 mg, 62%); mp 165–168°C (radial chromatography (Silica gel 60), eluent chloroform/methanol; 5:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.59 (3H, s, Me), 2.67 (3H, s, Me), 7.51–7.64 (3H, m, Ph), 7.79 (1H, d, *J* = 9.0 Hz, $H_{5'}$), 7.96–8.01 (3H, m, Ph, H_3), 8.05 (1H, d, *J* = 9.0 Hz, $H_{4'}$), 9.95 (1H, s, NHCO). *Anal*. Calcd for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.15; N, 23.87. Found: C, 65.70; H, 5.41; N, 23.82.

4-Benzoylamino-1-(6-chloropyridazin-3-yl)-5-methyl-1*H*-pyrazole (8h). This compound was prepared from 6-chloro-3-hydrazinopyridazine (**5h**) (145 mg, 1 mmol), stirred for 0.5 h. The precipitate was, after cooling, collected by filtration to give **8h** (241 mg, 77%); mp 195–197°C (from ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.61 (3H, s, Me), 7.51–7.65 (3H, m, Ph), 7.96–8.02 (2H, m, Ph), 8.06 (1H, s, H_3), 8.07 (1H, d, *J* = 9.4 Hz, $H_{4'}$), 8.25 (1H, d, *J* = 9.4 Hz, $H_{5'}$), 10.01 (1H, br s, NHCO). *Anal*. Calcd for $C_{15}H_{12}N_5OCl$: C, 57.42; H, 3.85; N, 22.32. Found: C, 57.43; H, 3.63; N, 22.33.

4-Benzoylamino-5-methyl-1-(6-phenylpyridazin-3-yl)-1*H*-pyrazole (8i). This compound was prepared from 3-hydrazino-6-phenylpyridazine (**5i**) (186 mg, 1 mmol), stirred for 0.5 h. The precipitate was, after cooling, collected by filtration to give **8i** (171 mg, 48%); mp 196–198°C (from ethanol). ^{1}H NMR (300

MHz, DMSO-d_6): δ 2.69 (3H, s, Me), 7.51–7.65 (6H, m, Ph), 7.99–8.04 (2H, m, Ph), 8.07 (1H, s, H_3), 8.19–8.23 (2H, m, Ph), 8.25 (1H, d, J = 9.4 Hz, $H_{5'}$), 8.46 (1H, d, J = 9.4 Hz, $H_{4'}$), 9.99 (1H, br s, NHCO). *Anal*. Calcd for $C_{21}H_{17}N_5O$: C, 70.97; H, 4.82; N, 19.70. Found: C, 71.02; H, 4.53; N, 19.67.

4-Benzoylamino-5-methyl-1-(pyrimidin-2-yl)-1*H*-pyrazole (8j). This compound was prepared from 2-hydrazinopyrimidine (**5j**) (110 mg, 1 mmol), stirred for 2 h. Volatile components were evaporated *in vacuo*, the residue was triturated with water, and the precipitate was collected by filtration to give **8j** (218 mg, 78%); mp 191–194°C (from ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.54 (3H, s, Me), 7.51 (1H, t, J = 4.9 Hz, $H_{5'}$), 7.50–7.63 (3H, m, Ph), 7.92 (1H, s, H_3), 7.97–8.01 (2H, m, Ph), 8.92 (2H, d, J = 4.9 Hz, $H_{4'}$, $H_{6'}$), 9.91 (1H, br s, NHCO). *Anal*. Calcd for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.69; N, 25.07. Found: C, 64.36; H, 4.52; N, 25.10.

4-Benzoylamino-5-methyl-1-(*s*-triazolo[4,3-*b*]pyridazin-6-yl)-1*H*-pyrazole (8k). This compound was prepared from 6-hydrazino-*s*-triazolo[4,3-*b*]pyridazine (**5k**) (150 mg, 1 mmol), stirred for 4 h. The precipitate was, after cooling, collected by filtration to give **8k** (226 mg, 71%); mp 244–246°C (from ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.64 (3H, s, Me), 7.51–7.65 (3H, m, Ph), 7.98 (1H, d, J = 10.2 Hz, $H_{7'}$), 7.97–8.02 (2H, m, Ph), 8.01 (1H, s, H_3), 8.50 (1H, dd, J = 1.1, 10.2 Hz, $H_{8'}$), 9.64 (1H, d, J = 1.1 Hz, $H_{3'}$), 10.02 (1H, br s, NHCO). *Anal*. Calcd for $C_{16}H_{13}N_7O$: C, 60.18; H, 4.10; N, 30.70. Found: C, 59.91; H, 3.99; N, 30.72.

4-Benzoylamino-5-methyl-1-(3-phenyl-*s*-triazolo[4,3-*b*]pyridazin-6-yl)-1*H*-pyrazole (8l). This compound was prepared from 6-hydrazino-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (**5l**) (226 mg, 1 mmol), stirred for 45 min. The precipitate was, after cooling, collected by filtration to give **8l** (151 mg, 38%); mp 244–245°C (from ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.66 (3H, s, Me), 7.51–7.68 (6H, m, Ph), 7.97–8.03 (2H, m, Ph), 8.04 (1H, d, J = 9.8 Hz, $H_{7'}$), 8.12 (1H, s, H_3), 8.31–8.36 (2H, m, Ph), 8.58 (1H, d, J = 9.8 Hz, $H_{8'}$), 10.03 (1H, br s, NHCO). *Anal*. Calcd for $C_{22}H_{17}N_7O$: C, 66.82; H, 4.33; N, 24.79. Found: C, 66.86; H, 4.34; N, 24.94.

General Procedure for the Preparation of 4-Substituted 3-Benzoylamino-2-oxo-3-butenes (11a–n):
A mixture of an amine (**10**) (1 mmol) and (*Z*)-3-benzoylamino-4-dimethylamino-2-oxo-3-butene (**4**) (232 mg, 1mmol) in acetic acid (2 mL) was stirred at rt for several hours. The reaction was followed by TLC (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 5:1, 15:1 and 25:1 as solvent). The following compounds were prepared in this manner:

(*Z*)-3-Benzoylamino-4-(4-methoxyphenyl)amino-2-oxo-3-butene (11a). This compound was prepared from 4-methoxyaniline (**10a**) (123 mg, 1 mmol), stirred for 48 h. Volatile components were evaporated *in*

vacuo, the residue was triturated with ethanol and water, and the precipitate was collected by filtration to give **11a** (196 mg, 63%); mp 73–76°C (from water and ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (3H, s, Me), 3.81 (3H, s, OMe), 6.90 (2H, d, *J* = 9.0 Hz, Ar), 7.04 (2H, d, *J* = 9.0 Hz, Ar), 7.45–7.59 (3H, m, Ph), 7.50 (1H, d, *J* = 12.1 Hz, *CH*NH), 7.89–7.93 (2H, m, Ph), 8.95 (1H, br s, NHCO), 9.69 (1H, d, *J* = 12.1 Hz, CH*NH*). *Anal*. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.40; H, 5.95; N, 9.23.

(*Z*)-3-Benzoylamino-4-(4-fluoro-3-chlorophenyl)amino-2-oxo-3-butene (11b). This compound was prepared from 4-fluoro-3-chloroaniline (**10b**) (146 mg, 1 mmol), stirred for 8 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **11b** in (240 mg, 72%); mp 163–166°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (3H, s, Me), 6.89–6.95 (1H, m, Ar), 7.08–7.15 (2H, m, Ar), 7.40 (1H, d, *J* = 11.7 Hz, *CH*NH), 7.47–7.61 (3H, m, Ph), 7.89–7.93 (2H, m, Ph), 8.98 (1H, br s, NHCO), 9.98 (1H, d, *J* = 11.7 Hz, CH*NH*). *Anal*. Calcd for $C_{17}H_{14}N_2O_2FCl$: C, 61.36; H, 4.24; N, 8.42. Found: C, 61.22; H, 4.31; N, 8.17.

(*Z*)-3-Benzoylamino-4-phenylamino-2-oxo-3-butene (11c). This compound was prepared from aniline (**10c**) (93 mg, 1 mmol), stirred for 24 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **11c** (224 mg, 80%); mp 155–159°C (from ethanol and toluene). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (3H, s, Me), 7.02–7.10 (3H, m, Ph), 7.31–7.38 (2H, m, Ph), 7.46–7.59 (3H, m, Ph), 7.58 (1H, d, *J* = 12.1 Hz, *CH*NH), 7.90–7.94 (2H, m, Ph), 8.95 (1H, br s, NHCO), 9.85 (1H, d, *J* = 12.1 Hz, CH*NH*). *Anal*. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.20; H, 5.79; N, 10.08.

(*Z*)-3-Benzoylamino-4-(3-bromophenyl)amino-2-oxo-3-butene (11d). This compound was prepared from 3-bromoaniline (**10d**) (172 mg, 1 mmol), stirred for 5 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **11d** (169 mg, 47%); mp 145–147°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (3H, s, Me), 6.99 (1H, ddd, *J* = 1.9, 1.9, 7.2 Hz, Ar), 7.16 (1H, ddd, *J* = 1.9, 1.9, 7.9 Hz, Ar), 7.17–7.23 (2H, m, Ar), 7.48 (1H, d, *J* = 11.2 Hz, *CH*NH), 7.46–7.60 (3H, m, Ph), 7.89–7.93 (2H, m, Ph), 8.97 (1H, br s, NHCO), 10.01 (1H, d, *J* = 11.2 Hz, CH*NH*). *Anal*. Calcd for $C_{17}H_{15}N_2O_2Br$: C, 56.84; H, 4.21; N, 7.80. Found: C, 57.07; H, 4.13; N, 7.63.

(*Z*)-3-Benzoylamino-4-(2-methylphenyl)amino-2-oxo-3-butene (11e). This compound was prepared from 2-methylaniline (**10e**) (107 mg, 1 mmol), stirred for 24 h. Volatile components were evaporated *in vacuo*, the residue was triturated with water and ethanol, and the precipitate was collected by filtration to

give **11e** (256 mg, 87%); mp 108–110°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (3H, s, 2-Me), 2.44 (3H, s, Me), 6.99 (1H, ddd, *J* = 1.1, 7.4, 7.4 Hz, Ar), 7.06 (1H, br d, *J* = 1.1 Hz, Ar), 7.17–7.24 (2H, m, Ar), 7.45–7.58 (3H, m, Ph), 7.59 (1H, d, *J* = 11.7 Hz, *CH*NH), 7.90–7.94 (2H, m, Ph), 8.94 (1H, br s, NHCO), 9.80 (1H, d, *J* = 11.7 Hz, CH*NH*). *Anal*. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.32; H, 6.11; N, 9.46.

(*Z*)-3-Benzoylamino-4-(3-nitrophenyl)amino-2-oxo-3-butene (11f). This compound was prepared from 3-nitroaniline (**10f**) (138 mg, 1 mmol), heated under reflux for 45 min. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **11f** (198 mg, 61%); mp 177–179°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (3H, s, Me), 7.36 (1H, ddd, *J* = 1.1, 2.2, 8.2 Hz, Ar), 7.46–7.62 (5H, m, Ph, Ar, *CH*NH), 7.85–7.96 (4H, m, Ph, Ar), 9.03 (1H, br s, NHCO), 10.36 (1H, d, *J* = 10.9 Hz, CH*NH*). *Anal*. Calcd for $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.80; H, 4.73; N, 12.62.

(*Z*)-3-Benzoylamino-4-(5-chloropyridin-2-yl)amino-2-oxo-3-butene (11g). This compound was prepared from 2-amino-5-chloropyridine (**10g**) (129 mg, 1 mmol), stirred for 24 h. The precipitate was collected by filtration to give **11g** (275 mg, 87%); mp 175–178°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (3H, s, Me), 6.81 (1H, dd, *J* = 0.7, 8.6 Hz, $H_{3'}$), 7.46–7.61 (3H, m, Ph), 7.55 (1H, dd, *J* = 2.6, 8.6 Hz, $H_{4'}$), 7.89–7.94 (2H, m, Ph), 8.23 (1H, dd, *J* = 0.7, 2.6 Hz, $H_{6'}$), 8.34 (1H, d, *J* = 10.5 Hz, *CH*NH), 9.05 (1H, br s, NHCO), 10.59 (1H, d, *J* = 10.5 Hz, CH*NH*). *Anal*. Calcd for $C_{16}H_{14}N_3O_2Cl$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.88; H, 4.50; N, 13.38.

(*Z*)-3-Benzoylamino-4-(4-methylpyridin-2-yl)amino-2-oxo-3-butene (11h). This compound was prepared from 2-amino-4-methylpyridine (**10h**) (108 mg, 1 mmol), stirred for 48 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol and water, and the precipitate was collected by filtration to give **11h** (80 mg, 27%); mp 170–173°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (3H, s, 4-Me), 2.50 (3H, s, Me), 6.68–6.76 (2H, m, $H_{3'}$, $H_{5'}$), 7.46–7.60 (3H, m, Ph), 7.90–7.95 (2H, m, Ph), 8.14 (1H, d, *J* = 5.3 Hz, $H_{6'}$), 8.44 (1H, d, *J* = 11.7 Hz, *CH*NH), 9.03 (1H, br s, NHCO), 10.35 (1H, d, *J* = 11.7 Hz, CH*NH*). *Anal*. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.39; H, 5.81; N, 14.32.

(*Z*)-3-Benzoylamino-4-(pyridin-2-yl)amino-2-oxo-3-butene (11i). This compound was prepared from 2-aminopyridine (**10i**) (94 mg, 1 mmol), stirred for 48 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol and water, and the precipitate was collected by filtration to give

11i (76 mg, 27%); mp 161–163°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (3H, s, Me), 6.85 (1H, ddd, *J* = 0.8, 1.0, 8.2 Hz, $H_{3'}$), 6.91 (1H, ddd, *J* = 1.0, 5.0, 7.3 Hz, $H_{5'}$), 7.46–7.57 (3H, m, Ph), 7.59 (1H, ddd, *J* = 2.0, 7.3, 8.2 Hz, $H_{4'}$), 7.90–7.95 (2H, m, Ph), 8.29 (1H, ddd, *J* = 0.8, 2.0, 5.0 Hz, $H_{6'}$), 8.45 (1H, d, *J* = 10.9 Hz, *CH*NH), 9.03 (1H, br s, NHCO), 10.42 (1H, d, *J* = 10.9 Hz, CH*NH*). *Anal*. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.46; H, 5.36; N, 14.82.

(*Z*)-3-Benzoylamino-4-(3-hydroxypyridin-2-yl)amino-2-oxo-3-butene (11j). This compound was prepared from 2-amino-3-hydroxypyridine (**10j**) (110 mg, 1 mmol), stirred for 24 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **11j** (74 mg, 25%); mp 222–224°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (3H, s, Me), 6.75 (1H, dd, *J* = 4.9, 7.5 Hz, $H_{5'}$), 6.96 (1H, dd, *J* = 1.5, 7.5 Hz, $H_{4'}$), 7.45–7.60 (3H, m, Ph), 7.84 (1H, dd, *J* = 1.5, 4.9 Hz, $H_{6'}$), 7.92–7.96 (2H, m, Ph), 8.49 (1H, d, *J* = 12.0 Hz, *CH*NH), 9.02 (1H, br s, NHCO), 10.22 (1H, d, *J* = 12.0 Hz, CH*NH*). *Anal*. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.06; N, 14.13. Found: C, 65.01; H, 5.18; N, 14.26.

(*Z*)-3-Benzoylamino-4-(5-nitropyridin-2-yl)amino-2-oxo-3-butene (11k). This compound was prepared from 2-amino-5-nitropyridine (**10k**) (139 mg, 1 mmol), stirred for 24 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **11k** (114 mg, 35%); mp 205–208°C (from ethanol and toluene). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (3H, s, Me), 6.88 (1H, d, *J* = 9.0 Hz, $H_{3'}$), 7.49–7.63 (3H, m, Ph), 7.90–7.95 (2H, m, Ph), 8.36 (1H, dd, *J* = 2.6, 9.0 Hz, $H_{4'}$), 8.37 (1H, d, *J* = 10.9 Hz, *CH*NH), 9.14 (1H, br s, NHCO), 9.17 (1H, d, *J* = 2.6 Hz, $H_{6'}$), 11.42 (1H, d, *J* = 10.9 Hz, CH*NH*). *Anal*. Calcd for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.97; H, 4.29; N, 17.22.

(*Z*) 3-Benzoylamino-4-(pyrimidin-2-yl)amino-2-oxo-3-butene (11l). This compound was prepared from 2-aminopyrimidine (**10l**) (95 mg, 1 mmol), stirred for 48 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **11l** (116 mg, 41%); mp 168–170°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (3H, s, Me), 6.88 (1H, t, *J* = 4.9 Hz, $H_{5'}$), 7.46–7.59 (3H, m, Ph), 7.93–7.98 (2H, m, Ph), 8.31 (1H, d, *J* = 11.3 Hz, *CH*NH), 8.50 (2H, d, *J* = 4.9 Hz, $H_{4'}$, $H_{6'}$), 8.94 (1H, br s, NHCO), 10.52 (1H, d, *J* = 11.3 Hz, CH*NH*). *Anal*. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.79; H, 4.93; N, 19.78.

(*Z*)-3-Benzoylamino-4-(4,6-dimethylpyrimidin-2-yl)amino-2-oxo-3-butene (11m). This compound was prepared from 2-amino-4,6-dimethylpyrimidine (**10m**) (123 mg, 1 mmol), stirred for 48 h. Volatile

components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **11m** (124 mg, 40%); mp 178–180°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (6H, s, 2 × Me), 2.51 (3H, s, Me), 6.63 (1H, s, $H_{5'}$), 7.45–7.59 (3H, m, Ph), 7.92–7.97 (2H, m, Ph), 8.39 (1H, d, *J* = 11.3 Hz, *CH*NH), 8.87 (1H, br s, NHCO), 10.09 (1H, d, *J* = 11.3 Hz, CH*NH*). *Anal*. Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.84; N, 18.05. Found: C, 65.76; H, 5.88; N, 17.91.

(*Z*)-3-Benzoylamino-4-(pyrazin-2-yl)amino-2-oxo-3-butene (11n). This compound was prepared from 2-aminopyrazine (**10n**) (95 mg, 1 mmol), stirred for 48 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **11n** (175 mg, 62%); mp 159–161°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (3H, s, Me), 7.48–7.62 (3H, m, Ph), 7.91–7.96 (2H, m, Ph), 8.15 (1H, d, *J* = 2.6 Hz, $H_{6'}$), 8.20 (1H, dd, *J* = 1.5, 2.6 Hz, $H_{5'}$), 8.29 (1H, d, *J* = 10.9 Hz, *CH*NH), 8.30 (1H, d, *J* = 1.5 Hz, $H_{3'}$), 9.08 (1H, br s, NHCO), 10.84 (1H, d, *J* = 10.9 Hz, CH*NH*). *Anal*. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.67; H, 4.94; N, 19.89.

3-Benzoylamino-4-(6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-oxo-3-butene Dimethylamine (13). A mixture of 1,3-dimethylbarbituric acid (**12**) (156 mg, 1 mmol) and (*Z*)-3-benzoylamino-4-dimethylamino-2-oxo-3-butene (**4**) (232 mg, 1 mmol) in acetic acid (2 mL) was stirred at rt for 24 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ether and ethanol, and the precipitate was collected by filtration to give **13** (346 mg, 89%); mp 164–168°C (from ethyl acetate and ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (3H, s, Me), 2.77 (6H, s, NMe_2), 3.31 (6H, s, 2 × NMe), 6.97 (1H, s, CH), 7.43–7.57 (3H, m, Ph), 8.01–8.06 (2H, m, Ph), 11.64 (1H, br s, NHCO). *Anal*. Calcd for $C_{17}H_{17}N_3O_5$ ×·$NHMe_2$: C, 58.75; H, 6.23; N, 14.42. Found: C, 58.78; H, 6.27; N, 14.44.

3-Benzoylamino-4-(6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl-)-2-oxo-3-butene (13a). To the 3-benzoylamino-4-(6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidinyl-5)-2-oxo-3-butene dimethylamine (**13**) (388 mg, 1 mmol) hydrochloric acid (2%, 10 mL) was added and stirred at rt for 15 min and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo* to give **13a** (295 mg, 86%); mp 127–130°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 (3H, s, Me), 3.38 (6H, s, 2 × NMe), 7.48–7.65 (4H, m, Ph, OH), 8.09–8.15 (2H, m, Ph), 8.54 (1H, s, CH) 14.09 (1H, br s, NHCO). *Anal*. Calcd for $C_{17}H_{17}N_3O_5$: C, 59.47; H, 4.99; N, 12.24. Found: C, 59.28; H, 4.96; N, 11.93.

6-Benzoylamino-1,3,7-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine (14). To the 3-benzoylamino-4-(6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-oxo-3-butene

dimethylamine (**13a**) (388 mg, 1 mmol) in ethanol (4 mL) aqueus ammonia (25%, 2 mL) was added and the mixture was stirred at rt for 3 days. The precipitate was collected by filtration to give **14** (48 mg, 15% yield; mp 225–226°C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64 (3H, s, Me), 3.43 (3H, s, NMe), 3.47 (3H, s, NMe), 7.50–7.59 (3H, m, Ph), 8.05–8.09 (2H, m, Ph), 8.43 (1H, s, H_5), 14.04 (1H, br s, NHCO). *Anal*. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.94; H, 4.87; N, 17.00.

ACKNOWLEDGEMENTS

The financial support from the Ministry of Education, Science and Sport, Slovenia, through grant PS-0502-0103, is gratefully acknowledged.

The crystallographic data were collected on the Kappa CCD Nonius diffractometer in the Laboratory of Inorganic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia. We acknowledge with thanks the financial contribution of the Ministry of Education, Science and Sport, Republic of Slovenia through grant Packet X-2000 and PS-511-103, which thus made the purchase of the apparatus possible.

REFERENCES

1. For a recent review see: J. Elguero, "*Pyrazoles"* in "*Comprehensive Heterocyclic Chemistry II"*, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Vol. 3, Elsevier Science Ltd., Oxford, 1996, pp. 1–75.
2. G. Varvounis, Y. Fiamegos and G. Pilidis, *Adv. Heterocycl. Chem*. 2001, **80**, 73.
3. A. M. Costero, *Adv. Heterocycl. Chem*. 1993, **58**, 171.
4. R. M. Claramunt and J. Elguero, *Org. Prep. Proc. Int*., 1991, **23**, 275.
5. B. Stanovnik and J. Svete, "*Pyrazoles"* in "*Science of Synthesis, Houben-Weyl Methods of Organic Transformations*", Vol. 12, Georg Thieme Verlag, Stuttgart, 2002, pp. 15–225.
6. J. D. Kendall, Brit. Pat. 650.911, 1951 (*Chem. Abstr*., 1952, **46**, 144g).
7. R. J. I. Eubanks and L. K. Johnson, US. Pat. US 4.835.285, 1989 (*Chem. Abstr*., 1989, **111**, 194757).
8. A. Kamitakahara and K. Ogi, US. Pat. US 4.840.879, 1989 (*Chem. Abstr*., 1989, **111**, 222036).
9. Y. Abe, S. Osanai, and H. Tenmyo, *Yukagaku* 1978, **27**, 230 (*Chem. Abstr*., 1978, **89**, 191670).
10. S. R. Challand, F. C. Copp, C. V. Denyer, K. E. Eakins, J. M. G. Walker, N. Whittaker, and A.G. Caldwell, Eur. Pat. Appl. 22.578, 1981 (*Chem. Abstr*., 1981, **95**, 62193).

11. Y. Ling, W. Li, W. Liu, and Y. Pei, *Yiyao Gongye* 1986, **17**, 66 (*Chem. Abstr*., 1986, **105**, 172347).
12. J. Frigola, A. Colombo, J. Parés, L. Martinéz, R. Sagarra, and R. Roser, *Eur. J. Med. Chem*., 1989, **24**, 435.
13. D. Riendeau, J. P. Falgueyret, D. J. Nathaniel, J. Rokach, N. Ueda, and S. Yamamoto, *Biochem. Pharmacol*., 1989, **38**, 2313.
14. L. A. Marshall, J. Y. Chang, W. Calhoun, J. Yu, and R. P. Carlson, *J. Cell Biochem*., 1989, **40**, 147.
15. J. Elguero, "*Pyrazoles and Their Benzo Derivative"* in "*Comprehensive Heterocyclic Chemistry"*, ed. by A. R. Katritzky, C. W. Rees, Vol. 5, Pergamon Press Ltd., Oxford, 1984, pp. 167–303.
16. R. Fusco, "*Pyrazoles"* in "*Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings"*, ed. by R. H. Wiley, John Wiley Interscience, New York, 1967, pp. 1–174.
17. R. H. Wiley and P. Wiley, "*Pyrazolones, Pyrazolidones and Derivatives*" in "*The Chemistry of Heterocyclic Compounds*", Wiley-Interscience, New York 1964, pp. 3–110.
18. J. Drummond, G. Johnson, D. G. Nickell, D. F. Ortwine, R. F. Bruns, and B. Welbaum, *J. Med. Chem*., 1989, **32**, 2116.
19. U. Bratušek, A. Hvala, and B. Stanovnik, *J. Heterocycl. Chem*., 1998, **35**, 1281.
20. S. Zupančič, J. Svete, and B. Stanovnik, *J. Heterocycl. Chem*., 1999, **36**, 607.
21. A. Prešeren, J. Svete, and B. Stanovnik, *J. Heterocycl. Chem*., 1999, **36**, 799.
22. J. Svete, B. Stanovnik, *Heterocycles*, 1999, **51**, 2073.
23. C. Turk, J. Svete, B. Stanovnik, L. Golič, A. Golobič, and L. Selič, *Org. Lett*., 2000, **2**, 423.
24. C. Turk, L. Golič, L. Selič, J. Svete, and B. Stanovnik, *ARKIVOC*, 2001 (V), 87.
25. C. Turk, J. Svete, B. Stanovnik, L. Golič, S. Golič Grdadolnik, A. Golobič, and L. Selič, *Helv. Chim. Acta*, 2001, **84**, 146.
26. A. N. Bowler, P. M. Doyle, and D. W. Young, *J. Chem. Soc*., *Chem. Commun*., 1991, 314.
27. A. Dinsmore, P. M. Doyle, and D. W. Young, *Tetrahedron Lett*., 1995, **36**, 7503.
28. A. N. Bowler, A. Dinsmore, P. M. Doyle, and D. W. Young, *J. Chem. Soc*., *Perkin Trans. 1*, 1997, 1297.
29. M. Škof, J. Svete, and B. Stanovnik, *Heterocycles*, 1999, **51**, 1051.
30. M. Škof, J. Svete, and B. Stanovnik, *Heterocycles*, 2000, **52**, 845.
31. M. Škof, J. Svete, and B. Stanovnik, *J. Heterocycl. Chem.*, 2000, **37**, 703.
32. M. Škof, J. Svete, B. Stanovnik, L. Golič, S. Golič Grdadolnik, and L. Selič, *Helv. Chim. Acta*, 1998, **81**, 2332.
33. M. Škof, J. Svete, M. Kmetič, B. Stanovnik, and S. Golič Grdadolnik, *Eur. J. Org. Chem.*, 1999, 1581.
34. M. Škof, J. Svete, and B. Stanovnik, *Heterocycles*, 2000, **53**, 339.
35. J. C. Martins, R. Willem, and M. Biesemans, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1513.

36. N. Matsumori, D. Kaneno, M. Murata, H. Nakamura, and K. Tachibana, *J. Org. Chem*., 1999, **64**, 866.
37. A. Nagatsu, R. Tanaka, H. Mizukami, Y. Ogihara, and J. Sakakibara, *Tetrahedron*, 2001, **57**, 3369.
38. M. Kurz, P. Schmieder, and H. Kessler, *Angew. Chem., Int. Ed. Engl*., 1991, **30**, 1329.
39. U. Wollborn, W. Willker, and D. Leibfritz, *J. Magn. Reson., Ser. A*, 1993, **103**, 86.
40. W. Kozminski, *J. Magn. Reson*., 1999, **137**, 408.
41. A. Bax and R. Freeman, *J. Am. Chem. Soc*., 1982, **104**, 1099.
42. K. Furihata and H. Seto, *Tetrahedron Lett*., 1999, **40**, 6271.
43. H. Seki, T. Tokunaga, H. Utsumi, and K. Yamaguchi, *Tetrahedron*, 2000, **56**, 2935.
44. W. Willker and D. Leibfritz, *Magn. Reson. Chem*., 1995, **33**, 632.
45. P. Fischer, E. Schweizer, J. Langner, and U. Schmidt, *Magn. Reson. Chem*., 1994, **32**, 567.
46. K. Ding, *Magn. Reson. Chem*., 2000, **38**, 321.
47. S. Golič Grdadolnik and B. Stanovnik, *Magn. Reson. Chem*., 1997, **35**, 482.
48. T. Ando, N. Koseki, R. F. Toia, and J. E. Casida, *Magn. Reson. Chem*., 1993, **31**, 90.
49. J. J. Titman, J. Foote, J. Jarvis, J. Keeler, and D. Neuhaus, *J. Chem. Soc., Chem. Commun*., 1991, 419.
50. For a review see: B. L. Marquez, W. H. Gerwick, and R. T. Williamson, *Magn. Reson. Chem*., 2001, **39**, 499.
51. R. Jakše, S. Rečnik, J. Svete, A. Golobič, L. Golič, and B. Stanovnik, *Tetrahedron*, 2001, **57**, 8395.
52. D. Bevk, M. Kmetič, S. Rečnik, J. Svete, L. Golič, A. Golobič, and B. Stanovnik, *Chemistry of Heterocyclic Compounds*, 2001, 1651.
53. A. Altomare, M. C. Burla, M. Camalli, G. Dascarano, C. Giacovazzo, A. Guagliardi, and G. Polidori, *J. Appl. Cryst*., 1994, **27**, 435.
54. A. C. Larson, *Crystallographic Computing*, ed. by F. R. Ahmed, S. R. Hall and C. P. Huber, Copenhagen, Munksgaard, 1970, p. 291.
55. S. R. Hall, G. S. D. King, and J. M. Stewart, *The Xtal3.4 User's Manual*, University of Western Australia, Lamb, Perth, 1995.
56. C. K. Johnson, *ORTEPII*, Report ORNL-5138, Oak Ridge National Laboratory, Tennessee, USA, 1976.
57. British Patent 711,756 (*Chem. Abstr*., 1955, **49**, 11724).
58. N. Takahayashi, *J. Pharm. Soc. Japan*, 1956, **76**, 765 (*Chem. Abstr*., 1957, **51**, 1192).
59. A. Pollak and M. Tišler, *Tetrahedron*, 1966, **22**, 2073.