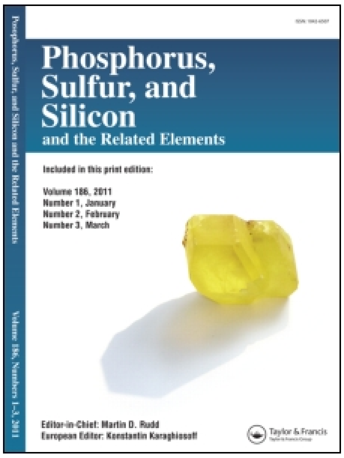


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Adenosine Cyclic 3', 5'-Phosphoramidate and N,N-Dimethylphosphoramidate: Synthesis Via Symmetrical and Mixed Anhydrides and Hydrolysis

Jenö Tomasz[a]; Sandor Bottka[a]; Janos Ludwig[a]; Istvan Pelczer[b]
[a] Institute of Biophysics, Biological Research Centre, Hungarian Academy of Sciences, Szeged, Hungary [b] Spectroscopic Department, EGIS Pharmaceuticals, Budapest, Hungary

To cite this Article Tomasz, Jenö , Bottka, Sandor , Ludwig, Janos and Pelczer, Istvan(1987) 'Adenosine Cyclic 3', 5'-Phosphoramidate and N,N-Dimethylphosphoramidate: Synthesis Via Symmetrical and Mixed Anhydrides and Hydrolysis', Phosphorus, Sulfur, and Silicon and the Related Elements, 30: 3, 597 — 600

To link to this Article: DOI: 10.1080/03086648708079136

URL: http://dx.doi.org/10.1080/03086648708079136

Phosphorus and Sulfur, 1987, Vol. 30, pp. 597–600
Photocopying permitted by license only

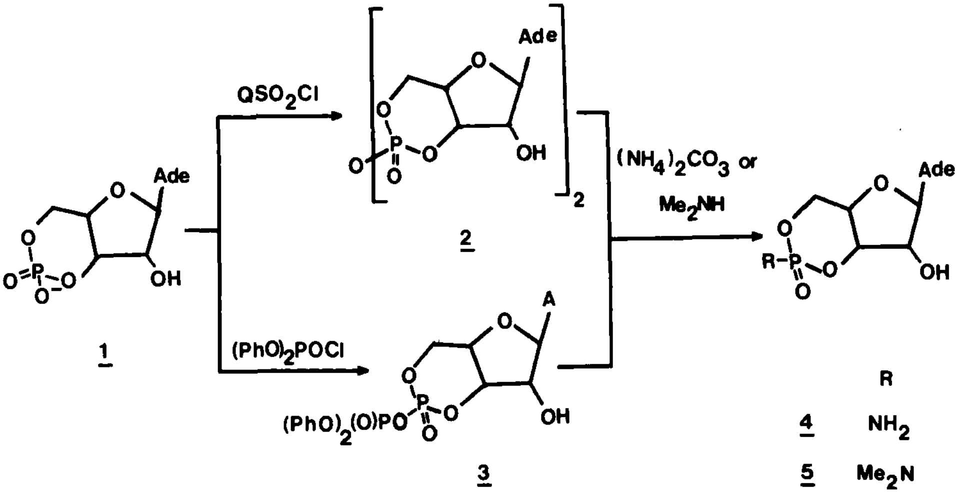
ADENOSINE CYCLIC 3',5'-PHOSPHORAMIDATE AND N,N-DIMETHYLPHOSPHORAMIDATE: SYNTHESIS VIA SYMMETRICAL AND MIXED ANHYDRIDES AND HYDROLYSIS

JENŐ TOMASZ, SÁNDOR BOTTKA, JÁNOS LUDWIG
Institute of Biophysics, Biological Research
Centre, Hungarian Academy of Sciences,
H-6701 Szeged, Hungary
ISTVÁN PELCZER
EGIS Pharmaceuticals, Spectroscopic Department
H-1475 Budapest, Hungary

Abstract The title compounds were synthesized by converting cyclic AMP with a sulfonyl chloride to the symmetrical anhydride or with diphenyl phosphorochloridate to the mixed anhydride, then aminolyzing the anhydrides without isolation. The synthesis preferentially gave S_P-amides. Characteristic differences were observed in the behavior of the unsubstituted amide and the dimethylamide under hydrolysis conditions.

In the course of the extensive studies on nucleoside phosphorodiamidates and phosphoramidates performed in our laboratory in the last decade, our attention has recently been focused on amide derivatives of adenosine cyclic 3',5'-monophosphate (1), the fundamental intracellular mediator and regulatory molecule of living systems. The synthesis of the individual diastereoisomers of adenosine cyclic 3',5'-phosphoramidate (R_P-4 and S_P-4)[1] and the elaboration of a new method for the preparation of adenosine cyclic 3',5'-N,N-dimethylphosphoramidate diastereoisomers (R_P-5 and S_P-5)[2] were our first goals in this field.

The synthesis of 4 and 5 was based on the activation of 1 (tri-n-butylammonium salt) with a sulfonyl chloride or $(PhO)_2POCl$ (or $POCl_3$) followed by in situ treatment of the reactive intermediate with $(NH_4)_2CO_3$ or Me_2NH (Scheme 1).

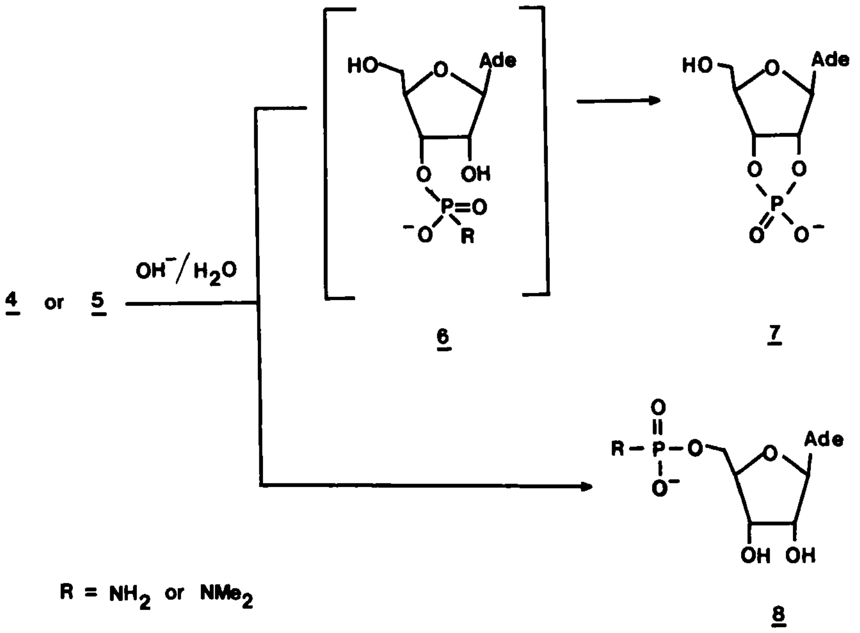


SCHEME 1

^{31}P NMR studies showed that the structure of the reactive intermediate differed according to the nature of the activating reagent: it was the symmetrical anhydride of 1 (2) for sulfonyl chlorides[3] and the diphenyl phosphoric mixed anhydride of 1 (3) for $(PhO)_2POCl$.[4] All the theoretically possible phosphorus diastereoisomers, i.e. R_PR_P-2, $R_PS_P(S_PR_P)$-2 and S_PS_P-2 as well as R_P-3 and S_P-3 were formed, but S_PS_P-2 and S_P-3 in unimportant quantities (<10%).

The syntheses preferentially gave the S_P amide diastereoisomers. For example, in the synthesis of 5 via 2, more than 90% of S_P-5 was formed.[2] Taking into consideration the relative distribution of diastereoisomers 2 $\{R_PR_P + R_PS_P(S_PR_P) > 90\%\}$, preferential attack by Me_2NH at R_P atoms with the inversion of configuration may be concluded. Similarly the reaction of 3 with Me_2NH afforded 5 as the main product (75-80%) with the inversion of configuration at phosphorus: an R_P-3/S_P-3 (∿98:2) mixture yielded an S_P-5/R_P-5 (∿91:9) mixture.[4] In addition to 5, $(PhO)_2P(O)NMe_2$ (20-25%) was also formed, though the liberation of $(PhO)_2P(O)O^-$ anion would have been expected to play the decisive role in this reaction.[5]

Comparative studies on the S_P diastereoisomers indicate characteristic differences in the behavior of 4 and 5 under hydrolysis conditions.[1,4] The very fast alkaline hydrolysis of 4 (completed within 1 min in 0.1 N NaOH at 37°C) resulted in the formation of a mixture of adenosine cyclic 2',3'-monophosphate (7) and adenosine 5'-phosphoramidate (8, $R=NH_2$) (∿6:4). The same compounds were formed in neutral solution. Compound 7 and adenosine 5'-N,N-dimethylphosphoramidate (8, $R=NMe_2$) (∿9:1) were the products of the much slower alkaline hydrolysis of 5 (∿90% conversion in 30 h). Compound 7 was probably formed *via* 3'-phosphoramidate 6 as demonstrated in the hydrolysis of adenylyl-(3'-5')-thymidine (P→N) amide.[6] On the basis of the differences between the hydrolysis rates of 4 and 5, an elimination-addition type mechanism[7] was proposed for the alkaline hydrolysis of 4. The preferential formation of 7 might be a consequence of the better leaving group property of the $CH_2O^-(CH_2OH)$ group (Scheme 2). Acid hydrolysis of 4 (∿50% conversion during 0.5 h in 0.1 N HCl at 37°C) gave a mixture of 7,



SCHEME 2

8 (R=NH$_2$) and 1 (∿86:11:3). Considering the sensitivity of P-N bonds towards acid, the insignificant quantity of 1 is surprising. More than 99% of compound 1 was formed in the acid hydrolysis of 5 (∿50% conversion in 2.5 h). Differences in acid hydrolysis of 4 and 5 may be interpreted on the basis of stereoelectronic effects.

REFERENCES

1. S. Bottka and J. Tomasz, Tetrahedron Lett., 26, 2909 (1985).
2. W.G. Bentrude and J. Tomasz, Synthesis, 27 (1984).
3. J. Tomasz, S. Bottka and I. Pelczer, submitted for publication.
4. S. Bottka and J. Tomasz, unpublished results.
5. N.S. Corby, G.W. Kenner and A.R. Todd, J. Chem. Soc., 1234 (1952); A. Todd, Proc. N.A.S., 45, 1389 (1959); A.J. Lambie, Tetrahedron Lett., 3709 (1966).
6. J. Tomasz and J. Ludwig, Nucleosides & Nucleotides, 3, 45 (1984).
7. F.H. Westheimer, Chem. Revs. 81, 313 (1981).