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Synthesis and Characterization of 5-Deoxy-3-O-methyl-5-C-[(R)- and (S)-phenylphosphinothioyl]-α- and β-D-xylopyranoses. The First Sugar Analogue Having a Phosphinothioyl Group in the Hemiacetal Ring

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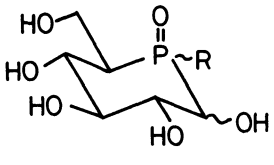
Treatment of 5-deoxy-5-iodo-1,2-O-isopropylidene-3-O-methyl-α-D-xylofuranose with ethyl phenylphosphinothioate in the presence of sodium hydride, followed by the reduction with sodium dihydrobis-(2-methoxyethoxy)aluminate, and then with 0.5 M HCl-EtOH gave the title compounds, which were characterized as the 1,2,4-O-triacetates.

Various sugar analogues possessing a phosphorus atom in the hemiacetal ring have been prepared:[1] e.g., D-glucopyranoses **1**[2] and D-ribofuranoses **2**.[3] Such compounds are of interest for their physicochemical properties and potential biological activity.[1] Although a large number of the analogues having an alkyl-, aryl-,or hydroxyphosphinyl group in the hemiacetal ring have been synthesized, no derivatives containing a phosphinothioyl group in the ring have been, to the best of our knowledge, reported so far. Meanwhile, it is well known that many organophosphorus insecticides of thiono (P=S) type, such as fenithion[4] (**3**) and EPN[5] (**4**), are in wide use and the P=S functional group of these compounds is effective in the relatively facile permeability through the skin of insects and then the slow oxidative desulfurization to generate the active oxo (P=O) form by the action of a microsomal oxidase *in vivo*.[6] We now describe a synthetic route to a new sugar analogue having a phosphinothioyl group in the hemiacetal group, taking a D-xylopyranose analogue as a model compound.



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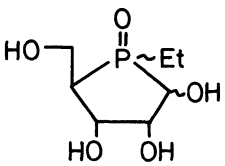

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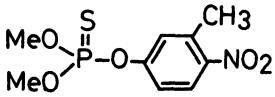

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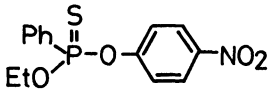

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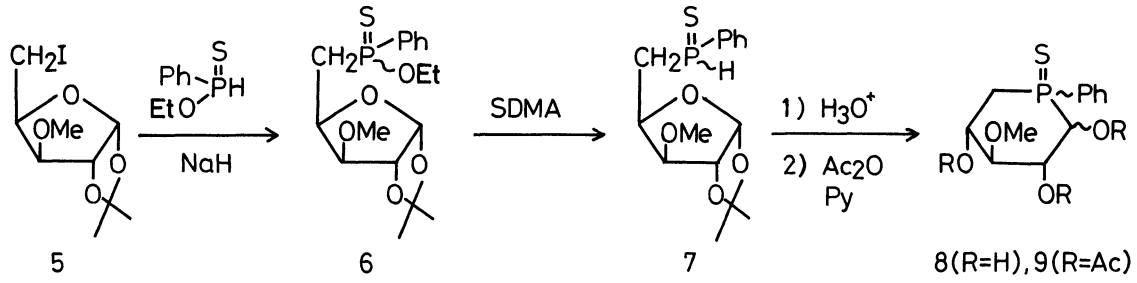
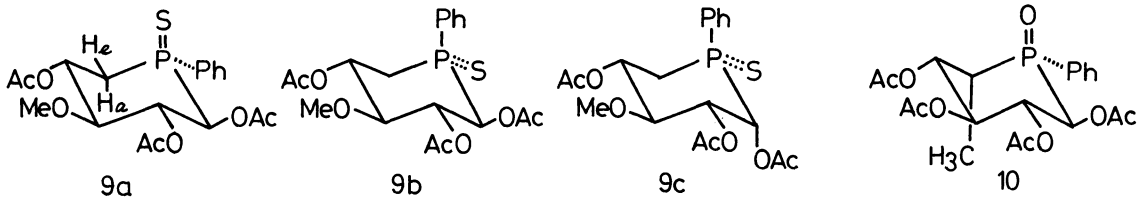
After examination of various reaction conditions, introduction of a phosphinothioyl group to a sugar moiety was found to be best achieved by the reaction of 5-deoxy-5-iodo-1,2-O-isopropylidene-3-O-methyl-α-D-xylofuranose[7] (**5**) with ethyl phenylphosphinothioate[8] in dry N,N-dimethylformamide (DMF) containing an equivalent of sodium hydride at 0 °C for 3 h under argon, and the 5-[(R,S)-(ethoxy)phenylphosphinothioyl] derivative **6** was obtained in 84% yield.[9] Reduction of **6** was best effected by using sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) in dry benzene at 20 °C for 17 h, thus giving the unstable 5-C-(phenylphosphinothioyl) compound **7**.[10] The acid-catalyzed deprotection and ring transposition of **7** [in oxygen-free 0.5 M HCl-EtOH (1:1 v/v, pH ≈ 1) at 80 °C for 2 h] provided 5-deoxy-3-O-methyl-5-C-(phenylphosphinothioyl)-D-xylopyranoses (**8**). The structural assignment of **8** was made by converting it into the triacetates **9** by treatment with acetic anhydride-pyridine (1:2 v/v) at 20 °C for 20 h. Purification of the crude mixture by column chromatography on silica-gel using ethyl acetate-hexane as eluant gave three diastereomers: **9a**[11] (mp 166.5-167 °C, 1.8% overall yield from **6**), **9c**[11] (mp 181-182 °C, 3.4%) as pure compounds, and **9b**[11] (colorless crystals, 2.3%) contaminated by a small amount of inseparable **9c**.





The precise configurations and the $^4C_1$(D) conformation of **9a-c** were established by complete analysis of their 500-MHz ^{1}H NMR spectra by taking into account the known parameters of structurally similar compounds obtained before; e.g., 5-deoxy-5-C-[(S)-phenylphosphinyl]-α-L-idopyranose peracetate[12] (**10**). These exact parameters for **9a-c** that are summarized in Table 1 would be highly important in determining other unknown 5-deoxy-5-C-phosphinothioyl-D-aldopyranoses. In view of stereochemistry of the pyranose ring as well as the torsion angles between the P=S bond and the plane of the P-phenyl ring, it is particularly interesting to note that some of the characteristic features in the and J values for **9a-c** are appreciably different from those[2,3,12] for **1**, **2**, and **10** [e.g., δ 5.77 (H-1) and $J_{1,P}$ = 0.3 Hz for **9a** vs. δ 6.11 (H-1) and $J_{1,P}$ = 2.75 Hz for **10**].[11]

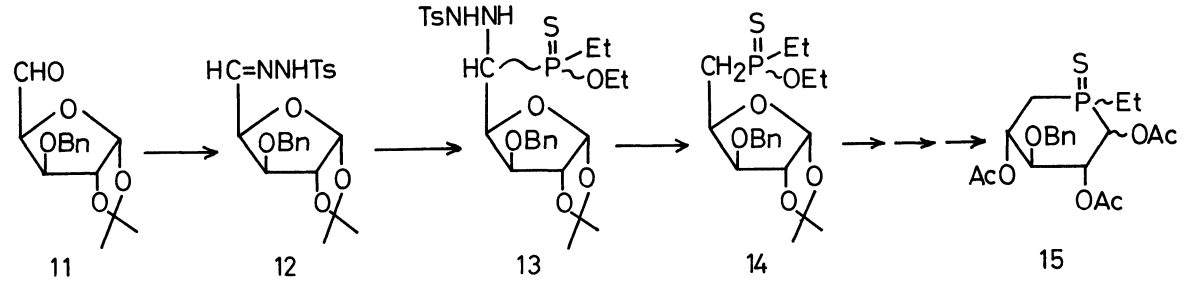
Table 1. ^{1}H NMR (500 MHz) Parameters for **9a-c** in $CDCl_3$[a)]

	Chemical shift								
Compd	H-1	H-2	H-3	H-4	Ha-5	He-5	Ac-1,2,4[b)]	MeO-3	Ph(o,m,p)
9a	5.77	5.76	3.55	5.63	2.42	2.59	1.89,2.07,2.05	3.49	7.87,7.49,7.56
9b	5.78	5.08	3.66	4.93	2.37	3.24	2.31,2.16,2.07	3.47	7.97,7.59,7.53
9c	6.12	4.78	3.49	4.83	2.56	3.16	2.31,2.14,2.04	3.47	7.85,7.59,7.52

	Coupling constants											
	$J_{1,2}$	$J_{1,P}$	$J_{1,5e}$	$J_{2,3}$	$J_{2,P}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5e}$	$J_{4,P}$	$J_{5a,5e}$	$J_{5a,P}$	$J_{5e,P}$
9a[c)]	11.0	0.3	0	9.6	3.4	9.6	11.8	4.2	3.4	13.8	8.5	16.7
9b	10.6	6.2	0	9.6	5.0	9.6	12.0	4.0	4.0	15.0	15.0	15.0
9c	2.2	7.0	2.2	10.0	0	10.0	12.0	4.0	2.8	15.0	15.0	15.0

a) The assignments of all signals were made by exploying a first-order analysis with the aid of decoupling technique and the parameters were confirmed a computer-assisted simulation analysis. b) The assignments of acetoxyl groups may have to be interchanged. c) J values for the P-phenyl ring protons: $J_{P,2} = J_{P,6} = 13.9$ Hz, $J_{P,3} = J_{P,5} = 3.3$ Hz, $J_{P,4} = 2.0$ Hz, $J_{2,3} = J_{5,6} = 7.3$ Hz, $J_{2,4} = J_{2,6} = J_{4,6} = J_{3,5} = 1.5$ Hz, and $J_{3,4} = J_{4,5} = 7.5$ Hz.

Another approach for synthesizing the title sugar analogues was also made, which, however, turned out to be less satisfactory. Namely, condensation of 3-O-benzyl-1,2-O-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose **11**[13)] with p-tolylsulfonylhydrazine in methanol at 20 °C for 5 h gave the hydrazone **12**[11)] (mp 129-132 °C, 73% yield), which was treated with ethyl ethylphosphinothioate in the presence of trifluoromethanesulfonic acid at 0-20 °C for 7 h, thus affording the 5-C-[(ethoxy)ethylphosphinothioyl] derivative **13** (syrup, 55%). Although reduction of **13** with sodium borohydride in THF was repeatedly examined at 25-50 °C for 7-48 h, the desired compound **14**[11)] was obtained in fluctuating yields (10-40%) besides a major amount of unidentified byproducts. The same treatment of **14** (as in the case of **6**) with SDMA, followed by the 0.5 M HCl-EtOH and then Ac_2O-pyridine, afforded a diastereomeric mixture of the chromatographically inseparable triacetates **15** (colorless tar)[11)] in only ca. 1% overall yield from **14**.



Although improvement of the yields of some steps particularly of the ring-enlargement reactions remains to be done, present work demonstrates an effective way for preparation of the first 5-deoxy-5-C-(phenylphosphinothioyl)-D-xylo-pyranoses from an appropriate D-xylofuranose and this scheme is expected to be readily applicable for preparation of various other 5-deoxy-5-C-phosphinothioyl-D- and L-aldofuranoses and pyranoses.

References

1) For a review, see H. Yamamoto and S. Inokawa, Adv. Carbohydr. Chem. Biochem., 42, 131 (1984).
2) H. Yamamoto, K. Yamamoto, S. Inokawa, M. Yamashita, M.-A. Armour, and T.T. Nakashima, J. Org. Chem., 48, 435 (1983); H. Yamamoto, T. Hanaya, H. Kawamoto, S. Inokawa, M. Yamashita, M.-A. Armour, and T.T. Nakashima, J. Org. Chem., 50, 3516 (1985).
3) H. Yamamoto, Y. Nakamura, S. Inokawa, M. Yamashita, M.-A. Armour, and T.T. Nakashima, J. Org. Chem., 49, 1364 (1984).
4) Y. Nishizawa, K. Fujii, T. Kadota, J. Miyamoto, and H. Sakamoto, Agric. Biol. Chem., 25, 605 (1961).
5) A.G. Jelinek, U. S. Patent 2503390 (1950); Chem. Abstr., 44, 6435f (1950). N. Shindo, S. Wada, K. Ota, F. Suzuki, and Y. Ohata, U. S. Patent 3327026 (1967); Chem. Abstr., 67, 64531q (1968).
6) M. Eto, Yuki Gosei Kyokai Shi, 45, 549 (1987), and references cited therein.
7) H. Yamamoto, T. Hanaya, S. Inokawa, K. Seo, M.-A. Armour, and T.T. Nakashima, Carbohydr. Res., 114, 83 (1983).
8) J. Michalski and Z. Tulimowski, Rocz. Chem., 36, 1781 (1962); K.A. Petrov, A. A. Basyuk, V.P. Evdakov, and L.I. Mizrakh, Zh. Obshch. Khim., 34, 2226 (1964).
9) **6** was obtained in less satisfactory yields when the reaction was carried out at room temp in DMF or at elevated temps in benzene or xylene.
10) The following conditions resulted in less satisfactory yields of **7** from **6**: SDMA/benzene (50 °C, 30 h), SDMA/benzene (20 °C, 35-44 h), SDMA/THF (0 °C, 26 h), and $LiAlH_4$/ether (20 °C, 60 h).
11) MS (high-resolution) and ^1H NMR data (mostly at 500 or 400 MHz) were in agreement with the products described in this paper. The complete data for the newly isolated products as well as more precise conformational study will be presented in full paper (in preparation).
12) H. Yamamoto, K. Yamamoto, H. Kawamoto, S. Inokawa, M.-A. Armour, and T.T. Nakashima, J. Org. Chem., 47, 191 (1982).
13) T. Iida, M. Funabashi, and J. Yoshimura, Bull. Chem. Soc. Jpn., 46, 3203 (1973).

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