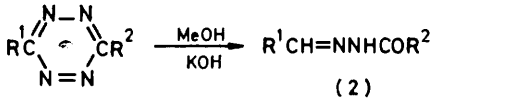
Synthesis and *X*-Ray Determination of the Structure of 3-Benzyl-7-methoxy-6-phenylimidazo[1,2-*b*]-*s*-tetrazines prepared by the Action of Potassium Hydroxide in Methanol on 3,6-Dibenzyl-*s*-tetrazines

By **Douglas G. Neilson,* Kathleen M. Watson,** and **Timothy J. R. Weakley,** Department of Chemistry, The University, Dundee DD1 4HN, Scotland

Compounds with the novel imidazo[1,2-*b*]-*s*-tetrazine structure have been obtained by the action of alkali in methanol on 3,6-dibenzyl-*s*-tetrazines, and their molecular structure has been confirmed by *X*-ray analysis.

THE 1,2,4,5- or *s*-tetrazines consist of a group of compounds with properties which depend to a marked extent on the nature of their 3,6-substituents,[1,2] *e.g.* 3,6-diphenyl-*s*-tetrazine is stable unless subjected to fairly vigorous conditions, whereas the parent compound, *s*-tetrazine, must be prepared and stored out of contact with air. The effect of alkali on tetrazines has not been studied to any great extent. However, Wystrach [1] does comment that *s*-tetrazine, although stable to mild alkali, turns brown in strongly alkaline conditions (but no mention is made of products) and Pinner [3] has shown that 3,6-diphenyl-*s*-tetrazine yields benzaldehyde benzoylhydrazone on reaction with alcoholic potassium hydroxide. This paper describes further work on the action of alkali on tetrazines.

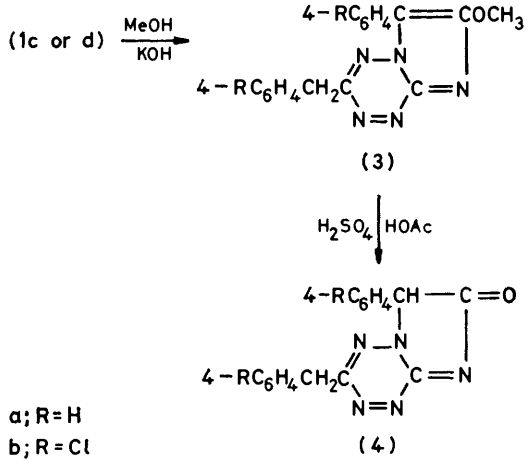
It was confirmed [3] that benzaldehyde benzoylhydrazone (2a) was in fact the product of the reaction of hot methanolic potassium hydroxide on 3,6-diphenyl-*s*-tetrazine (1a). 3-Phenyl-*s*-tetrazine [4] (1b) at room temperature yielded the corresponding formaldehyde benzoylhydrazone (2b) and an unidentified orange product. However, when 3,6-dibenzyl-*s*-tetrazine (1c)



(1) (2)

a; $R^1 = R^2 = Ph$ c; $R^1 = R^2 = PhCH_2$
b; $R^1 = H$, $R^2 = Ph$ d; $R^1 = R^2 = 4-ClC_6H_4CH_2$

was treated similarly no product of type (2c) was isolated but instead the reaction mixture precipitated yellow needle crystals of a compound (3a) of molecular formula $C_{18}H_{15}N_5O$. The only by-products identified were benzoic and phenylacetic acids. A gas, probably nitrogen, was evolved at the commencement of the reaction. The somewhat surprising analytical results were supported by mass spectral data and by the n.m.r. spectrum which showed the presence of a phenyl, a benzyl, and a methoxy group. Hydrolysis of compound (3a) in aqueous acetic acid–sulphuric acid yielded a further yellow solid (4a), $C_{17}H_{13}N_5O$, which exhibited a keto group absorption (*ca.* 1 670 cm^{-1}) in its i.r. spectrum. However this evidence could point to more than one structure for compound (3a) and hence an *X*-ray analysis of the structure was undertaken. This proved that compound (3a) had the novel imidazo[1,2-*b*]-*s*-tetrazine skeleton and hence its hydrolysis product had the related structure (4a). The 4-chloro-derivative (3b) was



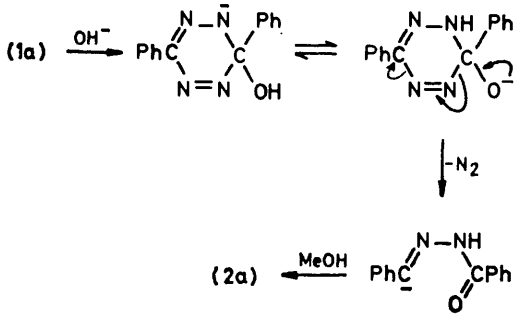
prepared similarly from tetrazine (1d) and hydrolysed to compound (4b).

The crystal structure determination proves that the ring system (3) is essentially planar (Table 2). The lengths of the C–N bonds vary considerably but all fall within the ranges of values observed for the ring systems in, *e.g.* tricycloquinazoline,[5] azanaphthalenes,[6] a substituted tetra-azapentalene,[7] and *s*-triazolo[1,5-*a*]triazine [8] in all of which there appears to be extensive π delocalisation. The bond lengths of our compound *cannot* be reconciled with that sole valence bond structure (3) which leaves the bridgehead nitrogen [N(3)] without a formal charge. The planes of the rings in the attached benzyl and phenyl groups are twisted out of the plane of the heterocyclic system (Figure and Table 2) to minimise intramolecular repulsions involving phenyl hydrogen atoms. As a result there are no close intermolecular contacts. A short bond [C(1)–C(16), 1.46 Å] exists between the phenyl and imidazole rings despite the large twist angle (50°): this has a parallel in bi-*p*-tolyl [9] (1.46 Å, 40°). The lengths of bonds involving the methoxy group and the benzyl methylene carbon atom are normal.

The use of ethanol or propan-2-ol in place of methanol in this reaction did not appear to give products comparable with compound (3a).

A possible mechanism giving rise to products of type

(2) is readily envisaged (Scheme 1). However, the pathway for the formation of compound (3a) from tetrazine



SCHEME 1

(1c) is much less obvious and we are very indebted to Dr. P. Edwards (I.C.I. Ltd., Pharmaceuticals Division) for helpful discussions on this problem (Scheme 2). The suggested mechanism involves removal of a benzyl proton by base from the starting material [(1) ⟶ (5)]. This benzylic anion (5) then reacts with a further molecule of starting material (1) to yield, *via* intermediates (6) and (7), the species (8) which undergoes a 1,3-benzyl shift for which the driving force would be aromatisation of the five-membered ring. Replacement by methoxide ion of the side chain at position 7 of compound (9) would give rise to the identified product (3a).

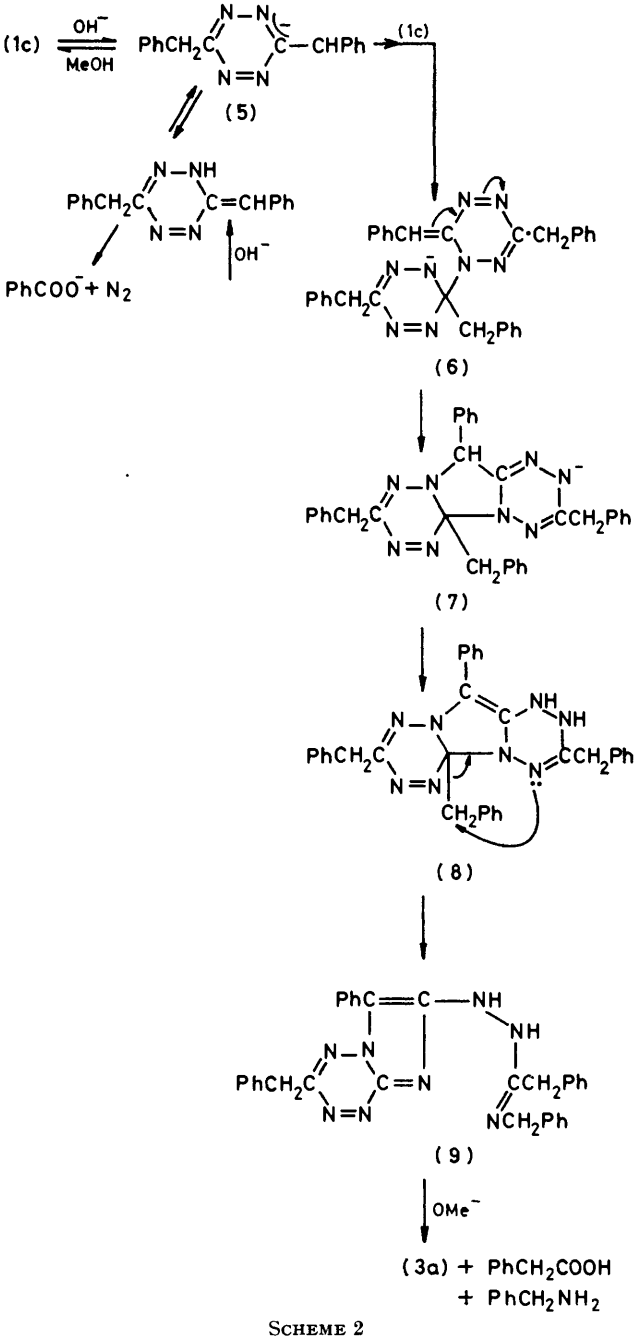
Crystal Data.—$C_{18}H_{15}N_5O$, $M = 317.3$. Orthorhombic, $a = 13.281(7)$, $b = 16.995(10)$, $c = 6.802(4)$ Å, $U = 1\,535.3$ Å^3, $D_c = 1.373$ g cm^{-3}, $F(000) = 664$, $Z = 4$. Space group $P2_12_12_1$ from systematic absences; Cu radiation, $\lambda = 1.541\,8$ Å; μ(Cu-K_α) = 6.4 cm^{-1}.

TABLE 1

Positional parameters (× 10^4) for non-hydrogen atoms

Atom	*x/a*	*y/b*	*z/c*
C(1)	2 953(3)	5 173(2)	2 132(6)
C(2)	2 028(3)	5 560(2)	2 424(6)
C(3)	1 984(3)	6 383(2)	2 323(7)
C(4)	2 843(3)	6 813(2)	1 911(7)
C(5)	3 761(4)	6 421(2)	1 606(7)
C(6)	3 818(3)	5 608(2)	1 714(6)
C(7)	−829(3)	3 982(3)	2 471(8)
C(8)	−1 276(3)	3 678(3)	4 166(8)
C(9)	−1 691(4)	4 207(3)	5 535(10)
C(10)	−1 656(4)	5 001(4)	5 250(11)
C(11)	−1 193(4)	5 285(3)	3 609(11)
C(12)	−780(3)	4 791(3)	2 208(9)
C(13)	−360(4)	3 417(3)	1 023(8)
C(14)	747(3)	3 285(2)	1 444(7)
C(15)	2 637(3)	3 033(2)	2 146(7)
C(16)	3 025(3)	4 319(2)	2 235(6)
C(17)	3 859(3)	3 806(2)	2 584(7)
C(18)	5 537(4)	3 509(3)	3 405(10)
N(1)	3 637(3)	3 050(2)	2 519(6)
N(2)	2 056(3)	2 418(2)	1 967(7)
N(3)	2 260(2)	3 802(2)	1 969(5)
N(4)	1 059(3)	2 547(2)	1 611(7)
N(5)	1 288(3)	3 946(2)	1 583(5)
O(1)	4 767(2)	4 090(2)	3 002(5)

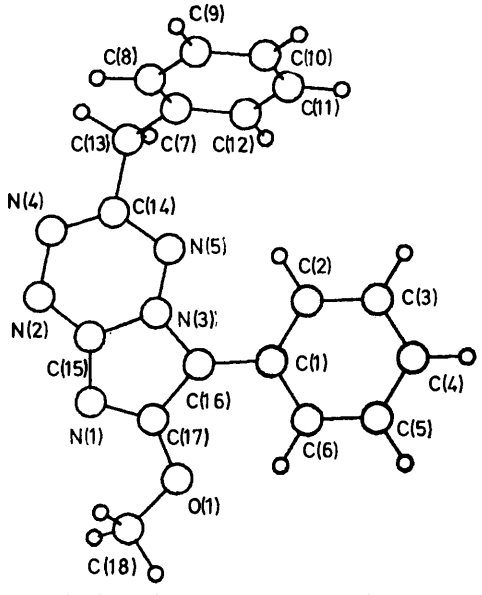
Data were collected by use of a Wooster four-circle diffractometer operating in the ω-scan mode; 1 898 independent reflections were classified as observed. Local programs were used for data reduction (no absorption correction), and the SHELX-76 system [10] for solution and refinement of the structure. The structure was solved with some difficulty by direct methods (multisolution tangent formula). Phases were assigned to 331 reflections with $|E| > 1.2$. The majority of the 80 E-maps of high figure-of-merit which were generated by use of 20 different sets of origin- and enantiomorph-defining and multisolution reflections showed what were



SCHEME 2

later recognised as overlapping parts of the true molecule shifted by *ca.* ±0.04*b*. This appeared to be due to the

occurrence of a number of interatomic vectors with a principal component 0.075—0.08*b*. Only three *E*-maps showed a well defined molecule, but they agreed with regard to its shape, position, and orientation (apart from trivial shifts of origin), and the choice of this molecule as the correct one was justified by the successful refinement of the structure and by the absence of anomalies in the final difference map. The nitrogen atoms were identified from their stronger Fourier peaks, and from their low thermal parameters when refined as carbon atoms. A difference synthesis following full-matrix least-squares refinement to *R* 0.134 showed peaks attributable to hydrogen atoms near all the expected positions (none within bonding distance of the nitrogen atoms); as these were of similar height to the stronger



Structure of 3-benzyl-7-methoxy-6-phenylimidazo[1,2-*b*]-*s*-tetrazine

' noise ' peaks the hydrogen atoms were included at calculated positions in subsequent cycles of refinement. After five strong low-angle reflections judged to be affected by extinction had been removed, refinement converged at *R* 0.063 (1 893 data, 220 parameters, unit weights, anisotropic thermal parameters for non-hydrogen atoms). Positional parameters are given in Table 1, and derived dimensions in Table 2. Thermal parameters and observed and calculated structure factors are listed in Supplementary Publication No. SUP 22373 (13 pp.).*

EXPERIMENTAL

Preparation of Imidate Salts.—Using the standard Pinner synthesis,[11,12] benzyl cyanide and its 4-chloro-derivative were converted into ethyl phenylacetimidate hydrochloride (65%), m.p. 100—102° (decomp.) [lit.,[13] 99—100° (decomp.)] and ethyl 4-chlorophenylacetimidate hydrochloride (73%), m.p. 180—183°, after shrinkage and decomposition at 130° [lit.,[14] 130° (decomp.)]. Authentic 4-chlorophenylacetamide prepared by decomposition of ethyl 4-chlorophenylacetimidate hydrochloride had m.p. 180—182°.

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.

TABLE 2

(*a*) Bond lengths (Å)

C(1)–C(16)	1.457(5)	N(3)–C(16)	1.355(5)
C(7)–C(13)	1.510(7)	N(4)–C(14)	1.327(6)
C(13)–C(14)	1.514(7)	N(5)–C(14)	1.336(5)
C(16)–C(17)	1.429(5)	N(2)–N(4)	1.363(6)
N(1)–C(15)	1.353(6)	N(3)–N(5)	1.341(5)
N(1)–C(17)	1.319(5)	C(17)–O(1)	1.329(5)
N(2)–C(15)	1.306(5)	C(18)–O(1)	1.447(6)
N(3)–C(15)	1.405(5)		

In phenyl rings: ring A, 1.383(6)—1.406(5), mean 1.396; ring B, 1.362—1.407(8), mean 1.383

(*b*) Interbond angles (°)

C(7)–C(13)–C(14)	111.8(4)	N(1)–C(17)–C(16)	114.5(4)
C(13)–C(14)–N(4)	117.4(8)	N(1)–C(17)–O(1)	124.3(4)
C(13)–C(14)–N(5)	114.3(4)	C(15)–N(1)–C(17)	104.3(3)
N(4)–C(14)–N(5)	128.4(4)	C(15)–N(2)–N(4)	117.5(3)
N(1)–C(15)–N(2)	128.0(4)	C(15)–N(3)–C(16)	108.9(3)
N(1)–C(15)–N(3)	110.2(3)	C(15)–N(3)–N(5)	122.0(3)
N(2)–C(15)–N(3)	121.8(4)	C(14)–N(4)–N(2)	118.1(4)
C(1)–C(16)–N(3)	126.2(6)	C(14)–N(5)–N(3)	112.3(3)
C(17)–C(16)–N(3)	102.0(3)	C(17)–O(1)–C(18)	115.7(3)

(*c*) Dihedral angles (°) between mean planes of rings

A,D 49.7; B,C, 71.8; C,D 0.8

(*d*) Maximum deviations (Å) of ring atoms from mean planes: A, 0.005 [C(2)]; B, 0.011 [C(7)]; C, 0.008 [N(5)]; D, 0.004 [C(17)]; E, 0.012 [N(5)]

The rings are defined by: A, C(1)–C(6); B, C(7)–C(12); C, C(14), C(15), N(2)—N(5); D, C(15)—C(17), N(1), N(3); E, rings C and D combined.

Preparation of Tetrazines.—In a typical preparation ethyl 4-chlorophenylacetimidate hydrochloride (11.6 g) was added over 15 min to a stirred solution of hydrazine hydrate (99%; 15 ml) in ethanol (25 ml) at 0°. The mixture was stirred for a further 4 h at 0° and finally for 2 h at room temperature. The crude dihydrotetrazine (9.2 g) was filtered off and added to sodium nitrite (6.5 g) dissolved in water (25 ml) at 0°. Glacial acetic acid (39 ml) was added dropwise to the cooled, stirred mixture which was kept for 2 h at 0° when further portions of sodium nitrite (1 g) and acetic acid (7.5 ml) were added. After stirring for 1 h at room temperature the crude tetrazine was filtered, washed well with water, and recrystallised from methanol. *Compound* (1d) (3.6 g) had m.p. 135—137° (Found: C, 57.7; H, 3.6; N, 16.6. $C_{16}H_{12}Cl_2N_4$ requires C, 58.0; H, 3.6; N, 16.9%). The liquors yielded an impure solid which was purified by dry column chromatography [15] [silica eluted with petroleum (b.p. 60—80°)–ether (3 : 1)] and shown to be 3,5-*bis*-(4-*chlorobenzyl*)-1,2,4-*triazole*, m.p. 184—185° (from ethanol) (Found: C, 60.7; H, 4.2; N, 13.1. $C_{16}H_{13}Cl_2N_3$ requires C, 60.4; H, 4.1; N, 13.2%).

Compound (1c) prepared similarly had m.p. 74—75° (lit.,[16] 74°).

Action of Methanolic Potassium Hydroxide on 3,6-*Dibenzyl-and* 3,6-*Bis*-(4-*chlorobenzyl*)-s-*tetrazine.*—Tetrazine (1c) (3 g) was dissolved in methanol (30 ml) and to the stirred solution there was added slowly at room temperature potassium hydroxide (0.9 g) dissolved in methanol (15 ml).

The addition took place under nitrogen and the solvents were boiled out to exclude air. (Although the same identified products were obtained when air was not excluded, better yields were obtained in the absence of air, hence the addition under nitrogen.) The colour of the

solution changed from red to brown and a gas (N_2) was evolved. The flask was sealed and left for 24 h by which time a yellow precipitate had formed. This and a subsequent crop (48 h later) was filtered and washed with a little methanol. The yellow *3-benzyl-7-methoxy-6-phenylimidazo*-[1,2-b]-s-*tetrazine* (3a) (0.42 g) on recrystallisation from acetone had m.p. 191—193° (decomp.) (Found: C, 68.2; H, 4.8; N, 22.2%; M^+, 317.125 2. $C_{18}H_{15}N_5O$ requires C, 68.1; H, 4.7; N, 22.1%; M^+, 317.127 6). The n.m.r. spectrum ($CDCl_3$) exhibited peaks at δ 4.4 (3 H, s, OCH_3), 4.5 (2 H, s, $CH_2C_6H_5$), 7.2—7.7 (8 H, m, aryl), and 8.3—8.5 (2 H, m, aryl). In addition to aromatic bands the i.r. spectrum (Nujol mull) had a peak at 1 560 cm^{-1} (C=N). The original liquors were evaporated *in vacuo* to small bulk, water was added, and the solution extracted with ether and ethyl acetate. Evaporation of these solvents, after drying, yielded oils. The aqueous solution was then acidified and again extracted with ether. This extract was shaken with aqueous sodium hydrogencarbonate solution and the hydrogencarbonate solution acidified and extracted with ether. The final extract, on drying, yielded a solid which was separated on a dry column [15] [silica eluted with petroleum (b.p. 40—60°)–ether (2 : 1)]. The small samples were purified by sublimation and proved by mixed melt and comparison of i.r. spectra to be benzoic and phenylacetic acids.

Tetrazine (1d) (2 g), potassium hydroxide (1 g), and methanol (21 ml) were treated as for compound (1c). Yellow-brown solid which was precipitated was purified on a dry column [15] [silica eluted with ethyl acetate–petroleum (b.p. 40—60°) (2 : 3)]. A red-brown forerun was obtained and finally yellow *compound* (3b) (0.1 g), m.p. 192—193° (decomp.) [from acetone–petroleum (b.p. 40—60°)] (Found: C, 55.9; H, 3.3; N, 17.9. $C_{18}H_{13}Cl_2N_5O$ requires C, 56.0; H, 3.4; N, 18.1%). The n.m.r. spectrum (C_2D_6CO) showed peaks at δ 4.45 and 4.4 (5 H, 2 × s, OCH_3 and CH_2), 7.2—7.4 (4 H, m, C_6H_4), and 7.4—8.6 (4 H, dd, C_6H_4). After extracting with ether and ethyl acetate, the original liquors were acidified and yielded a precipitate (0.25 g) of 4-chlorobenzoic acid which gave no depression of m.p. with an authentic sample.

Hydrolysis of Compounds (3a *and* b).—Compound (3a) (0.3 g) was refluxed in a mixture of acetic acid (5 ml), water (1 ml), and concentrated sulphuric acid (5 drops) for 6 h. The cooled solution, on dilution with water, yielded yellow *solid* (4a) (0.1 g) which melted at 269—270° (decomp.) after crystallisation from aqueous acetic acid, $\nu_{max.}$ 1 670 cm^{-1} (C=O) (Found: C, 67.4; H, 4.3; N, 22.7. $C_{17}H_{13}N_5O$ requires C, 67.3; H, 4.3; N, 23.1%).

Compound (3b) (0.2 g) was treated as above, the reflux time being 4½ h. Yellow *product* (4b) (0.11 g) obtained on recrystallisation from dimethylformamide–water (9 : 1) had m.p. 279—281° (decomp.) (Found: C, 54.7; H, 3.1; N, 18.6. $C_{17}H_{11}Cl_2N_5O$ requires C, 54.8; H, 3.0; N, 18.8%).

We are grateful to Professor J. Iball and Dr. B. C. Williams for collecting crystal data and to Mr. G. Ogg and Mr. D. Hunter for technical assistance. We are also indebted to Dr. R. Hull and Dr. P. Edwards, I.C.I. Ltd., Pharmaceutical Division for helpful discussions.

[8/206 *Received*, 8*th February*, 1978]

REFERENCES

[1] P. F. Wiley, ' The Chemistry of Heterocyclic Compounds, The 1,2,3, and 1,2,4-Triazines, Tetrazines and Pentazines ', eds. J. G. Erickson, P. F. Wiley, and V. P. Wystrach, Interscience, New York, 1956, p. 179.
[2] V. P. Wystrach, ' Heterocyclic Compounds ', ed. R. C. Elderfield, Wiley, New York, 1967, vol. 8, p. 105.
[3] A. Pinner, *Ber.*, 1894, **27**, 984.
[4] V. A. Grakauskas, A. J. Tomasewski, and J. P. Horwitz, *J. Amer. Chem. Soc.*, 1958, **80**, 3155.
[5] J. Iball and W. D. S. Motherwell, *Acta Cryst.*, 1969, **B25**, 882.
[6] (*a*) C. Sabelli, P. Tangocci, and P. F. Zanazzi, *Acta Cryst.*, 1969, **B25**, 2231; (*b*) T. M. Hamor and J. M. Robertson, *J. Chem. Soc.*, 1956, 3586; (*c*) C. Huizoon, B. W. van der Waal, A. B. van Egmond, and S. Harkema, *Acta Cryst.*, 1972, **B28**, 3415; (*d*) A. Clearfield, M. J. Sims, and P. Singh, *ibid.*, p. 350.
[7] M. Brufani, G. Casini, W. Fedelli, F. Mazza, and A. Vaciago, *Gazzetta*, 1971, **101**, 322.
[8] R. D. Gilardi, *Acta Cryst.*, 1973, **B29**, 2089.
[9] G. Casalone, C. Mariani, A. Mugnoli, and M. Simonetta, *Acta Cryst.*, 1969, **B25**, 1741.
[10] G. M. Sheldrick, SHELX-76 Program for Crystal Structure Determination, Cambridge University, 1975.
[11] A. Pinner, ' Die Imidoäther und ihre Derivate ', Oppenheim, Berlin, 1892.
[12] D. G. Neilson, ' The Chemistry of Amidines and Imidates ', ed. S. Patai, Wiley, New York, 1975, p. 385.
[13] R. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 1930, 397.
[14] G. Cavallini, E. Milla, E. Grumelli, E. Massarini, and D. Nardi, *Farmaco* (*Pavia*) *Ed. Sci.*, 1956, **11**, 633 (*Chem. Abs.*, 1959, **53**, 8125).
[15] B. Loev and M. M. Goodman, *Chem. and Ind.*, 1967, 2026.
[16] A. Pinner, *Ber.*, 1897, **30**, 1889.