Fused Dihydropyrimidines by a Tandem Aza-Wittig–Heterocumulene-Mediated Annulation Reaction: Synthesis of 4,5-Dihydropyrazolo[3,4-*d*]pyrimidine Derivatives

Pedro Molina,* Antonio Arques, María Victoria Vinader

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Murcía, Campus de Espinardo, E-30071 Murcia, Spain

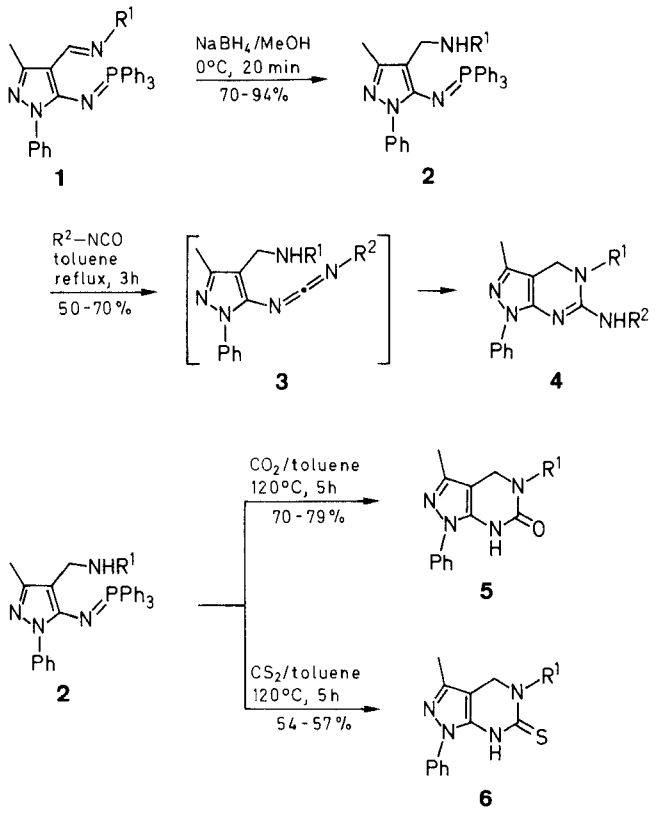
4-Aminomethyl-3-methyl-1-phenyl-5-[(triphenylphosphoranylidene)amino]-1*H*-pyrazoles **2** (iminophosphoranes), prepared from 4-aminomethylene-3-methyl-1-phenyl-5-[(triphenylphosphoranylidene)amino]-1*H*-pyrazoles **1**, react with aliphatic and aromatic isocyanates in refluxing toluene to give the corresponding 5-substituted 6-alkyl(aryl)amino-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidines **4**. Iminophosphoranes **2c** and **2d** also react with carbon dioxide and carbon disulfide to give 6-oxo- and 6-thioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines **5** and **6** respectively. 4-(*N*-4-Methylphenyl)aminomethyl-3-methyl-1-phenyl-5-[(triphenylphosphoranylidene)amino]-1*H*-pyrazole (**2d**) reacts with acyl chlorides to give 4-[*N*-acyl(*N*-4-methylphenyl)amino]methyl-3-methyl-1-phenyl-5-[(triphenylphosphoranylidene)amino]-1*H*-pyrazoles **7**, which by thermal treatment proved resistant to cyclization to give fused pyrimidines.

Compounds containing a fused pyrimidine ring play a very important part in the biochemistry of the living cell. Many potential drugs have been modeled on these compounds, particularly in cancer and virus research.[1] There are many reports on the annulation of a pyrimidine ring,[2] but few on the prepartion of fused dihydropyrimidines, particularly, when the pre-existing ring is five-membered and heteroaromatic. Reaction of 4-amino-5-aminomethyl-1,2,3-triazole derivatives with ortho esters, amidines,[3] ethyl chloroformate[4] and carbon disulfide[5] leads to 1,6-dihydro-8-azapurines.

We now report a simple general procedure for the preparation of the previously unreported 4-unsubstituted 4,5-dihydropyrazolo[3,4-*d*]pyrimidine ring system, bearing an amino group, an oxygen, or a sulfur atom in the 6-position under neutral conditions based on the ready synthesis and subsequent aza-Wittig type reaction of iminophosphoranes derived from 5-azido-4-aminomethylpyrazoles. Dihydropyrimido-annulation occurs via a heterocumulene moiety, available from the reaction of the iminophosphorane and an isocyanate, carbon dioxide or carbon disulfide, which then undergoes ring closure by nucleophilic attack of the adjacent amino group to give a six-membered heterocyclic ring.

The starting iminophosphoranes **1**, available from 5-azido-4-formyl-3-methyl-1-phenyl-1*H*-pyrazole by sequential treatment with the appropriate amine and triphenylphosphine,[6] react with sodium borohydride in methanol at 0°C to give the corresponding 4-aminomethyl-3-methyl-1-phenyl-5-[(triphenylphosphoranylidene)amino]-1*H*-pyrazoles **2** as crystalline solids in 70–94% yield (Table 1). The IR spectra of the iminophosphoranes **2** show absorption due to the N–H stretch at 3300–3284 cm^{-1}. In the ^{1}H-NMR spectra, the *C*-methyl and *N*-methylene groups appear characteristically as singlets at $\delta = 2.20-2.23$ and 3.16–3.61 respectively. In the ^{13}C-NMR spectra the methyl group at position 3 and the methylene group at position 4 appear at $\delta = 12.78-12.82$ and 38.06–42.68 respectively. Salient features of the ^{1}H- and ^{13}C-NMR spectra are given Table 1. The EI-mass spectra show the expected molecular ion peaks and the fragmentation pattern is in accord with the proposed structures.

Iminophosphoranes **2**, react with aliphatic and aromatic isocyanates in refluxing toluene to give the corresponding 5-substituted 6-alkyl(aryl)amino-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidines **4** as crystalline solids in moderate to good yield (Table 2). The IR spectra of the fused dihydropyrimidines **4** show absorption bands due to the N–H stretch at 3443–3234 cm^{-1}. The ^{1}H-NMR spectra suggests an exocyclic N–H for **4**; e.g. (**4e**,



1, 2	R^1	4	R^1	R^2
a	CH_2=$CHCH_2$	a	CH_2=$CHCH_2$	4-$CH_3C_6H_4$
b	HC≡CCH_2	b	HC≡CCH_2	4-$CH_3C_6H_4$
c	Ph	c	Ph	Et
d	4-$CH_3C_6H_4$	d	Ph	Ph
		e	Ph	4-$CH_3C_6H_4$
		f	4-$CH_3C_6H_4$	Et
		g	4-$CH_3C_6H_4$	Ph
		h	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$

5, 6	R^1
a	Ph
b	4-$CH_3C_6H_4$

Table 1. Iminophosphoranes **2** and **7** Prepared

Product	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	IR (Nujol)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	MS (70 eV)[f] m/z (%)
2a	70	148–149	$C_{32}H_{31}N_4P$ (502.6)	3284, 1591, 1562, 1500	2.20 (s, 3H), 2.85 (dt, 2H, J = 5.8, 1.2), 3.16 (s, 2H), 4.90–4.95 (m, 1H, J_{cis} = 10.2, J_{gem} = 1.9), 4.97–5.06 (m, 1H, J_{trans} = 17.3, J_{gem} = 1.9), 5.62–5.81 (m, 1H, J_{cis} = 10.2, J_{trans} = 17.3), 7.07–7.22 (m, 3H), 7.34–7.51 (m, 17H)	12.82, 42.62, 51.64 (C̲H$_2$C=), 105.74 (J = 4.9, C-4), 114.88 (C̲H$_2$=), 125.34, 125.41, 127.81, 128.34 (J = 12.2, C_m), 130.94 (J = 102, C_i), 131.64 (J = 2.8, C_p), 132.25 (J = 10, C_o), 137.17 (CH=), 140.47, 145.99 (J = 2.6, C-5), 147.98 (J = 2.3, C-3)	502 (M^+, 5), 447 (21), 446 (58), 262 (15), 185 (26), 184 (24), 183 (100), 108 (61), 107 (20), 77 (30), 56 (39)
2b	80	155–156	$C_{32}H_{29}N_4P$ (500.6)	3284, 3205, 1591, 1562	2.02 (t, 1H, J = 2.3), 2.21 (s, 3H), 3.00 (d, 1H, J = 2.3), 3.22 (s, 2H), 7.13–7.18 (m, 3H), 7.31–7.58 (m, 17H)	12.78, 37.27 (C̲H$_2$C≡), 42.01, 70.78 (HC̲≡C), 82.62 (≡C̲–), 105.22 (J = 5, C-4), 125.43, 125.56, 127.92, 128.42 (J = 12.2, C_m), 130.95 (J = 102, C_i), 131.74 (J = 2.8, C_p), 132.35 (J = 9.8, C_o), 140.52, 146.35 (J = 2.5, C-5), 148.20 (J = 2.4, C-3)	500 (M^+, 8), 447 (10), 446 (28), 262 (23), 185 (31), 184 (24), 183 (100), 157 (5), 154 (3), 133 (5), 108 (60), 107 (18), 91 (4), 77 (30), 55 (6), 54 (43)
2c	94	167–168	$C_{35}H_{31}N_4P$ (538.6)	3284, 1602, 1557, 1500	2.23 (s, 3H), 3.30 (s, 1H, NH), 3.61 (s, 2H), 6.29 (d, 2H, J = 7.6), 6.66 (t, 1H, J = 7.3), 7.10 (t, 2H, J = 7.9), 7.21–7.32 (m, 9H), 7.40–7.61 (m, 11H)	12.78, 38.06, 103.74 (J = 4.5, C-4), 112.40, 116.49, 125.31, 125.65, 128.04, 128.46 (J = 11.1, C_m), 128.80, 130.88 (J = 102.4, C_i), 131.74 (J = 2.9, C_p), 132.22 (J = 9.9, C_o), 140.60, 146.70 (J = 4.1, C-5), 148.11 (J = 2.2, C-3), 148.32	538 (M^+, 3), 447 (12), 446 (34), 262 (4), 185 (10), 184 (6), 183 (26), 108 (14), 105 (59), 104 (55), 93 (100), 92 (13), 77 (61)
2d	70	164–165	$C_{36}H_{33}N_4P$ (552.7)	3300, 1602, 1596, 1579	2.18 (s, 3H), 2.22 (s, 3H), 2.95 (s, 1H, NH), 3.54 (s, 2H), 6.20 (d, 2H, J = 8.3), 6.89 (d, 2H, J = 8.3), 7.14–7.30 (m, 9H), 7.39–7.56 (m, 11H)	12.78, 20.39 (C̲H$_3$Ph), 38.37, 104.11 (J = 4.4, C-4), 112.58, 125.38, 125.55, 125.68, 128.05, 128.48 (J = 12.3, C_m), 129.31, 130.92 (J = 102.4, C_i), 131.75 (J = 2.9, C_p), 132.28 (J = 10, C_o), 140.61, 146.22, 146.63 (J = 3.9, C-5), 148.12 (J = 2.3, C-3)	552 (M^+, 5), 433 (3), 277 (3), 262 (22), 185 (15), 183 (85), 120 (6), 119 (74), 118 (55), 107 (63), 106 (100), 91 (84), 77 (18)
7a	56	146–147	$C_{38}H_{35}N_4PO$ (594.7)	1653, 1597, 1556	1.72 (s, 3H, C̲H$_3$CO), 2.05 (s, 3H), 2.31 (s, 3H, CH$_3$Ph), 4.34 (s, 2H), 6.69 (d, 2H, J = 6.5), 7.00–7.50 (m, 22H)	13.05, 21.04, 22.72, 41.14, 103.13 (J = 6.4, C-4), 125.70, 125.78, 127.97, 128.26 (J = 12.2, C_m), 128.55, 129.56, 130.71 (J = 102.2, C_i), 131.58 (J = 3, C_p), 132.28 (J = 8.9, C_o), 137.16, 139.52, 140.53, 147.18, 148.35 (J = 2.5, C-3), 169.88	594 (M^+, 10), 447 (30), 446 (83), 262 (11), 185 (48), 184 (22), 183 (100), 149 (10), 108 (39), 107 (45), 106 (19), 91 (10), 77 (29)
7b	57	166–167	$C_{43}H_{36}N_4ClPO$ (691.2)	1630, 1596, 1562, 1500	2.05 (s, 3H), 2.23 (s, 3H, C̲H$_3$Ph), 4.46 (s, 2H), 6.63 (d, 2H, J = 8.1), 6.88 (d, 2H, J = 8.1), 7.06–7.34 (m, 21H), 7.43–7.50 (m, 3H)	13.21, 21.06, 42.68, 103.13 (J = 5.7, C-4), 125.80, 125.91, 127.82, 128.16, 128.45 (J = 12.2, C_m), 128.87, 129.32, 130.02, 130.83 (J = 107.5, C_i), 131.78 (J = 2.6, C_p), 132.34 (J = 9.8, C_o), 135.02, 135.36, 136.65, 139.64, 140.65, 147.52, 148.55 (J = 2.4, C-3), 169.27	692 (M^+ + 2, 2), 690 (M^+, 6), 551 (2), 447 (4), 446 (11), 245 (10), 183 (11), 141 (32), 139 (100), 113 (9), 111 (26), 77 (9)
7c	72	164–165	$C_{44}H_{39}N_4PO$ (670.8)	1630, 1596, 1563, 1508	2.07 (s, 3H), 2.21 (s, 6H, C̲H$_3$Ph), 4.46 (s, 2H), 6.65 (d, 2H, J = 8.2), 6.88 (t, 4H, J = 8.2), 7.12–7.35 (m, 20H), 7.41–7.55 (m, 2H)	13.14, 20.95, 21.17, 42.52, 103.33 (J = 5.7, C-4), 125.69, 125.73, 128.03, 128.08, 128.33 (J = 12.2, C_m), 128.60, 128.72, 129.03, 130.71 (J = 102.1, C_i), 131.64 (J = 2.8, C_p), 132.28 (J = 9.9, C_o), 133.85, 136.04, 138.96, 140.12, 140.59, 147.28, 148.55 (J = 2.4, C-3), 170.35	670 (M^+, 5), 447 (17), 446 (46), 262 (7), 225 (9), 185 (22), 184 (11), 183 (52), 120 (10), 119 (100), 108 (20), 91 (38), 77 (12)

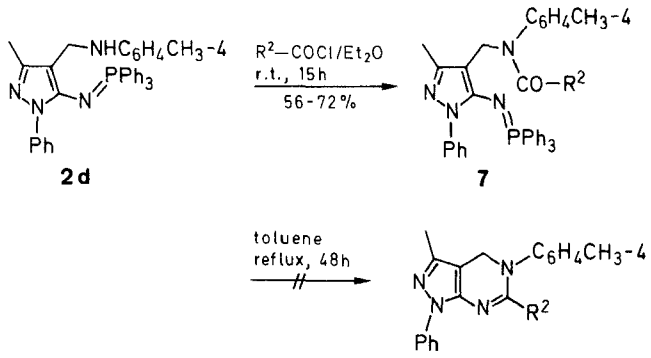
[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalyses: C ±0.25, H ±0.23, N ±0.26.
[d] Recorded on a Nicolet FT 5DX spectrophotometer.
[e] Recorded at 200 MHz on a Bruker AC-200 spectrometer.
[f] Recorded on a Hewlett-Packard 5993 C instrument.

R^1 = Ph, R^2 = Et) and (**4f**, R^1 = 4-$CH_3C_6H_4$, R^2 = Et), the methylene signal appears as a complex multiplet, and the amino proton as a triplet. Two characteristic signals appear as singlets at $\delta = 2.15-2.20$ and $\delta = 4.49-4.82$ due to the methyl group at position 3 and the methylene group of the dihydropyrimidine ring, respectively. In the ^{13}C-NMR spectra the methyl group at position 3 appears at $\delta = 12.28-12.42$, while the methylene group of the dihydropyrimidine ring appears at $\delta = 47.21-49.97$. Salient features of the ^{1}H- and ^{13}C-NMR spectra are given in Table 2. The EI-mass spectra show the expected molecular ion peaks in moderate to high intensity and the fragmentation pattern is in accord with the proposed structure.

We believe that the conversion of **2** to **4** involves an initial aza-Wittig reaction between the iminophosphorane and the isocyanate to give a carbodiimide,[3] as a highly reactive intermediate, which undergoes cyclization by nucleophilic attack of the adjacent amino group to give the corresponding 4,5-dihydropyrazolo[3,4-*d*]pyrimidine derivative. Although, reaction of carbodiimides with compounds containing an amino group have been reported,[7] to our knowledge this is the first reported example of a dihydropyrimido annulation based on the reaction of carbodiimides with secondary amino groups.

Iminophosphoranes **2c** and **2d** react with carbon dioxide at 120°C in a sealed glass tube to give directly the corresponding 6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]-pyrimidine derivatives **5** in good yields (Table 2). Similarly, the reaction with carbon disulfide under the same conditions leads to **6** in moderate yields (Table 2). The IR spectra of the fused tetrahydropyrazolo[3,4-*d*]-pyrimidines **5** and **6** show absorptions due to the N–H stretch at 3199–3160 cm^{-1}, in addition compounds **5** show a strong absorption band in the region 1660 cm^{-1} attributable to the carbonyl group. In the ^{13}C-NMR spectra the C-4 signal appears at $\delta = 47.50-48.02$ for compounds **5** and at $\delta = 51.53-51.75$ for compounds **6**, with the carbon atom of the carbonyl group in **5** at $\delta = 152.96-159.49$ and the thiocarbonyl group **6** at $\delta = 175.83-176.09$ (Table 2). The EI-mass spectra gives molecular ion peaks.

Although, it has been previously reported[8] that, iminophosphoranes react with acyl chlorides to give imidoyl chlorides, we now report that the reaction of iminophosphorane **2** with acyl chlorides in the presence of triethylamine leads to *N*-acyl-*N*-arylaminomethyl-substituted (triphenylphosphoranylidene)amino-1*H*-pyrazoles **7** instead of the expected imidoyl chloride. This conversion shows the preferential reactivity of the amino group of compound **2d** compared to the iminophosphorane moiety towards electrophilic reagents. Compounds **7** are potentially useful precursors of 4,5-dihydropyrazolo [3,4-*d*]pyrimidines bearing an alkyl or aryl substituent in the 6-position, via an intramolecular version of the aza-Wittig reaction. Despite their apparent simplicity, intramolecular aza-Wittig reactions involving amide carbonyl groups are rare; although some examples of this type of reaction have recently been reported.[9] When compounds **7** are refluxed in toluene for 48 hours, the starting material is recovered unchanged. This could be due to the restricted conformation of the side chain at position 4, which is entropically unfavorable for cyclization.



7	R^2
a	CH_3
b	4-ClC_6H_4
c	4-$CH_3C_6H_4$

The present study demonstrates that the tandem aza-Wittig-heterocumulene-mediated annulation strategy affords a new and general route to fused dihydropyrimidines containing various substituents on the pyrimidine ring. This synthetic approach compares favorably with existing methods.

4-Aminomethyl-3-methyl-1-phenyl-5-[(triphenylphosphoranylidene)-amino]-1*H*-pyrazoles 2; General Procedure:
A solution of $NaBH_4$ (0.28 g, 7.5 mmol) in dry MeOH (20 mL) is added dropwise to a solution of the appropriate iminophosphorane **1** (5 mmol) in dry CH_2Cl_2 (10 mL) at 0°C, and the reaction mixture is stirred for 20 min. Then, the volatile materials are removed under reduced pressure at 25°C and the residual material is slurried with H_2O (50 mL). The solid is collected by filtration, air dried and recrystallized from EtOH to give **2**. (Table 1).

5-Substituted 6-Alkyl(aryl)amino-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidines (4); General Procedure:
The appropriate isocyanate (1 mmol) is added dropwise to a stirred solution of the iminophosphorane **2** (1 mmol) in dry toluene (25 mL). The resultant solution is heated at reflux for 3 h. After cooling, the solvent is removed under reduced pressure at 25°C and the residual material is purified by column chromatography (silica gel and EtOAc/hexane 1:1 as eluent) followed by recrystallization from EtOH to give **4**.

5-Substituted 3-Methyl-1-phenyl-6-oxo(thioxo)-4,5,6,7-tetrahydro-7*H*-pyrazolo[3,4-*d*]pyrimidines 5 and 6; General Procedure:
A solution of the appropriate iminophosphorane **2** (1 mmol) in dry toluene (15 mL), and excess of solid CO_2 or CS_2 are heated in a sealed tube at 120°C for 5 h. After cooling, the solvent is removed under reduced pressure, and the crude product is slurried with Et_2O (20 mL), filtered, and recrystallized from toluene.

4-[*N*-Acyl(*N*-aryl)-amino]methyl-3-methyl-1-phenyl-5-[(triphenyl-phosphoranylidene)amino]-1*H*-pyrazoles (7); General Procedure:
To a solution of the iminophosphorane **(2d)** (1.10 g, 2 mmol) in dry Et_2O (25 mL), the appropriate acyl chloride (2 mmol) is added. The reaction mixture is stirred at r.t. for 15 min. The solid is collected by filtration and dissolved in dry THF (50 mL). To the resultant solution triethylamine (2 mmol) is added, and the solution is stirred at r.t. for 2 h. The salt formed is separated by filtration and the solvent is removed from the filtrate. The residual material is washed with cold H_2O (10 mL), air-dried and recrystallized from EtOH to give **7**. When compounds **7** were heated in dry toluene at reflux for 48 h, they were recovered unchanged.

Table 2. Compounds **4**, **5** and **6** Prepared

Product	Yield[a] (%)	mp (°C)[b], Appearance	Molecular Formula[c]	IR (Nujol)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[e] δ	MS (70 eV)[f] m/z (%)
4a	63	99–100, yellow prisms	$C_{22}H_{23}N_5$ (357.5)	3404, 1613, 1569, 1506	2.18 (s, 3H), 2.31 (s, 3H, CH_3Ph), 3.95–3.98 (m, 2H, $CH_2C=$), 4.58 (s, 2H), 5.35–5.50 (m, 2H, $CH_2=$), 5.70–7.90 (m, 1H, CH=), 6.00 (s, 1H, NH), 7.09 (d, 2H, J = 8.5), 7.12 (t, 1H, J = 7.3), 7.23 (d, 2H, J = 8.5), 7.32 (t, 2H, J = 7.3), 8.00 (dd, 2H, J = 7.3 and 1.5)	12.42, 20.73 (CH_3Ph), 47.99, 53.44 ($CH_2C=$), 95.22, 117.45 ($CH_2=$), 120.64, 121.19, 124.55, 128.41, 129.09, 131.94 (CH=), 132.70, 136.57, 139.94, 143.19, 146.10, 151.56	358 (M^+ + 1, 21), 357 (M^+, 88), 357 (88), 316 (100), 315 (33), 314 (57), 210 (8), 186 (57), 185 (19), 184 (46), 183 (13), 172 (12), 171 (28), 170 (8), 133 (19), 132 (24), 106 (33), 105 (12), 91 (48), 77 (100)
4b	77	124–125, yellow prisms	$C_{22}H_{21}N_5$ (355.4)	3420, 1659, 1613, 1596	2.17 (s, 3H), 2.30 (s, 3H, CH_3Ph), 2.41 (t, 1H, J = 2.0, HC≡), 4.00 (d, 2H, J = 2.0, CH_2C≡), 4.49 (s, 2H), 6.29 (s, 1H, NH), 7.08 (d, 2H, J = 8.5), 7.14–7.34 (m, 5H), 7.97 (d, 2H, J = 8.1)	12.28, 20.66 (CH_3Ph), 39.74 (CH_2–C≡), 47.21, 74.26 (HC≡), 77.23 (≡C–), 95.81, 120.54, 121.30, 124.58, 128.35, 129.02, 132.79, 136.38, 139.74, 143.06, 145.69, 150.94	356 (M^+ + 1, 19), 355 (M^+, 89), 354 (100), 316 (3), 315 (9), 314 (17), 222 (22), 210 (11), 187 (11), 184 (19), 156 (6), 133 (28), 132 (24), 107 (35), 106 (29), 105 (11), 104 (19), 91 (57), 77 (72)
4c	50	126–127, white prisms	$C_{20}H_{21}N_5$ (331.4)	3443, 1608, 1545, 1511	1.09 (t, 3H, J = 7.1, CH_3CH_2), 2.16 (s, 3H), 3.35 (qd, 2H, J = 7.1, 5.1, CH_3CH_2), 3.83 (t, 1H, J = 5.1, NH), 4.72 (s, 2H), 7.13 (t, 1H, J = 7.3), 7.27–7.48 (m, 7H), 8.16 (d, 2H, J = 8.2)	12.37, 14.82 (CH_3CH_2), 36.38 (CH_3CH_2), 49.71, 94.83, 120.52, 124.20, 127.14, 127.77, 128.36, 130.31, 140.41, 142.89, 143.11, 147.18, 158.42	332 (M^+ + 1, 17), 331 (M^+, 84), 330 (100), 302 (3), 287 (2), 184 (10), 119 (12), 104 (5), 103 (4), 77 (43)
4d	62	184–185, white prisms	$C_{24}H_{21}N_5$ (379.5)	3420, 1610, 1601, 1583	2.20 (s, 3H), 4.82 (s, 2H), 5.85 (s, 1H, NH), 7.03 (t, 1H, J = 7.5), 7.20–7.47 (m, 12H), 8.12 (dd, 2H, J = 8.3, 1.5)	12.37, 49.72, 95.82, 120.63, 120.96, 123.08, 124.80, 126.80, 127.91, 128.48, 128.51, 130.41, 138.79, 139.96, 142.63, 143.26, 145.87, 149.52	380 (M^+ + 1, 11), 379 (M^+, 45), 378 (46), 287 (12), 184 (11), 118 (7), 117 (8), 116 (10), 104 (9), 103 (11), 92 (17), 91 (13), 77 (100)
4e	55	100–102, yellow prisms	$C_{25}H_{23}N_5$ (393.5)	3420, 1602, 1557, 1506	2.15 (s, 3H), 2.27 (s, 3H, CH_3Ph), 4.77 (s, 2H), 5.74 (s, 1H, NH), 7.02 (d, 2H, J = 8.3), 7.15–7.42 (m, 10H), 8.06 (d, 2H, J = 8.1)	12.33, 20.68 (CH_3Ph), 49.67, 95.76, 120.75, 120.95, 124.77, 126.79, 127.87, 128.97, 129.02, 130.40, 132.68, 136.19, 139.94, 142.71, 143.26, 146.08, 149.75	394 (M^+ + 1, 5), 393 (M^+, 22), 292 (23), 287 (13), 133 (21), 132 (22), 131 (10), 118 (21), 117 (8), 107 (83), 106 (71), 105 (8), 104 (24), 103 (29), 91 (41), 77 (100)
4f	52	167–168, yellow prisms	$C_{21}H_{23}N_5$ (345.5)	3234, 1601, 1553	1.09 (t, 3H, J = 7.2, CH_3CH_2), 2.16 (s, 3H), 2.38 (s, 3H, CH_3Ph), 3.35 (qd, 2H, J = 7.2, 5.4, CH_2CH_3), 3.81 (t, 1H, J = 5.4, NH), 4.71 (s, 2H), 7.10–7.45 (m, 7H), 8.15 (dd, 2H, J = 8.7, 1.2)	12.35, 14.85 (CH_3CH_2), 20.99 (CH_3Ph), 36.35 (CH_3CH_2), 49.88, 94.71, 120.54, 124.20, 127.07, 128.33, 130.96, 137.90, 140.16, 140.41, 143.12, 147.24, 152.69	346 (M^+ + 1, 15), 345 (M^+, 73), 344 (97), 316 (3), 301 (2), 275 (2), 186 (15), 185 (24), 184 (26), 160 (7), 145 (5), 144 (12), 143 (14), 133 (35), 132 (15), 131 (23), 119 (16), 118 (21), 117 (14), 104 (16), 103 (12), 91 (76), 77 (100)
4g	50	179–180, white needles	$C_{25}H_{23}N_5$ (393.5)	3420, 1602, 1585, 1562	2.17 (s, 3H), 2.39 (s, 3H, CH_3Ph), 4.81 (s, 2H), 5.76 (s, 1H, NH), 6.99 (t, 1H, J = 7.2), 7.13–7.30 (m, 9H), 7.37 (t, 2H, J = 7.8), 8.07 (d, 2H, J = 7.8)	12.36, 21.04 (CH_3Ph), 49.97, 95.59, 120.62, 120.96, 123.01, 124.73, 126.82, 128.42, 128.47, 131.11, 138.22, 138.79, 139.85, 139.96, 143.21, 145.91, 149.68	394 (M^+ + 1, 21), 393 (M^+, 92), 392 (97), 301 (15), 196 (18), 157 (9), 156 (3), 143 (11), 131 (11), 130 (9), 129 (26), 128 (25), 118 (14), 117 (15), 103 (15), 92 (22), 91 (53), 77 (100)
4h	50	177–178, white prisms	$C_{26}H_{25}N_5$ (407.5)	3420, 1608, 1562, 1534	2.16 (s, 3H), 2.27 (s, 3H, CH_3Ph), 2.36 (s, 3H, CH_3Ph), 4.77 (s, 2H), 5.71 (s, 1H, NH), 7.05 (d, 2H, J = 8.3), 7.15–7.20 (m, 5H), 7.28 (d, 2H, J = 8.3), 7.41 (d, 2H, J = 7.8), 8.12 (d, 2H, J = 7.8)	12.38, 20.67 (CH_3Ph), 21.04 (CH_3Ph), 49.90, 95.57, 120.70, 120.90, 124.63, 126.80, 128.42, 128.99, 131.07, 132.54, 136.26, 138.11, 139.92, 140.06, 143.20, 146.13, 149.86	408 (M^+ + 1, 5), 407 (M^+, 20), 406 (19), 301 (12), 222 (10), 157 (10), 131 (12), 129 (27), 128 (25), 118 (12), 117 (16), 116 (13), 106 (19), 92 (8), 91 (65), 77 (100)

Table 2. (continued)

Product	Yield[a] (%)	mp (°C)[b], Appearance	Molecular Formula[c]	IR (Nujol)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[e] δ	MS (70 eV)[f] m/z (%)
5a	70	237–238, white prisms	$C_{18}H_{16}N_4O$ (304.4)	3199, 1668, 1630, 1591	2.18 (s, 3H), 4.71 (s, 2H), 7.08–7.14 (m, 3H), 7.26–7.50 (m, 7H), 8.76 (s, 1H, NH)	12.09, 48.02, 94.24, 122.58, 126.57, 126.93, 127.10, 129.29, 129.35, 136.73, 137.34, 142.91, 144.46, 152.49	304 (M^+, 19), 185 (57), 184 (79), 143 (15), 119 (15), 92 (14), 91 (31), 77 (100)
5b	79	216–217, white prisms	$C_{19}H_{18}N_4O$ (318.4)	3160, 1662, 1631, 1597	2.28 (s, 3H), 2.43 (s, 3H, CH_3Ph), 4.73 (s, 2H), 7.15 (d, 2H, J = 8.4), 7.29 (d, 2H, J = 8.4), 7.34–7.38 (m, 5H), 9.45 (s, 1H, NH)	10.61, 47.50, 95.19, 144.01, 152.96	318 (M^+, 11), 185 (86), 184 (100), 144 (8), 143 (11), 133 (5), 132 (8), 91 (20), 77 (40)
6a	54	188–189, yellow needles	$C_{18}H_{16}N_4S$ (320.4)	3199, 1668, 1630, 1591	2.19 (s, 3H), 4.82 (s, 2H), 7.26–7.53 (m, 10H), 8.31 (s, 1H, NH)	12.06, 51.53, 95.24, 122.72, 126.83, 127.85, 128.01, 129.69, 129.81, 133.96, 136.90, 144.43, 145.62, 175.83	321 ($M^+ + 1$, 11), 320 (M^+, 50), 287 (8), 228 (8), 185 (70), 184 (100), 143 (15), 128 (9), 116 (7), 104 (6), 92 (7), 91 (9), 77 (96)
6b	57	181–182, yellow needles	$C_{19}H_{18}N_4S$ (334.4)	3165, 1625, 1598	2.20 (s, 3H), 2.39 (s, 3H, CH_3Ph), 4.82 (s, 2H), 7.22 (d, 2H, J = 8.5), 7.30 (d, 2H, J = 8.5), 7.37–7.55 (m, 5H), 8.20 (s, 1H, NH)	12.16, 21.13 (CH_3Ph), 51.75, 95.39, 122.88, 126.59, 128.03, 129.99, 130.51, 134.15, 137.10, 138.15, 143.31, 144.60, 176.09	335 ($M^+ + 1$, 8), 334 (M^+, 35), 333 (10), 301 (6), 228 (6), 186 (9), 185 (78), 184 (100), 143 (11), 128 (7), 91 (18), 77 (27)

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalyses: C ±0.23, H ±0.20, N ±0.27.
[d] Recorded on a Nicolet FT 5DX spectrophotometer.
[e] Recorded at 200 MHz on a Bruker AC-200 spectrometer. For compound **5b** $CDCl_3$/TFA was used as solvent.
[f] Recorded on a Hewlett-Packard 5993 C instrument.

We thank Dirección General de Investigación Científica y Técnica for financial support, Project Number PB86-0039.

Received: 27 September 1989

(1) Brown, D.J., in: Katritzky and Rees *Comprehensive Heterocyclic Chemistry*, Vol. 3, Boulton, A.J. Mckillop, A. (eds.), Pergamon Press, Oxford **1984**, p. 57.
(2) Albert, A., in: *Advances in Heterocycl. Chem.*, Vol. *32*, Katritzky, A.R. (ed.), Academic Press, New York, **1982**, p. 1.
(3) Albert, A. *J. Chem. Soc., Perkin Trans 1* **1976**, 291.
(4) Albert, A. *J. Chem. Soc., Perkin Trans 1* **1980**, 2918.
(5) Albert, A. *J. Chem. Soc., Perkin Trans 1* **1980**, 887.
(6) Molina, P.; Arques, A.; Vinader, M.V.; Becher, J.; Brondum, K. *J. Org. Chem.* **1988**, *53*, 4654.
(7) Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233.
(8) Zbiral, E.; Bauer, E. *Phosphorus* **1972**, *2*, 35.
(9) Molina, P.; Alajarín, M.; Vidal, A.; Elguero, J.; Claramunt, R.M. *Tetrahedron* **1988**, *44*, 2249.
Molina, P.; Alajarín, M.; López-Leonardo, C.; Madrid, I.; Foces-Foces, C.; Cano, F.H. *Tetrahedron* **1989**, *45*, 1823.