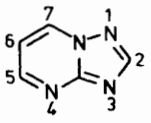
Generation of [1,2,4]Triazolo[1,5-*a*]pyrimidine *N*-Ylides and Their Ring Transformation Reactions

Mikio Hori,* Kiyomi Tanaka, Tadashi Kataoka, Hiroshi Shimizu, and Eiji Imai
Gifu Pharmaceutical University, 6-1, Mitahora-higashi 5-chome, Gifu 502, Japan
Kazuhiko Kimura and Yoshinobu Hashimoto
Kaken Pharmaceutical Co., Ltd., 2-28-8, Honkomagome, Bukyo-ku, Tokyo 113, Japan

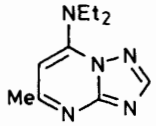
[1,2,4]Triazolo[1,5-*a*]pyrimidine (**1**) has been alkylated at the *N*(3)-position by treatment with alkyl halides in refluxing dry acetone. The ylides (**3**) were generated *in situ* from the iminium salts (**2**) and 1 equiv. of triethylamine. Thermolysis of the ylides (**3**) in dry acetonitrile gave the 2-cyanamidopyrimidines (**4**). The *N*(3)-phenylacyliminium salt (**2e**) when treated with 2 equiv. of triethylamine gave 2-(2-imino-5-phenyl-2,3-dihydro-oxazol-3-yl)pyrimidine (**5**) in 64.4% yield. The latter on hydrolysis gave the oxazolone (**7**), and on treatment with nucleophiles such as alcohols or amines under acidic conditions afforded the ring transposition products imidazol-2-ylpyrimidines (**8**) or (**9**), respectively. The reaction mechanism for the novel thermolysis of the ylides is discussed.

[1,2,4]Triazolo[1,5-*a*]pyrimidine, a nitrogen-positional isomer of adenine and guanine, would be expected to exhibit novel reactions as a result of the bridgehead nitrogen. This, together with the fact that 7-diethylamino-5-methyl[1,2,4]triazolo-[1,5-*a*]pyrimidine (Trapidil) is known as a useful antianginal drug, makes the skeleton of both chemical and medicinal interest.

This paper describes the thermal reactions of 5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidinio-3-methylides and ring transformation reactions of the products.[1]

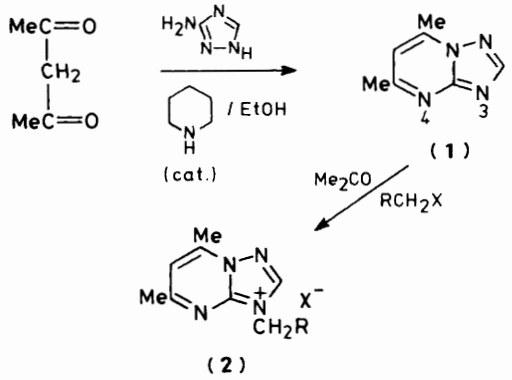


[1,2,4]Triazolo[1,5-*a*]pyrimidine



Trapidil

Synthesis of 3-Alkyl-5,7-dimethyl[1,2,4]*triazolo*[1,5-a]*pyrimidinium Salts* (**2**).—5,7-Dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine (**1**) which is a precursor of the iminium salts (**2**) was synthesized by Bülow's method.[2] Alkylation was carried out by heating the alkyl halides and (**1**) in refluxing dry acetone (Scheme 1) to afford the iminium salts (**2**) in 50—80% yield



Scheme 1.

Table 1. *N*(3)-Alkyl-5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidinium Salts

Compd.	R	X	Yield (%)	M.p. (°C)
(**2b**)	Me	I	82.3	237.5—238.5
(**2c**)	CN	Br	52.0	229
(**2d**)	CO_2Me	Br	50.2	oil
(**2e**)	COPh	Br	70.0	226
(**2f**)	COC_6H_4Br-*p*	Br	85.4	227.5

[a] Compound (**2a**) is a known compound.[3]

Table 2. ^{1}H N.m.r. chemical shifts of (**1**) and (**2e**) ($CDCl_3$, δ)

	(**1**)	(**2e**)	Δ(δ) = (**2e**—**1**)
2-H	8.43	10.13	1.70
5-Me	2.68	2.75	0.07
6-H	6.88	7.75	0.87
7-Me	2.83	3.00	0.17

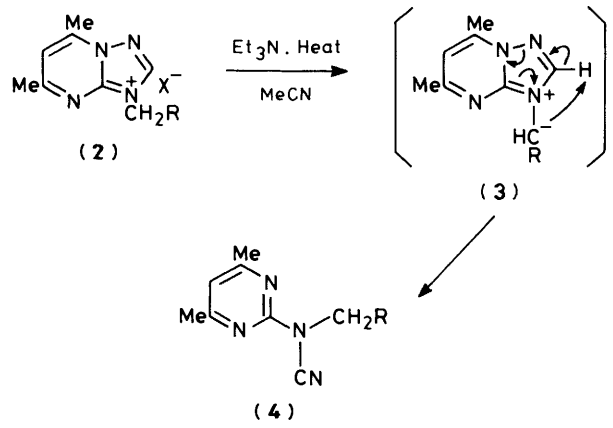
(Table 1). The iminium salts (**2c**—**f**) were prepared in order to produce the ylides stabilized by electron-withdrawing groups.

The alkylation of [1,2,4]triazolo[1,5-*a*]pyrimidine has already been investigated by two groups. Makisumi[3] has reported that a mixture of *N*(3)- and *N*(4)-alkylated products was obtained by the reaction of 7-hydroxy-5-methyl[1,2,4]-triazolo[1,5-*a*]pyrimidine with alkyl iodides in pyridine, while Paudler *et al.*[4] have reported that only an *N*(3)-methylated product was formed by the reaction of [1,2,4]triazolo[1,5-*a*]-pyrimidine with methyl iodide in dry acetone. Considering these facts, we expected that the alkylation of (**1**) would occur at *N*(3). This assumption was confirmed by the n.m.r. spectrum of the iminium salt (**2e**) which showed marked downfield shifts for 2-H and 6-H, with no involvement of 7-Me substituent in *peri*-interaction as would occur after *N*(1)-alkylation (Table 2). These n.m.r. observations are consistent with those reported in the literature.[3,5] Other iminium salts exhibited similar n.m.r. signals (Experimental section).

Generation of Ylides and Their Degradation Reactions.—The iminium salts (**2**) were treated with triethylamine in dry acetonitrile at 0 °C to afford a red solution of the corresponding ylides (**3**) which were too unstable to be isolated. The red solution of the ylides (**3**), was, therefore, heated under reflux

Table 3. 2-Cyanamido-5,7-dimethylpyrimidine (**4**)

Compd.	R	Yield (%)	M.p. (°C)
(**4a**)	H	71.6	110
(**4b**)	Me	99.0	68.0—68.5
(**4c**)	CN	90.8	109—111
(**4d**)	CO_2Me	98.9	88—89
(**4e**)	COPh	35.0	152—154
(**4f**)	COC_6H_4Br-*p*	21.6	164—166



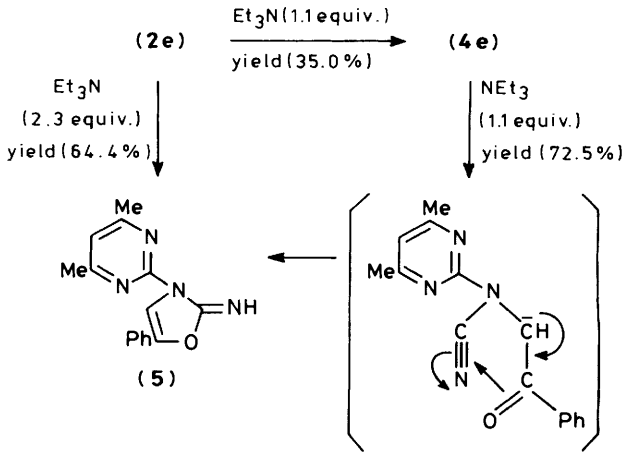
Scheme 2.

until the colour disappeared to yield 2-cyanamidopyrimidines (**4**) (Scheme 2).

In their i.r. spectra all the thermolysis products showed absorption at 2 240 cm^{-1} (C≡N) and in their n.m.r. spectra a singlet signal at δ 2.33—2.45 arising from the two pyrimidine methyl groups. Although Revankar *et al.*[5] reported the triazole ring cleavage of [1,2,4]-triazolo[1,5-*a*]pyrimidine in the glycosylation of 7-amino-5-chloro-*N*-trimethylsilyl[1,2,4]-triazolo[1,5-*a*]pyrimidine, no reaction mechanism was described. We therefore investigated the reaction mechanism for the above described thermal reaction. Since attempted thermolysis of the iminium salt (**2c**) in acetonitrile without base, gave none of the ring-opened product (**4c**), we followed by e.s.r. spectroscopy the thermal reaction of (**2c**) with 1.1 equiv. of triethylamine in acetonitrile. No radical was detected. Moreover, the ylide derived from the 2-methyltriazolopyrimidinium salt (**6**) which has no 2-H failed to undergo triazole ring cleavage under similar conditions.

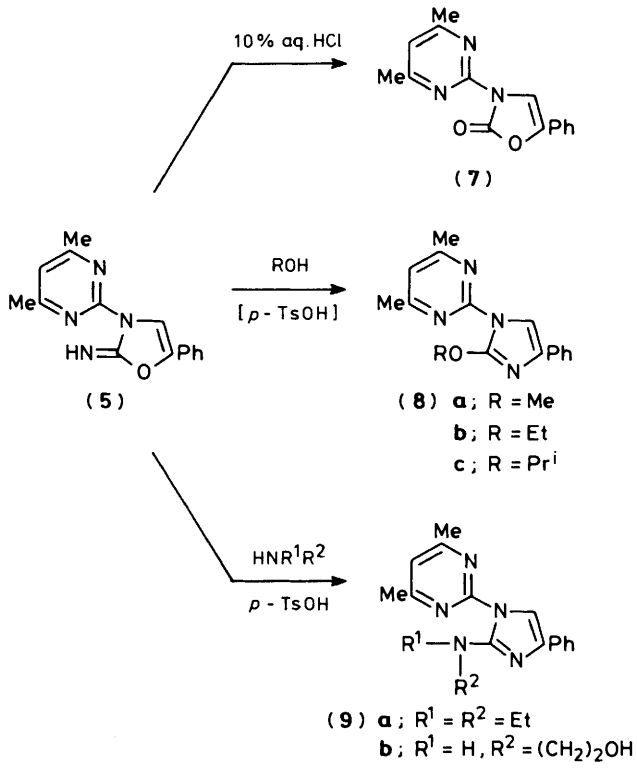
These results suggested that the thermolysis proceeds by an ionic process and that a 2-H was necessary to bring about the triazole ring cleavage. A plausible mechanism for the triazole ring opening is shown in Scheme 2. The ylide carbanion abstracts the 2-H and the C-2 carbanion thus formed assists the N(1)–N(8) bond cleavage to yield (**4**).

When (**2e**) was heated with 2.3 equiv. of triethylamine in acetonitrile, the 2-imino-oxazoline derivative (**5**) was produced in 64.4% yield. We can assume that the oxazoline ring is derived from the *N*-cyano-*N*-phenacylamino moiety. In fact *N*-cyano-*N*-phenacylaminopyrimidine (**4e**) was converted into compound (**5**) in 72.5% yield by treating it with 1.1 equiv. of triethylamine. This finding shows that (**4e**) is deprotonated by an excess of triethylamine to produce an enolate anion, which attacks the carbon atom of the cyano group to cyclize into the oxazoline (**5**) (Scheme 3).



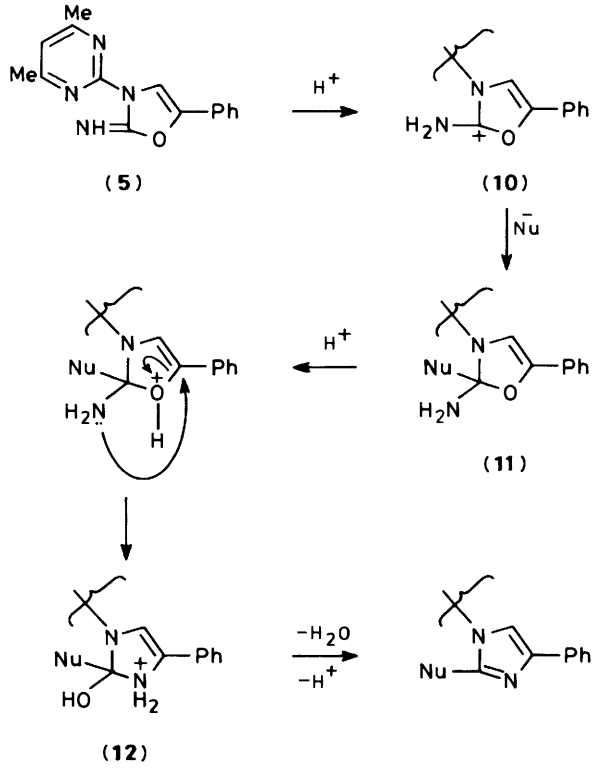
Scheme 3.

Ring Transformation of 2-*Imino-oxazoline* (**5**).—Since during purification by column chromatography on silica gel, we found that (**5**) was converted into (**7**), we examined its ring transformation under acidic conditions. The 2-imino-oxazoline (**5**) was converted into the 2-oxazolone derivative (**7**) by acid hydrolysis in 69.7% yield. Moreover, the reaction of (**5**) with nucleophiles such as alcohols or amines under acidic conditions gave imidazolyl derivatives (**8**) and (**9**).



Scheme 4.

It is known that treatment of oxazoles with ammonia (or amines) affords imidazoles.[6] However, in the conversion of (**5**) into (**8**) [or (**9**)], the imino group of (**5**) was utilized for the formation of the imidazole ring. The ring transformation of 2-imino-oxazoline (**5**) to the imidazoles (**8**) and (**9**) can be explained by the mechanism shown in Scheme 5. Protonation of the 2-imino nitrogen atom of (**5**) forms a carbocation (**10**), which is nucleophilically attacked by water, alcohols, or amines to yield an acetal (**11**). Ring transformation of (**11**) results from the sequence of processes protonation, ring opening, and recyclisation by the amino group. Finally the intermediate (**12**) is dehydrated to give (**8**) or (**9**).



Scheme 5.

In conclusion, [1,2,4]triazolo[1,5-*a*]pyrimidine *N*-ylides provided a number of pyrimidine derivatives by thermolysis. Studies of the reactions of the active ylides with dipolarophiles are in progress.

Experimental

M.p.s were determined on a Yanagimoto micro melting point apparatus and are uncorrected. I.r. spectra were recorded on a JASCO A-1 i.r. spectrophotometer. ^{1}H N.m.r. spectra were obtained on Hitachi R-20B (60 MHz) or Bruker WH-400 (400 MHz) spectrometers with tetramethylsilane as internal standard. ^{13}C N.m.r. spectra were run on a JEOL FX-100 spectrometer. Mass spectra were obtained using a JEOL-D 300 spectrometer with a direct-insertion probe, at 70 eV. All exact mass determinations were obtained on the JMA 2000 online system. Elemental analyses were performed at the Microanalytical Laboratory of Gifu Pharmaceutical University. Ether refers to diethyl ether.

Preparation of 3-Alkyl-5,7-dimethyl[1,2,4]*triazolo*[1,5-a]*pyrimidinium Salts* (**2b**—**f**).—A solution of 5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine (1.48 g, 10 mmol) and alkylating agent (50 mmol) in dry acetone (30 ml) was refluxed for 24 h. The precipitated solid was collected, dried, and recrystallized from ethanol–ether to give the product (**2**).

(**2b**), δ(CDCl$_3$) 9.93 (s, 1 H), 7.73 (s, 1 H), 4.70 (q, 2 H), 2.98 (s, 3 H), 2.85 (s, 3 H), and 1.70 (t, 3 H) (Found: C, 35.5; H, 4.4; N, 18.55. Calc. for $C_9H_{13}N_4I$: C, 35.54; H, 4.31; N, 18.42%).

(**2c**), δ(CDCl$_3$) 9.78 (s, 1 H), 7.95 (s, 1 H), 5.83 (s, 2 H), 2.89 (s, 3 H), and 2.84 (s, 3 H) (Found: C, 40.45; H, 3.7; N, 26.25. Calc. for $C_9H_{10}BrN_5$: C, 40.32; H, 3.76; N, 26.12%).

(**2d**), δ(CDCl$_3$) 10.28 (s, 1 H), 8.00 (s, 1 H), 5.78 (s, 2 H), 3.83 (s, 3 H), 3.05 (s, 3 H), and 2.88 (s, 3 H).

(**2e**), δ(CDCl$_3$) 10.13 (s, 1 H), 8.13—7.45 (m, 5 H), 7.75 (s, 1 H), 6.60 (s, 2 H), 3.00 (s, 3 H), and 2.75 (s, 3 H) (Found: C, 51.7; H, 4.35; N, 16.0. Calc. for $C_{15}H_{15}BrN_4O$: C, 51.89; H, 4.35; N, 16.14%).

(**2f**), δ(CDCl$_3$) 9.65 (s, 1 H), 8.19—7.80 (m, 5 H), 6.23 (s, 2 H), 2.93 (s, 3 H), and 2.75 (s, 3 H) (Found: C, 42.35; H, 3.3; N, 13.1. Calc. for $C_{15}H_{14}Br_2N_4O$: C, 42.28; H, 3.31; N, 13.15%).

Preparation of 2-Cyanamidopyrimidines (**4a**—**f**).—Triethylamine (1.1 mmol) was added in portions to a solution of 3-alkyl[1,2,4]triazolo[1,5-*a*]pyrimidinium salt (**2b**—**f**) (1 mmol) in dry acetonitrile (10 ml) and the mixture was heated under reflux for 0.5—1 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was extracted several times with dichloromethane, and the extracts were washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the product which was recrystallized from hexane–ethyl acetate or purified by silica gel chromatography.

(**4a**), δ(CDCl$_3$) 6.68 (s, 1 H), 3.43 (s, 3 H), and 2.40 (s, 6 H) (Found: C, 59.3; H, 6.2; N, 34.45. Calc. for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54%).

(**4b**), δ(CDCl$_3$) 6.70 (s, 1 H), 3.93 (q, 2 H), 2.40 (s, 6 H), and 1.40 (t, 3 H) (Found: C, 61.4; H, 6.95; N, 31.6. Calc. for $C_9H_{12}N_4$: C, 61.34; H, 6.86; N, 31.79%).

(**4c**), δ(CDCl$_3$) 6.80 (s, 1 H), 4.78 (s, 2 H), and 2.45 (s, 6 H) (Found: C, 57.85; H, 4.75; N, 37.35. Calc. for $C_9H_9N_5$: C, 57.74; H, 4.85; N, 37.41%).

(**4d**), δ(CDCl$_3$) 6.75 (s, 1 H), 4.58 (s, 2 H), 3.78 (s, 3 H), and 2.40 (s, 6 H) (Found: C, 54.65; H, 5.6; N, 25.35. Calc. for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44%).

(**4e**), δ(CDCl$_3$) 8.10—7.43 (m, 5 H), 6.69 (s, 1 H), 5.28 (s, 2 H), and 2.35 (s, 6 H) (Found: C, 67.6; H, 5.3; N, 20.9. Calc. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04%).

(**4f**), δ(CDCl$_3$) 7.95—7.58 (m, 4 H), 6.70 (s, 1 H), 5.23 (s, 2 H), and 2.33 (s, 6 H) (Found: C, 52.35; H, 3.85; N, 15.95. Calc. for $C_{15}H_{13}BrN_4O$: C, 52.19; H, 3.80; N, 16.23%).

Preparation of 2-(2-Imino-5-phenyl-2,3-dihydro-oxazol-3-yl)-4,6-dimethylpyrimidine (**5**).—Triethylamine (200 mg, 2 mmol) was added in portions to a solution of 5,7-dimethyl-3-phenacyl[1,2,4]triazolo[1,5-*a*]pyrimidinium bromide (300 mg, 0.86 mmol) in dry acetonitrile (10 ml) and the mixture was heated under reflux for 6 h. After cooling to room temperature, the solvent was evaporated under reduced pressure, and the residue was extracted several times with dichloromethane. The extracts were washed with water and dried ($MgSO_4$) and the solvent was removed under reduced pressure to afford the product which was purified by alumina column chromatography (hexane–CH_2Cl_2 2:1) to give (**5**), (148 mg, 64.4%). Recrystallization from ethyl acetate gave colourless needles, m.p. 169—171 °C; *m/z* 266 (M^+); $\nu_{max.}$(KBr) 3 476 and 1 696 cm^{-1}; δ (CDCl$_3$; 400 MHz) 8.53 (br s, 1 H), 7.81 (s, 1 H), 7.63—7.31 (m, 5 H), 6.80 (s, 1 H), and 2.49 (s, 6 H); δ_C(CDCl$_3$) 168.0s, 154.8s, 154.1s, 139.2s, 128.6d, 128.2d, 127.2s, 123.4d, 115.4d, 106.1d, and

23.9q p.p.m. (Found: C, 67.71; H, 5.2; N, 20.85. Calc. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04%).

Preparation of 4,6-*Dimethyl*-2-(2-*oxo*-5-*phenyloxazol*-3-*yl*)-*pyrimidine* (**7**).—A solution of (**5**) (100 mg, 0.38 mmol) in aqueous 10% hydrochloric acid (2 ml) was refluxed for 2 h. It was then cooled to room temperature, extracted with dichloromethane, and the extracts dried ($MgSO_4$) and evaporated under reduced pressure, to afford the product. This was purified by p.l.c. (hexane–ethyl acetate 1:2.5) to give compound (**7**) (70 mg, 69.7%). Recrystallization of this from hexane–dichloromethane gave colourless needles, m.p. 158.5—159 °C; *m/z* 267 (M^+), $\nu_{max.}$(KBr) 1 800 cm^{-1}; δ($CDCl_3$) 7.80 (s, 1 H), 7.65—7.25 (m, 5 H), 6.88 (s, 1 H), and 2.50 (s, 6 H) (Found: C, 67.45; H, 5.05; N, 15.6. Calc. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72%).

Preparation of 2-(2-*Alkoxy*-4-*phenylimidazolyl*)-4,6-*dimethylpyrimidine* (**8a**—**c**).—A solution of (**5**) (100 mg, 0.38 mmol) and a catalytic amount of toluene-*p*-sulphonic acid in alcohol (2 ml) was refluxed for 3 h. It was then cooled to room temperature and the solvent removed under reduced pressure to afford the product which was purified by preparative t.l.c. (hexane–ethyl acetate 1:1) to give (**8**).

(**8a**) (56.6%), m.p. 171.5—172.5 °C (CH_2Cl_2–hexane); δ($CDCl_3$) 7.90—7.25 (m, 6 H), 6.85 (s, 1 H), 4.23 (s, 3 H), and 2.50 (s, 6 H) (Found: C, 68.8; H, 5.85; N, 20.2. Calc. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99%).

(**8b**) (54.3%), m.p. 96—97 °C (CH_2Cl_2–hexane); δ($CDCl_3$) 7.90—7.25 (m, 6 H), 6.85 (s, 1 H), 4.63 (q, 2 H), 2.48 (s, 6 H), and 1.50 (t, 3 H) (Found: C, 69.55; H, 6.0; N, 18.9. Calc. for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03%).

(**8c**) (34.5%), m.p. 140—140.5 °C (CH_2Cl_2–hexane); δ($CDCl_3$) 7.90—7.25 (m, 6 H), 6.83 (s, 1 H), 5.53—5.10 (quint, 1 H, *J* 6 Hz), 2.48 (s, 6 H), and 1.48 (d, 6 H, *J* 6 Hz) (Found: C, 70.15; H, 6.6; N, 18.0. Calc. for $C_{18}H_{20}N_4O$: C, 70.11; H, 6.54; N, 18.17%).

Preparation of 2-(2-*Alkylamino*-4-*phenylimidazolyl*)-4,6-*dimethylpyrimidine* (**9a**, **b**).—A solution of (**5**) (1 mmol), a large excess of the amine (5 ml), and toluene-*p*-sulphonic acid (1.1 mmol) in dry benzene (5 ml) was refluxed for 24 h. The mixture was then cooled to room temperature, the solvent was evaporated under reduced pressure, and the residue extracted several times with chloroform. The solvent was removed under reduced pressure to afford the product which was purified by preparative t.l.c. (hexane–ethyl acetate 5:1) to give (**9**).

(**9a**) (60.2%), oil; δ($CDCl_3$) 7.93—7.24 (m, 6 H), 6.83 (s, 1 H), 3.30 (q, 4 H), 2.48 (s, 6 H), and 1.18 (t, 6 H).

(**9b**) (50.2%), m.p. 148.5—149.5 °C (hexane–ethyl acetate); δ($CDCl_3$) 8.30 (br s, 1 H), 7.80—7.18 (m, 6 H), 6.75 (s, 1 H), 5.13 (br s, 1 H), 4.00—3.58 (m, 4 H), 2.43 (s, 6 H) (Found: C, 65.85; H, 6.2; N, 22.5. Calc. for $C_{17}H_{19}N_5O$: C, 66.00; H, 6.19; N, 22.64%).

References

1 M. Hori, K. Tanaka, T. Kataoka, H. Shimizu, E. Imai, K. Kimura, and Y. Hashimoto, *Tetrahedron Lett.*, 1985, **26**, 1321.
2 C. Bülow and K. Haas, *Ber.*, 1909, **42**, 4638.
3 Y. Makisumi, *Chem. Pharm. Bull.*, 1963, **11**, 129.
4 W. W. Paudler and L. S. Helmic, *J. Heterocycl. Chem.*, 1968, **5**, 691.
5 G. R. Revankar, R. K. Robins, and R. L. Tolman, *J. Org. Chem.*, 1974, **39**, 1256.
6 H. Brederec, R. Gompper, and H. Wild, *Ber.*, 1955, **81**, 1351; J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 1947, 96; J. W. Cornforth and H. T. Huang, *J. Chem. Soc.*, 1948, 1960.

Received 8*th February* 1985; *Paper* 5/229