Nitrogen Bridgehead Compounds, Part 49[1]. Synthesis and Stereochemistry of 9-Aminotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

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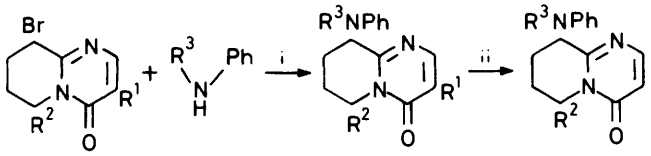
The 9-phenylaminotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**4**)—(**9**), synthesized from the 9-bromo compounds (**1**)—(**3**), displayed imine–enamine tautomerism. In solution (if $R^2 \neq H$) the equilibrium mixtures contain both *cis*- and *trans*-imines. The enamine form is stabilized by increasing polarity of the solvent and by increasing the electron-withdrawing effect of substituent R^1. Owing to 1,3-allylic strain, in the derivatives where R^2 = Me the imine form is energetically less favoured than in the derivatives with R^2 = H. The chemical structures of the synthesized products were studied by u.v., ^1H and ^{13}C n.m.r. spectroscopy.

9-Substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones deserve attention as antiallergic agents.[2] For their synthesis,[3] the reactivity of the 9-methylene group of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones[4] towards electrophilic reagents[5,6] has been utilized. This paper deals with the reactions of 9-bromo-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid derivatives[6] with anilines, and with the stereochemistry of the products.

Results

Reaction of the 9-bromotetrahydropyrido[1,2-*a*]pyrimidine-3-carboxylic acids[6a] (**1**) and (**3**) with aniline, or reaction of the ester (**2**)[6b] with *N*-methylaniline in acetonitrile under argon at ambient temperature afforded the 9-amino derivatives (**4**)—(**6**). Boiling with 2% sodium hydroxide under argon resulted in decarboxylation with the formation of compounds (**7**)—(**9**) (Scheme 1).



(**1**)–(**3**) (**4**)–(**6**) (**7**)–(**9**)

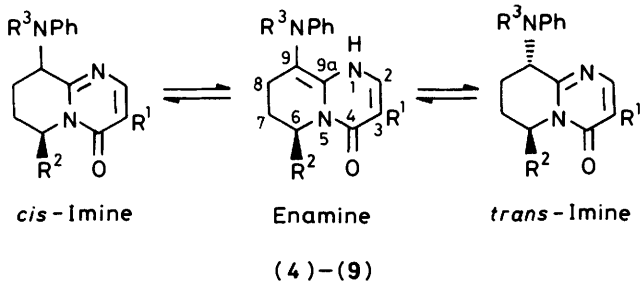
(**1**), (**4**), (**7**): $R^1 = CO_2H$, R^2 = Me, R^3 = H;
(**2**), (**5**), (**8**): $R^1 = CO_2Et$, R^2 = Me, R^3 = Me;
(**3**), (**6**), (**9**): $R^1 = CO_2H$, R^2 = H, R^3 = H.

Reagents: i, MeCN, ambient temperature, argon; ii, hot aqueous NaOH, argon

Scheme 1.

Since solvent-dependent imine–enamine tautomerism has been reported[5c,7] for tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, we have now investigated the tautomerism of the 9-amino derivatives (**4**)—(**9**) (Scheme 2).

U.V. Studies.—U.v. spectral data, recorded in ethanol, are shown in Table 1, together with similar data for some known[6b,8] tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines in the imine (**10**)—(**14**) and enamine (**15**)—(**19**) forms.



cis-Imine Enamine *trans*-Imine

(**4**)–(**9**)

Tautomerism of 9-phenylaminotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones

Scheme 2.

Imine Enamine

(**10**) $R^1 = CO_2H$, R^2 = Me (**15**)
(**11**) $R^1 = CO_2Et$, R^2 = Me (**16**)
(**12**) $R^1 = CO_2H$, R^2 = H (**17**)
(**13**) R^1 = H, R^2 = Me (**18**)
(**14**) R^1 = H, R^2 = H (**19**)

Comparison of these data reveals that the enamine tautomer predominates for the 6-methyl 3-carboxylic acid derivatives (**4**) and (**5**), while compounds (**6**)—(**9**) are mainly present as the imines.

In (**4**) or (**5**) the double bond between C-9 and C-9a may be conjugated with the non-bonding electron pair of either N(1) or C(9)–N. By analogy with *N*-phenyl enamines[9] and from the close similarity of the u.v. spectra of (**4**) and (**5**) to those of the models (**15**) and (**16**), it can be stated that the chromophoric system of our compounds is not (or is only slightly) conjugated with the *N*-phenyl function.

Table 1. U.v. data ($\lambda_{max.}$/nm, ε/l mol^{-1} cm^{-1} on 6,7,8,9- and 1,6,7,8-tetrahydro- and 9-phenylaminotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in EtOH

Compd.	Imine $\lambda_{max.}$ (ε)	Compd.	Enamine $\lambda_{max.}$ (ε)	Compd.	Imine $\lambda_{max.}$ (ε)	Enamine $\lambda_{max.}$ (ε)
(10)	230 (5 500)	**(15)**	256 (28 290)	**(4)**[a]		265
	300 (7 930)		362 (2 900)			363 infl.
(11)	230 (6 460)	**(16)**	258 (21 880)	**(5)**		254 infl. (29 400), 265 (31 460)
	303 (8 320)		356 (2 750)			356 (4 660)
(12)	228 (6 590)	**(17)**	256 (30 360)	**(6)**	238 (12 730)	
	300 (9 650)		362 (3 370)		299 (8 710)	
				(7)	242 (13 950)	
(13)	226 (6 030)	**(18)**[b]	344 (1 550)		281 (7 060)	
	278 (4 790)			**(8)**	247 (16 080)	
					288 (6 550)	
(14)	224 (9 010)	**(19)**[b]	340 (660)	**(9)**	243 (13 510)	
	277 (6 760)				280 (6 850)	

[a] In saturated solution. [b] The spectrum taken in acetonitrile.

Table 2. Substituent chemical shifts of 9-substituents of 6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidines

	Equatorial 9-substituent (*cis*-isomer)				Axial 9-substituent (*trans*-isomer)				
Compd.	α	β	γ	δ	α	β	γ	δ	Solvent
(4)	21.6	8.4	−1.0	0.4	20.0	7.7	−3.5	−0.1	$[(CD_3)_2SO]$
(5)	29.6	4.0	−1.1	0.6	26.1	4.5	−5.5	0.1	$CDCl_3$
(6)					20.1	7.0	−3.0	−1.7	$[(CD_3)_2SO]$
(7)	24.0	7.9	−1.5	1.2	20.8	10.2	−2.4	−0.5	$CDCl_3$
(8)	29.3	3.3	−1.4	0.3	25.9	4.1	−5.7	−0.2	$CDCl_3$
(9)					22.4	8.2	−2.0	−1.1	$CDCl_3$

Table 3. Isomeric ratios of 9-aminotetrahydropyrido[1,2-*a*]pyrimidin-4-ones

	After dissolution in $[(CD_3)_2SO]$			At equilibrium					
				in $CDCl_3$			in $[(CD_3)_2SO]$		
	Imine (%)			Imine (%)			Imine (%)		
Compd.	*cis*	*trans*	Enamine (%)	*cis*	*trans*	Enamine (%)	*cis*	*trans*	Enamine (%)
(4)			100	Insoluble			15	15	70
(5)			100	70	15	15	28	2	70
(6)	80		20	Insoluble			75		25
(7)	100			50	50		50	50	
(8)	100			62	38		66	34	
(9)	100			100			100		

*N.M.R. Studies.**—Spectra of the 9-anilino compounds (**4**)—(**9**) contain two or three sets of signals which change with time. This indicates the co-existence of tautomeric forms in solution. The amine and enamine tautomers were identified by the 2-H signal and also the C-2, C-9 and C-9a signals.

For the enamines of (**4**)—(**6**) the 2-H signal appears as a doublet at 7.66—7.71 p.p.m. (*J* 7.1—7.3 Hz), due to coupling with 1-H, and is shifted upfield relative to the corresponding singlet at 8.56—8.63 p.p.m. for the imine tautomers. A similar upfield shift was experienced for the C-2 and C-9a signals, at 147.6—148.5 and 131.2—133.1 p.p.m. for the enamines compared to the signals at 151.4—157.8 and 157.5—161.4 p.p.m. for the imines.

A further characteristic feature is that in the enamines C-9 is sp^2 hybridized, giving signals between 91.1 and 96.1 p.p.m., whereas in the imines it is sp^3 bonded and appears in the range 51.2—61.1 p.p.m.

^{15}N N.m.r. spectroscopy was used in two cases for the identification of tautomers. For compound (**5**) the N-1 signal appeared at −270.1 p.p.m. for the enamine form and at −143.1 p.p.m. for the *cis*-imine form. In the latter case the signal at −182.0 p.p.m. was assigned to N-5, and that at −325.9 p.p.m. to C(9)–N. In the spectrum of (**9**), only the signals for N-5 and C(9)–N in the *cis*-imine form could be identified (at δ = −191.2 and −328.5 p.p.m., respectively).

Similarly as for 6-methyltetrahydropyrido[1,2-*a*]pyrimidin-4-ones,[10] in the 6-methyl derivatives (**4**), (**5**), (**7**) and (**8**) the conformer with a quasi-axially oriented methyl group is dominant. Since only the most stable conformer, the half-chair, has to be considered for the piperidine ring, in the imine tautomers of the 6-methyl derivatives the 9-amino group is equatorial in the *cis*, and axial in the *trans* epimer (Scheme 2).

The orientation of the phenylamino group in compounds (**6**)—(**9**) is established with the aid of the coupling constants for 8-H and 9-H. In the spectra of compounds (**6**) and (**9**),

* ^1H and ^{13}C N.m.r. spectral results are available as a supplementary publication. [Sup. No. 56174 (4 pp)]. For details of the supplementary publications scheme see Instructions for Authors (1985), *J. Chem. Soc., Perkin Trans. 1*, 1985, issue 1.

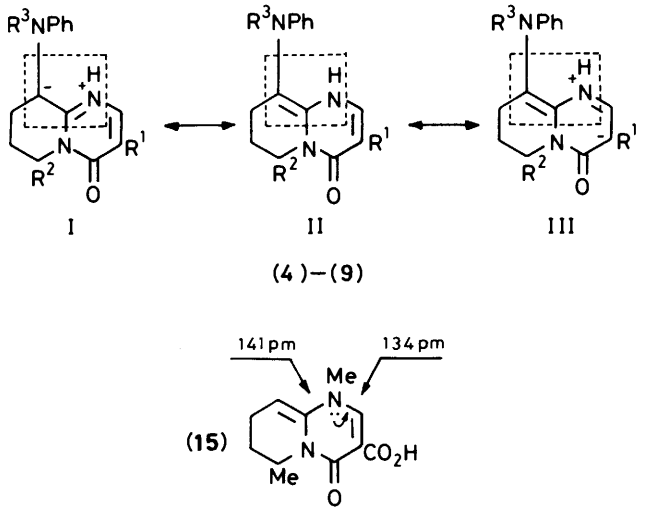
unsubstituted at C-6, couplings of 7.1, and of 7.5 and 5.8 Hz indicate that the conformational equilibrium is shifted in favour of the conformer with a quasi-axial phenylamino group. As for the 6-methyl derivatives, in the spectrum of (7) these coupling constants of both the *cis* (10.7 and 6.2 Hz) and *trans* stereoisomers (5.5 Hz) could be assigned, while for (8) only those associated with the major *cis* isomer (11.4 and 5.4 Hz) were recognizable. Finally, due to overlapping with other signals, the coupling constants for the individual stereoisomers of (4) and (5) could not be distinguished.

From the ^{13}C n.m.r. spectra, *cis*- and *trans*-imines were identified by means of the γ-effect of the 9-amino group on C-7. The effects of the 9-amino substituent on the chemical shifts of the ring carbons (SCS) in the imine tautomers are compiled in Table 2, the tetrahydropyrido[1,2-*a*]pyrimidines unsubstituted at C-9 being taken as reference. The γ-anti effect in the 6-methyl derivatives (4), (5), (7), and (8) is −1.0 to −1.5 p.p.m., while the γ-gauche effect is −2.4 to −5.7 p.p.m. From a comparison of the effects observed in the 6-demethyl derivatives (6) and (9) with those in the 6-methyl derivatives (4) and (7), it can be concluded that, in accordance with the ^1H n.m.r. results, the predominant conformer of (6) and (9) is the one with a quasi-axial phenylamino group.

Discussion on Isomeric Ratio.—Isomeric ratios for the tetrahydro derivatives (4)—(9) determined by ^1H and ^{13}C n.m.r. spectroscopy are presented in Table 3. Values obtained immediately after dissolution suggest that compounds (4) and (5) are present in the solid phase as enamines, and the other compounds as imines.

In deuteriochloroform under equilibrium conditions the imine tautomer of compound (5) predominates, and in $[(CD_3)_2SO]$ the enamine tautomer. This is in accord with earlier observations that highly polar solvents stabilize the enamine form.[11]

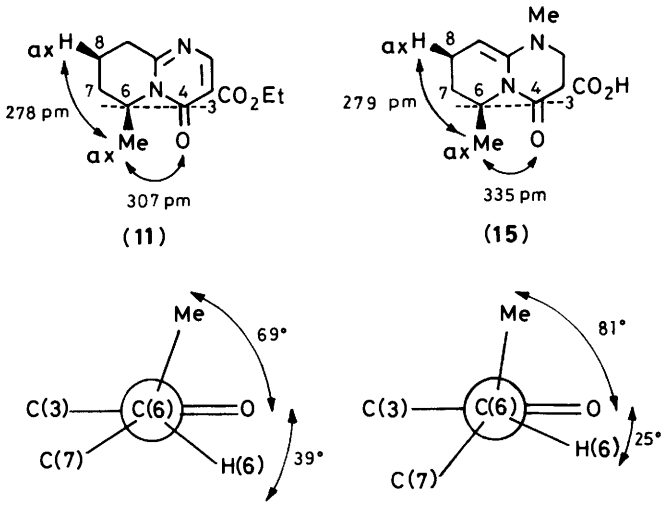
The tautomeric equilibrium is also influenced by substituents at C-3. In $[(CD_3)_2SO]$ the enamine tautomer is dominant for the 6-methyl derivatives (4) and (5) having an electron-attracting carboxy or ester group at C-3, whereas those unsubstituted at C-3, *e.g.* (7) and (8), are mainly in the imine form. The phenomenon



Scheme 3.

can be explained by considering the mesomeric structures I—III (Scheme 3) of the enamine tautomer, of which III is stabilized by a carboxyl or ester group.[9] This also implies the preponderance of mesomer III over I, *i.e.* the non-bonding pair of electrons of the enamine nitrogen is mainly shifted towards C-2. This hypothesis was corroborated by an *X*-ray analysis of a similar enamine carboxylic acid (15).[12a] In this, the N(1)–C(9a) distance was 141 pm, and the N(1)–C(2) distance only 134 pm.

Besides an electron-attracting substituent at C-3, a 6-methyl group also makes a significant contribution to the stability of the enamine form. Thus in $[(CD_3)_2SO]$ the imine form prevails in the demethyl 3-carboxylic acid (6), whereas the enamine form does so in the 6-methyl analogue (4). This methyl group is the source of two unfavourable interactions (Scheme 4). One is the 1,3-allylic strain[10,13] between C(4)=O and C(6)–Me, which is relieved when the methyl group assumes a quasi-axial



Scheme 4.

Characteristic atomic distances and torsion angles for compounds (11) and (15)[12]

orientation. The other is a 1,3-diaxial interaction between a quasi-axial methyl group and 8-H_{ax}. The role of the 6-methyl group was studied by comparing the imine (11) and the enamine (15). The constitutions and (according to u.v. data) the chromophoric systems of these compounds are highly similar to those of the imine and enamine tautomers, respectively, of the phenylamino compounds (4)—(9) (see Table 1). A comparison of the *X*-ray data[12] reveals that the distance between C(6)–Me and 8-H_{ax} is practically the same in (11) and (15) (278 and 279 pm, respectively), whereas the distance between C(6)–Me and C(4)=O is 307 pm in the imine (11) and 335 pm in the enamine (15). The torsion angle of the methyl and carbonyl groups around the C(4)–C(6) axis is 69° in the imine (11) and 81° in the enamine (15). Similar conclusions can be drawn by comparing data on the 9-carboxymethyl derivative of compound (11)[14] and the 9-formyl-6-methyl-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.[5b]

These data suggest that stabilization of the enamine form by the 6-methyl group is not to be attributed to a decrease in the 1,3-diaxial interaction between that group and 8-H_{ax}, but rather to further relief of the 1,3-allylic strain still present in the imine tautomer and involving the methyl and 4-oxo groups.

Experimental

M.p.s. are uncorrected. Yields were not optimized. U.v. spectra were recorded in ethanol with a UNICAM SP-800 spectrophotometer. ^1H N.m.r. spectra of (7) were recorded at 250 MHz on a Bruker WM-250 instrument; ^1H and ^{13}C n.m.r. spectra of (4)—(8) at 100 and 25 MHz respectively on a Jeol FX-100

instrument. That of (**9**) were recorded on a Bruker WP-80 instrument at 80 and 20.1 MHz, respectively. ^{1}H N.m.r. spectra were taken in 5—10% solutions, ^{13}C n.m.r. spectra in saturated solutions using $SiMe_4$ as internal standard in both cases. ^{15}N N.m.r. spectra were recorded at 10.04 MHz on a Jeol FX-100 instrument with proton broadband decoupling. The chemical shifts were determined relative to the signal of external aqueous $K^{15}NO_3$ and then converted to the signal of external nitromethane [$\delta(MeNO_2) = 0.0$ p.p.m.]. Shifts upfield from the reference have negative values. (Typical acquisition parameters are: spectral width 5000 Hz, flip angle 30°, and pulse delay 5 s.) The tautomer and *cis–trans* ratios were obtained by integration of the ^{1}H n.m.r. spectra and from the peak heights of the corresponding signal of the ^{13}C n.m.r. spectrum, averaging the values of 4—6 signals. The maximum deviation was ±2%. Analytical results on the new compounds agreed with calculated data. Details are given in the supplementary publication (see p. 1016).

Synthesis of the 9-Amino-4-oxo-tetrahydro-4H-pyrido[1,2-a]-*pyrimidine-3-carboxylic Acid Derivatives* (**4**)—(**6**).—A solution of 9-bromotetrahydropyridopyrimidinone[6] (**1**)—(**3**) (10 mmol) and aniline or *N*-methylaniline (22 mmol) in acetonitrile (5 ml), was stirred at ambient temperature for 3—6 days under an argon atmosphere. Water (20 ml) was then added and the reaction mixture was stirred for 0.5 h. The precipitated crystals (**4**)—(**6**) were filtered off, washed with ethanol, and dried. Thus prepared were compound (**4**) (2.7 g, 90%). m.p. 200—202 °C (refluxed in MeOH) (lit.,[2a] 198—199 °C); compound (**5**) (1.7 g, 50%), m.p. 180—181 °C (from MeCN), (lit.,[2a] 180—181 °C); compound (**6**) (2.5 g, 88%), m.p. 178—180 °C (refluxed in MeOH).

Decarboxylation of Compounds (**4**)—(**6**).—A solution of the 9-anilinotetrahydropyridopyrimidine-3-carboxylic acid derivative (**4**)—(**6**) (10 g) in 2% aqueous sodium hydroxide solution (100 ml) was refluxed for 5 h under an argon atmosphere. After the mixture had been cooled to 5 °C, the precipitated crystals (**7**)—(**9**) were filtered off, washed with water and dried. Thus prepared were compound (**7**) (7.3 g, 85%), m.p. 165—167 °C (from MeOH); compound (**8**) (5.8 g, 74%), m.p. 188—189 °C (from MeOH); compound (**9**) (6.8 g, 80%), m.p. 155—156 °C (from MeOH).

References

1 Part 48, I. Hermecz, M. Kajtár, K. Simon, T. Breining, P. R. Surján, G. Tóth, and Z. Mészáros, *J. Org. Chem.*, in the press.

2 (*a*) I. Hermecz, T. Breining, L. Vasvári-Debreczy, Á. Horváth, Z. Mészáros, I. Bitter, C. DeVos, and L. Rodriguez, *J. Med. Chem.*, 1983, **26**, 1494; (*b*) I. Hermecz, T. Breining, Z. Mészáros, Á. Horváth, L. Vasvári-Debreczy, F. Dessy, C. DeVos, and L. Rodriguez, *ibid.*, 1982, **25**, 1140; (*c*) I. Hermecz, T. Breining, Z. Mészáros, J. Kökösi, L. Mészáros, F. Dessy, and C. DeVos, *ibid.*, 1983, **26**, 1126; (*d*) I. Hermecz, Á. Horváth, Z. Mészáros, C. DeVos, and L. Rodriguez, *ibid.*, 1984, **27**, 1253.

3 (*a*) I. Hermecz, T. Breining, L. Vasvári-Debreczy, Á. Horváth, Z. Mészáros, I. Bitter, and J. Kökösi, German Patent 3 017 564 (*Chem. Abstr.*, 1981, **94**, 121591t); (*b*) I. Hermecz, T. Breining, L. Vasvári-Debreczy, Á. Horváth, and J. Kökösi, German Patent 3 017 560 (*Chem. Abstr.*, 1981, **95**, 81007u).

4 (*a*) G. Náray-Szabó, I. Hermecz, and Z. Mészáros, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1753; (*b*) J. Kökösi, I. Hermecz, Gy. Szász, Z. Mészáros, G. Tóth, and M. Csákvári-Pongor, *J. Heterocycl. Chem.*, 1982, **19**, 909.

5 (*a*) I. Hermecz, I. Bitter, Á. Horváth, G. Tóth, and Z. Mészáros, *Tetrahedron Lett.*, 1979, **20**, 2557; (*b*) Á. Horváth, I. Hermecz, L. Vasvári-Debreczy, K. Simon, M. Pongor-Csákvári, Z. Mészáros, and G. Tóth, *J. Chem. Soc., Perkin Trans. 1*, 1983, 369; (*c*) I. Bitter, I. Hermecz, G. Tóth, P. Dvortsák, Z. Bende, and Z. Mészáros, *Tetrahedron Lett.*, 1979, **20**, 5039.

6 (*a*) I. Hermecz, T. Breining, Z. Mészáros, G. Tóth, and I. Bitter, *Heterocycles*, 1980, **14**, 1953; (*b*) Z. Mészáros, J. Knoll, P. Szentmiklósi, Á. Dávid, G. Horváth, and I. Hermecz, *Arzneim.-Forsch.*, 1972, **22**, 815.

7 (*a*) H. Wamhoff and L. Lichtenthäler, *Chem. Ber.*, 1978, **111**, 2813; (*b*) I. Hermecz, J. Engler, Z. Mészáros, and G. Tóth, *Tetrahedron Lett.*, 1979, **20**, 1337; (*c*) G. Tóth, C. De La Cruz, I. Bitter, I. Hermecz, B. Pete, and Z. Mészáros, *Org. Magn. Reson.*, 1982, **20**, 229.

8 (*a*) G. Horváth, Á. I. Kiss, Z. Mészáros, and I. Hermecz, *Acta Chim. Acad. Sci. Hung.*, 1974, **83**, 15; (*b*) I. Hermecz, P. R. Surján, T. Breining, K. Simon, G. Horváth, Z. Mészáros, M. Kajtár, and G. Tóth, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1413.

9 (*a*) H. Ahlbrecht and S. Fischer, *Tetrahedron*, 1970, **26**, 2837; (*b*) W. Walter and H.-W. Meyer, *Justus Liebigs Ann. Chem.*, 1974, 776.

10 G. Tóth, I. Hermecz, and Z. Mészáros, *J. Heterocycl. Chem.*, 1979, **16**, 1181.

11 (*a*) H. Ahlbrecht, J. Blecher, and F. Kröhnke, *Tetrahedron Lett.*, 1969, 439; (*b*) H. Ahlbrecht and R.-D. Kalas, *Justus Liebigs Ann. Chem.*, 1979, 102.

12 (*a*) K. Simon, Z. Mészáros, and K. Sasvári, *Acta Crystallogr.*, 1975, **B31**, 1702; (*b*) K. Sasvári and K. Simon, *Acta Crystallogr.*, 1973, **B29**, 1245.

13 F. Johnson, *Chem. Rev.*, 1968, **68**, 375.

14 K. Simon, *God. Jugosl. cent. kristalogr.*, 1980, **15**, 87.

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