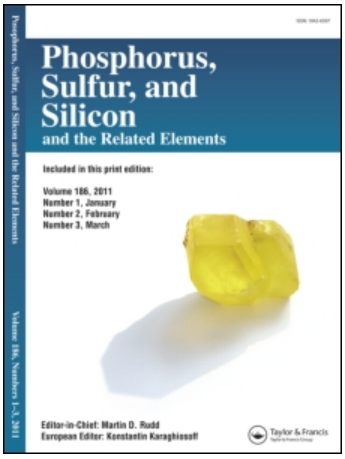


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

The Phosphorylation of Organic Compounds By Phosphoric Anhydride. Part 2, Phosphorylated Azoles

D. A. Efremov[a]; J. C. Tebby[a]; P. M. Zavlin[b]
[a] Staffordshire University, U.K. [b] St. Petersburg Institute of Cinema and Television, St. Petersburg, Russia

To cite this Article Efremov, D. A. , Tebby, J. C. and Zavlin, P. M.(1994) 'The Phosphorylation of Organic Compounds By Phosphoric Anhydride. Part 2, Phosphorylated Azoles', Phosphorus, Sulfur, and Silicon and the Related Elements, 92: 1, 167 — 170
To link to this Article: DOI: 10.1080/10426509408021468
URL: http://dx.doi.org/10.1080/10426509408021468

Phosphorus, Sulfur, and Silicon, 1994, Vol. 92, pp. 167-170
Reprints available directly from the publisher
Photocopying permitted by license only

THE PHOSPHORYLATION OF ORGANIC COMPOUNDS BY PHOSPHORIC ANHYDRIDE. PART 2, PHOSPHORYLATED AZOLES

D. A. EFREMOV* and J. C. TEBBY
Staffordshire University, Stoke-on-Trent, ST4 2DE, U.K.

and

P. M. ZAVLIN
St. Petersburg Institute of Cinema and Television, 191126, St. Petersburg, ul. Pravdi, 13, Russia

(Received June 14, 1994; in final form June 28, 1994)

Benzimidazoles and benzotriazoles are phosphorylated by phosphoric anhydride to give pyroamidophosphates (**2**) and their corresponding phosphoroamidic acids (**3**). N.m.r. data of the phosphorylated, 5,6-dimethylbenzotriazoles supported the existence of facile phosphorotropy.

Key words: Phosphoric anhydride, benzimidazoles, benzotriazoles, phosphorylation, phosphorotropy.

Benzimidazoles and benzotriazoles have attracted much attention over the recent decade often with the interest of establishing new pharmacological properties such as anti-tumour, anti-ulcer and cardiotonic.[2-4] Phosphorylated benzimidazole is an active plant growth stimulant.[5] The study of tautomeric properties of benzotriazoles was reviewed by Katritski and Lagowski.[6] Recent work[7] has shown that the non-substituted benzotriazole does not exhibit significant dynamic tautomeric equilibrium and is stable as the 1N-H tautomer (1; R = H, X = N). However certain N-substituted benzotriazoles are characterised by a pronounced equilibrium (Scheme I) in non-polar solvents,[7-9] whereas polar solvents induce the localisation of the substituent. Molecular orbital calculations on the parent benzotriazole[10] indicate a high energy barrier between the tautomers in the gas phase.

Although the tautomeric equilibria have been intensively studied, there has been no systematic study of the influence of the substituent.

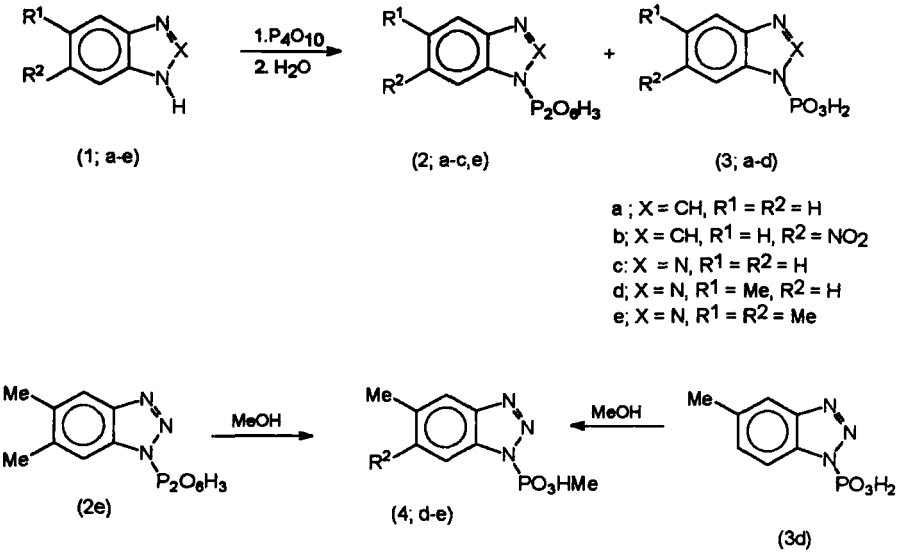
The phosphorylation of benzimidazole has been reported[11] the final products usually being the corresponding phosphoramidic esters. For example phosphorylated benzimidazole is an active plant growth stimulant.[12] This paper concerns the reaction of benzimidazoles (**1a–b**) and benzotriazoles (**1c–e**) with phosphoric anhydride to produce phosphoramidic acids.

SCHEME I Benztriazole tautomeric equilibria

The reactions were carried out using an excess of the anhydride in trichloromethane or tetrachloromethane, which is a modification of the method described earlier.[13] In most reactions high yields of the phosphorylated products were obtained usually as a mixture of the amidopyrophosphates (**2**) and the corresponding phosphoroamidic acids (**3**). Non-substituted benzotriazole and benzimidazole had a pronounced tendency to give mainly the latter compounds but the presence of small quantities of tetrahydrofuran favoured the formation of the amidopyrophosphates (**2**). The substituents on the aryl ring of benzotriazole had a pronounced influence upon the reaction pathway. The only product of the phosphorylation of 5-methylbenzotriazole (**1d**) was the phosphoramidic acid (**3d**) whereas 5,6-dimethylbenzotriazole (**1e**) gave the amidopyrophosphoric acid (**2e**). It is tentatively suggested that the monosubstituted pyrophosphoric acid (**2e**) from dimethylbenzotriazole is more resistant to hydrolysis due to its slightly more hydrophobic character. However it cannot be ruled out that the phosphorotropy of the dimethylbenzotriazoles induces further phosphorylation of the initially formed monoester of phosphoric acid (**3**) by phosphoric anhydride.

Prolonged treatment of the amidophosphoric acids (**3d**) by dry methanol led to the formation of the methyl esters (**4d**) whereas the amidopyrophosphoric acid (**2e**) underwent rapid cleavage of the P—O—P bond to give the ester (**4e**) (Scheme II).

The ^1H and ^{13}C n.m.r. spectra of the product from the phosphorylation of 5-methylbenzotriazole indicated that the methyl group and the phosphorylated nitrogen are oriented 1,5 because the signals of C7-H and C7 were broadened due to the influence of the adjacent phosphorus group. The ^1H and ^{13}C n.m.r. spectra of the phosphorylated 5,6-dimethylbenzotriazole (**2e**) showed no chemical shift difference between the two methyl groups in polar solvents such as DMSO, acetone, methanol and ethanol. Thus it appears probable that there is facile phosphorotropy between the two nitrogen atoms of the triazole ring in polar solvents (Scheme III).



SCHEME II Esterification

SCHEME III Triazole phosphorotropy

This is supported by the spectra of a pyridine solution in which the methyl groups are non-equivalent in the ^{13}C n.m.r. spectrum giving two signals (20.82 and 20.91 3 ppm). In the ^{1}H nmr spectrum the methyl groups give one broad signal. The non-equivalence of the signals is attributed to the formation of a pyridinium salt which retards phosphorotropy. The possibility of magnetic equivalence of the two methyl substituents of triazole (**2e**) in the positions 5 and 6, due to substitution of the dihydroxyphosphoryl group at the atom N2 is rejected because there was no spectroscopic evidence for the formation of o-quinonoid structure. On the other hand for the phosphorylated 5-methylbenzotriazole (**4d**), steric forces may favour the tautomer shown sufficiently to minimise the presence of its tautomer with 1,6 orientation of the substituents.

The influence of the phosphoryl group on the IR and UV spectra of the aryl ring of the benzotriazoles and benzimidazoles is very similar to those previously reported for the dialkyl benzimidolophosphoramidates.[12]

EXPERIMENTAL

IR spectra (KBr discs) were recorded on a Pye Unicam SP3-200 instrument. The solid state n.m.r. spectra were determined on a Brucker 100 and the n.m.r. spectra of DMSO-d6, deuterioacetone, ethanol-d6 solutions were determined on a Jeol FX90Q instrument. The n.m.r. data below are those recorded for solid samples (**2a–c, 3a–c**) and DMSO-d6 solutions (**2e, 3d, 4d–e**).

Phosphorylation of azoles (**1a–e**): The azole (1.1 molar equivalent) as a 10% solution in trichloromethane was heated under reflux for three hours with phosphoric anhydride (P_4O_{10}; 0.25 molar equivalent). Decantation of the solvent left a residue consisting of two layers—an amorphous solid and a heavy oil. The solid was triturated with diethyl ether or acetone to give the monoesters of phosphoric acid (**3**) as white powders and trituration of the oily residue with diethyl ether gave the pyrophosphoramidic acids (**3**).

1-(Benzimidazolyl) pyrophosphoric acid (**2a**): Benzimidazole (**1a**) was phosphorylated using the above method. Trituration of the heavy oil gave the pyrophosphoramidic acid in 6% yield isolated as a white powder m.p. 130° (dec.); $\nu(cm^{-1})$ 3300–3000, 1620, 1260, 620; ^{31}P nmr −16.70, −4.15 ppm. Found: P, 22.20, calc. P, 22.30%.

1-(Benzimidazolyl) phosphoric acid (**3a**): Benzimidazole (**1a**) was phosphorylated using the above method. Trituration of the amorphous solid gave the phosphoramidic acid in 90% yield obtained as a white powder m.p. 215°; $\nu(cm^{-1})$ 3300–3000, 1620, 1260, 1220; ^{31}P nmr −16.08 ppm. Found: P, 15.80; calc. P, 15.66%.

1-(6-Nitrobenzimidazoyl) pyrophosphoric acid (**2b**): 6-Nitrobenzimidazole (**1b**) was phosphorylated using the above method. Trituration of the heavy oil gave the pyrophosphoramidic acid in 18% yield isolated as a white powder m.p. 135°(dec.); $\nu(cm^{-1})$ 3300–3000, 1600, 1530, 1327, 1260, 1240, 620; ^{31}P nmr −18.20, −5.10 ppm. Found: P, 19.04; calc. P, 19.19%.

1-(6-Nitrobenzimidazolyl) phosphoric acid (**3b**): Nitrobenzimidazole (**1b**) was phosphorylated using the above method. Trituration of the amorphous solid gave the phosphoramidic acid in 42%

yield isolated as a white powder m.p. 205°; $\nu(cm^{-1})$ 3300–3000, 1630, 1525, 1330, 1270, 1250; ^{31}P nmr −16.95 ppm. Found: P, 12.64; calc. P, 12.76%.

1-(Benzatriazolyl) pyrophosphoric acid (**2c**): Benzotriazole (**1c**) was phosphorylated using the above method. Trituration of the heavy oil gave the pyrophosphoramidic acid in 9% yield isolated as a white powder m.p. 170°(dec.); $\nu(cm^{-1})$ 3380–3000, 1260, 1220, 625; ^{31}P nmr −12.80, −1.75 ppm. Found: P, 22.09; calc. P, 22.23%.

1-(Benzotriazolyl) phosphoric acid (**3c**): Benzotriazole (**1c**) was phosphorylated using the above method. Trituration of the amorphous solid gave the phosphoramidic acid in 84% yield isolated as a white powder m.p. 203°; $\nu(cm^{-1})$ 3350–3000, 1280, 1260, ^{31}P nmr −8.30 ppm. Found: P, 15.82; calc. P, 15.58%.

1-(5-Methylbenzatriazolyl) phosphoric acid (**3d**): 5-Methylbenzotriazole (**1d**) was phosphorylated using the above method. Trituration of the amorphous solid gave the phosphoramidic acid in 64% yield obtained as a white powder m.p. 196°(dec.); $\nu(cm^{-1})$ 3400(br), 1240; ^{1}H nmr 2.54 (CH_3), 7.35 (H6, J_{HH} 8 Hz, J_{PH} 1.5 Hz), 7.63 (H4), 7.78 (J_{HH} 8 Hz); ^{31}P nmr −11.56 ppm. Found: P, 14.26; calc. P, 14.08%.

1-(5,6-Dimethylbenzatriazolyl) pyrophosphoric acid (**2e**): 5,6-Dimethylbenzotriazole (**1e**) was phosphorylated using the above method. Trituration of the heavy oil gave the pyrophosphoramidic acid in 76% yield isolated as a white powder m.p. 201°(dec.); $\nu(cm^{-1})$ 3000 (br), 1615, 1260, 705; ^{1}H nmr 2.44 (br, CH_3), 7.63 (Ar); ^{13}C nmr 20.34 (CH_3), 114.20 (CH), 136.85 ($\underline{C}CH_3$), 138.69 (br, C—N); ^{31}P nmr 2.08 (J_{PP} 22 Hz), −13.79 ppm. Found: P, 20.14; calc. P, 20.33%.

Methyl 1-(5-methylbenzatriazolyl) phosphoric acid (**4d**): The phosphoramide (**2e**) was heated under reflux in methanol for two hours. Evaporation of the alcohol gave the product in 26% yield as a viscous oil; $\nu(cm^{-1})$ 3400(br), 1250, 1045; ^{1}H nmr 2.66 (CH_3), 3.84 (J_{PH} 12 Hz), 7.50 (J_{HH} 9 Hz, J_{PH} 1.5 Hz) 7.83, 7.99 (J_{HH} 9 Hz); ^{31}P nmr −12.42 ppm. Found: P, 13.39%; calc. P, 13.65%.

Methyl 1-(5,6-dimethyl-benzatriazolyl) phosphoric acid (**4e**): The phosphoramide (**3d**) was heated under reflux in methanol for two hours. Evaporation of the alcohol gave the product in 44% yield as a viscous oil; $\nu(cm^{-1})$ 3350(br), 1240, 1030; ^{1}H nmr 2.10 ($2CH_3$), 3.49 ($OCH_3 J_{PH}$ 12 Hz), 7.47 (br, CH); ^{13}C nmr 20.22 ($2CH_3$), 46.62 (OCH_3), 114.12 (C7), 136.89 (C5, C6), 138.66 (C8), 128.05 (C9) ppm; ^{31}P nmr −12.25 ppm. Found: P, 12.62; calc. P, 12.86%.

REFERENCES

1. On sabbatical leave from St. Petersburg Institute of Cinema and Television.
2. W. A. Denny, G. W. Rewcastle and B. C. Bangley, *J. Med. Chem.*, **33,** 814 (1990).
3. N. Bru-Magniez, T. Gungor, J. Lacrampe, M. Launay and J. M. Teulon, European Patent 1990, 385850.
4. A. Mertens, B. Muller-Beckmann, W. Kampe, J.-P. Holck and W. von der Saal, *J. Med. Chem.*, **30,** 1279 (1986).
5. G. L. Matevosian and P. M. Zavlin, *Z. Obsch. Khim.*, **52,** 1441 (1982).
6. A. R. Katritski and J. M. Lagowski, *Adv. Heterocycl. Chem.*, **2,** 27 (1963).
7. F. Thomas, J.-L. M. Abboud, J. Laynez, R. Notario, L. Santos, S. D. Nilsson, J. Catalan, R. M. Claramunt and J. Elguero, *J. Am. Chem. Soc.*, **111,** 7348 (1989).
8. J. R. Lindsay-Smith and J. S. Sadd, *J. Chem. Soc., Perkin Trans. I*, **1975,** 1181.
9. A. R. Katritski, K. Yannakopoulou, W. Kuzmierkiewicz, J. M. Aurrecoechea, G. J. Palenik, A. E. Koziol and M. Szezesniak, *J. Chem. Soc., Perkin Trans. I*, **1987,** 2673.
10. A. R. Katritski, A. Jozwiak, P. Lue, K. Yannakopoulou, G. J. Palenik and Z. Y. Zhang, *Tetrahedron*, **46,** 633 (1990).
11. A. R. Katritski, K. Yannakopoulou, E. Anders, J. Stevens and M. Szafran, *J. Org. Chem.*, **55,** 5683 (1990).
12. G. L. Matevosian and P. M. Zavlin, *Khim. Geterociel. Soed.*, **1990,** 723.
13. P. M. Zavlin and D. A. Efremov, *Phosphorus Sulfur*, **49/50,** 247 (1990).