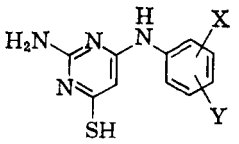
TABLE V
2-AMINO-6-THIO-4-(SUBSTITUTED ANILINO)PYRIMIDINES



X	Y	% Yield	M.P.	U.V. Absorption pH 1 λ_{max}	pH 1 $\epsilon \times 10^{-3}$	pH 11 λ_{max}	pH 11 $\epsilon \times 10^{-3}$	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	2-CH_3	63	259–260	237	13.0	243	17.6	56.6	5.2	24.1	56.4	5.0	24.0
				327	34.6	308	21.2						
H	3-CH_3	81	224–226	242	14.8	252	20.5	56.6	5.2	24.1	56.4	5.1	24.1
				326	32.0	314	26.5						
H	4-CH_3	85	284–285	244	12.8	252	17.6	56.6	5.2	24.1	56.5	5.2	24.0
				330	25.5	314	22.7						
H	4-CH_3O	79	238–239	241	12.6	251	17.6	53.1	4.9	22.5	53.1	4.9	22.3
				330	25.2	314	22.7						
H	2-Cl	67	237–238	322	23.6	252	18.0	47.5	3.6	22.0	47.8	3.3	22.0
						310	20.5						
H	3-Cl	80	285–286	240	13.9	253	22.7	47.5	3.6	22.0	47.4	3.3	21.9
				330	33.0	318	31.7						
3-CH_3	4-CH_3	83	220–222 (dec.)	224	38.6	252	15.5	57.3	5.7	22.7	57.6	5.7	22.8
				325	23.2	313	19.0						
4-CH_3	3-Cl	80	261–262 (dec.)	242	13.4	252	20.3	49.5	4.2	21.0	49.4	4.4	20.7
				326	30.4	315	26.2						
3-Cl	4-Cl	85	288–289 (dec.)	242	12.1	255	17.8	41.8	2.8	19.5	41.9	3.0	19.8
				268	10.9	320	26.4						
				332	30.7								

Acknowledgment. The authors wish to express their appreciation to Mr. Wayne H. Nyberg, Miss Phyllis G. Shaul, and Mrs. Carol R. Tuttle for their valuable assistance in performing analytical and instrumental measurements.

MIDWEST RESEARCH INSTITUTE
KANSAS CITY 10, MO.

A New Route to Glycosyl Phosphates

DONALD L. MACDONALD

Received October 16, 1961

Currently, there are very few methods available for the preparation of glycosyl phosphates. The direct phosphorylation of the glycosidic hydroxyl group of an otherwise protected sugar[1] has not been used extensively, because of the low yield obtained. The most widely used method, in fact the only practical one, is that involving the reaction of an acylglycosyl halide with some salt of either orthophosphoric acid or a diester thereof. The procedure of Cori, Colowick, and Cori[2] utilizing trisilver phosphate has been used for the preparation of a number of 1-phosphates; generally,[3] but not always,[3a,4] the anomer formed is that with the phosphate group *cis* to the hydroxyl group on carbon two of the sugar. The procedure using "monosilver phosphate"[3c,5] (the silver salt actually present is disilver phosphate[6]) appears to give, normally, the *trans*-anomer, as does the procedure using silver dibenzyl phosphate.[5,7] The use of silver diphenyl phosphate may result in the formation of either anomer, depending on the sugar employed.[1,4,8] Recently, certain improvements in the preparation of aldose 1-phosphates have been brought about by the use of tertiary amine salts, rather than silver salts, of phospho diesters.[9]

The present note describes the preparation of glycosyl phosphates by an entirely different procedure. The fully acetylated sugar is warmed *in vacuo* with anhydrous phosphoric acid; a vigor-

(1) T. Posternak, *J. Am. Chem. Soc.*, **72**, 4824 (1950).
(2) C. F. Cori, S. P. Colowick, and G. T. Cori, *J. Biol. Chem.*, **121**, 465 (1937).
(3) (a) S. P. Colowick, *J. Biol. Chem.*, **124**, 557 (1938); (b) W. R. Meagher and W. Z. Hassid, *J. Am. Chem. Soc.*, **68**, 2135 (1946); (c) E. W. Putman and W. Z. Hassid, *J. Am. Chem. Soc.*, **79**, 5057 (1957); (d) H. W. Kosterlitz, *Biochem. J.*, **33**, 1087 (1939).
(4) T. Posternak and J. P. Rosselet, *Helv. Chim. Acta*, **36**, 1614 (1953).
(5) F. J. Reithel, *J. Am. Chem. Soc.*, **67**, 1056 (1945).
(6) R. Flatt and G. Brunisholz, *Helv. Chim. Acta*, **34**, 692 (1951).
(7) M. L. Wolfrom, C. S. Smith, D. E. Pletcher, and A. E. Brown, *J. Am. Chem. Soc.*, **64**, 23 (1942).
(8) N. J. Antia and R. W. Watson, *J. Am. Chem. Soc.*, **80**, 6134 (1958).
(9) R. S. Wright and H. G. Khorana, *J. Am. Chem. Soc.*, **78**, 811 (1956); **80**, 1994 (1958); F. Maley, G. F. Maley, and H. A. Lardy, *ibid.*, **78**, 5303 (1956).

ous evolution of acetic acid takes place in the melt as the acetyl group on carbon one is replaced by a phosphate group. With β-D-glucose pentaacetate and β-D-galactose pentaacetate, the α-1-phosphates were obtained as crystalline potassium or cyclohexylammonium salts in yields of 31% and 35%, respectively. These yields are only slightly lower than those recorded in the literature,[1] and presumably they could be improved considerably. Putman and Hassid[3c] have reported that the air-dried cyclohexylammonium salts of α-D-glucose 1-phosphate and α-D-galactose 1-phosphate were anhydrous, but in our hands, the materials were hydrated even after drying *in vacuo*. In view of these differences, the potassium salts may be superior to the cyclohexylammonium salts for purposes of characterization of these two materials.

This new reaction, in which an aldose 1-phosphate is produced is, of course, analogous to the preparation of an acetylglycosyl bromide by reaction of a fully acetylated sugar with hydrobromic acid in acetic acid.[10] Furthermore, the similarity extends to the products of the two reactions, for in the examples reported here, the predominant anomer isolated is α. Further comparison of the two reactions will be deferred until more examples have been studied.

EXPERIMENTAL

α-D-Galactopyranose 1-phosphate. Crystalline phosphoric acid[11] (5.8 g.) was dried overnight at room temperature *in vacuo* over magnesium perchlorate and then melted (50°). Five grams of finely powdered β-D-galactose pentaacetate was mixed thoroughly into the melt with a glass rod; the odor of acetic acid became noticeable almost at once. The flask containing the mixture was evacuated with an oil pump provided with a trap, and placed in a water bath at 50°. A vigorous gas evolution took place, and the solid acetate gradually went into solution. After 2 hr., the gas evolution had usually ceased, and the solid had disappeared. The sirup was dissolved, with gentle warming, in 30 ml. of dry tetrahydrofuran, and the resulting solution was poured into 240 ml. of ice-cold *N*-lithium hydroxide; this was then left at room temperature overnight to saponify the acetyl groups. The precipitated lithium phosphate was removed by filtration through a filter aid and the remaining basic solution was passed through a column of Dowex 50W (1.9 × 20 cm.), and the column washed with 200 ml. of water after which the effluent was no longer acid. Ten milliliters of redistilled cyclohexylamine was added to the percolate, which was then concentrated *in vacuo*. Absolute alcohol was added and then removed *in vacuo* and when this process was repeated twice, a white crystalline solid remained. This was mixed at room temperature with 200 ml. of isopropyl alcohol, which dissolved the cyclohexylammonium acetate; the mixture was centrifuged and the solid washed twice in the same manner with 30-ml. portions of isopropyl alcohol. The product was filtered and washed with ether, and dried *in vacuo* over calcium chloride; yield 3.72 g. of hygroscopic material having $[\alpha]^{20}D$ +64° (*c* 1.5, water). Chromatography using isopropyl alcohol–ammonia–water (7:1:2)[12] on Whatman #41H paper revealed a little inorganic phosphate; the sugar phosphate had R_{Pi} 1.5 (Pi = orthophosphate).

Inorganic phosphate was removed as magnesium ammonium phosphate, using magnesium acetate (0.5 g.) in a solution of the sugar phosphate in 40 ml. of 1.5*N* ammonium hydroxide. Cations were removed with a small column of Dowex 50W and the percolate was made basic with cyclohexylamine and concentrated at reduced pressure to a sirup which was taken up in 15 ml. of 95% ethanol and seeded. The slightly hygroscopic salt was filtered off and, without excessive air drying, dried *in vacuo* over calcium chloride; it weighed 2.85 g. and showed $[\alpha]^{20}D$ +65.8° (*c* 1.5, water). Recrystallization in the same fashion did not change this constant, nor did purification *via* the brucine salt, as described.[3c] The brucine salt, twice crystallized from 80% ethanol and showing $[\alpha]^{20}D$ +30° (*c* 2, water), was converted back to the cyclohexylamine salt by addition of cyclohexylamine to its aqueous solution and extraction of the brucine; the cyclohexylamine salt thus prepared showed $[\alpha]^{20}D$ +64.6° (*c* 2, water). When dried overnight at 75° *in vacuo*, the salt showed $[\alpha]^{20}D$ +78.5° (*c* 2, water), and had the composition of a hemihydrate. When dried at 95° for 4 hr., the compound decomposed. Putman and Hassid[3c] reported +78.5° for their air-dried anhydrous material.

Anal. Calcd. for $C_{18}H_{39}N_2O_9P.{}^1/_2H_2O$ (467.5): C, 46.24; H, 8.62; N, 5.99; P, 6.63. Found: C, 46.15; H, 8.77; N, 5.97; P, 6.34.

For further characterization, the material was converted to the potassium salt. All of the remaining material from the above experiments was combined and concentrated to remove ethanol, and then taken up in 50 ml. of water. Cyclohexylamine (2 ml.) was added and traces of brucine were removed by methylene dichloride extraction, after which the cations were removed using a Dowex 50W column (1.5 × 18 cm.). The strongly acid percolate was brought to *p*H 8.5 with 0.5*N* potassium hydroxide solution, and then concentrated at reduced pressure to 40 ml. Ethanol was added gradually to the ice-cold solution (100 ml. over a period of 2 days) and the product (1.98 g.) was twice recrystallized in the same manner. After drying overnight at 15 mm. over calcium chloride, the dihydrate weighed 1.65 g. (35%) and showed $[\alpha]^{20}D$ +97.3° (*c* 2, water); literature +100°[1] and +98°.[3d] On drying at <1 mm. pressure over calcium chloride, part of the water of hydration was lost.

Anal. Calcd. for $C_6H_{11}K_2O_9P.2H_2O$ (372.4): C, 19.35; H, 4.06; P, 8.32. Found: C, 19.61; H, 4.02; P, 8.14.

α-D-Glucopyranose 1-phosphate. Five grams (12.7 mmoles) of β-D-glucose pentaacetate was treated with anhydrous phosphoric acid (5.7 g.) as described above, and after removal of the cyclohexylammonium acetate, there remained 3.38 g. of a white crystalline material which showed $[\alpha]^{20}D$ +41.3° (*c* 2, water). This D-glucose 1-phosphate contained only traces of inorganic phosphate, and it showed R_{Pi} 1.6 on Whatman #41H paper, using isopropyl alcohol–ammonia–water. Recrystallization from water (3 ml., gentle warming) plus ethanol (75 ml., warm) gave 1.98 g., $[\alpha]^{20}D$ +59.6°, and a second recrystallization gave 1.87 g. (31%), $[\alpha]^{20}D$ +60.9° (*c* 2, water), after drying in air or *in vacuo* over calcium chloride or phosphorus pentoxide. The salt was converted to the brucine salt, $[\alpha]^{20}D$ +21° (*c* 2, water) after two recrystallizations from 85% ethanol, and then back to the cyclohexylamine salt. The twice recrystallized monohydrate thus obtained had $[\alpha]^{20}D$ +60.8° (*c* 2, water). Putman and Hassid[3c] reported $[\alpha]D$ +64° for their air-dried anhydrous material.

Anal. Calcd. for $C_{18}H_{39}N_2O_9P.H_2O$ (476.5): C, 45.37; H, 8.67; N, 5.88; P, 6.50. Found: C, 45.33; H, 8.82; N, 5.80; P, 656.

For further characterization, the potassium salt was prepared in 96% yield from the cyclohexylammonium salt,

(10) L. J. Haynes and F. H. Newth, *Advances in Carbohydrate Chem.*, 10, 207 (1955).

(11) Available from Fluka, AG, Buchs, S. G., Switzerland.

(12) D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 2040 (1953).

as described for the D-galactose compound. After recrystallization from 15 parts of water by the gradual addition, at 0°, of two volumes of ethanol, the dihydrate showed $[\alpha]^{20}D$ +78.6° (*c* 2, water); literature +78°.[1,13] For analysis, the material was dried at room temperature in high vacuum over calcium chloride.

Anal. Calcd. for $C_6H_{11}K_2O_9P.2H_2O$ (372.4): C, 19.35; H, 4.06; P, 8.32. Found: C, 19.45; H, 4.17; P, 8.10.

(13) M. L. Wolfrom and D. E. Pletcher, *J. Am. Chem. Soc.*, **63**, 1050 (1941).

Acknowledgment. We thank the Analytical Services Unit of this laboratory, under the direction of Mr. H. G. McCann, for the analyses, and Dr. H. G. Fletcher, Jr., for helpful suggestions.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
NATIONAL INSTITUTES OF HEALTH
BETHESDA 14, MD.

Communications TO THE EDITOR

The Abnormal Claisen Rearrangement

Sir:

The "abnormal" Claisen rearrangement, *i.e.* the formation of *o*-(α,γ-dimethylallyl)phenol from γ-ethylallyl phenyl ether,[1] has generally been considered as a competitor to the normal Claisen rearrangement.[2] We wish to report evidence which proves this concept untenable, and shows conclusively that the formation of the abnormal product is due to rearrangement of the Claisen product, *o*-(α-ethylallyl)phenol. The experimental keystones of this conclusion are a kinetic examination of the rearrangement of γ-ethylallyl phenyl ether, and the preparation and rearrangement of *o*-(α-ethylallyl)phenol.

A 0.5 *M* solution of γ-ethylallyl phenyl ether[1] in *N*,*N*-diethylaniline was rearranged at 195 ± 1°. Samples withdrawn at intervals were taken up in petroleum ether and the diethylaniline removed by extraction with dilute hydrochloric acid. The product was analyzed for total phenol by infrared spectroscopy. After separation of phenolic material from residual ether, analysis for the normal and abnormal products was made via infrared measurements at 915 and 965 $cm.^{-1}$, respectively. A typical run is shown in Table I. While not sufficiently precise to warrant a detailed kinetic analysis, these data show clearly that the normal and abnormal products arise from consecutive processes.

Since the second rearrangement is slower than the first at 195°, lower temperatures permit easy isolation of the normal product. Thus heating a 1.0 *M* solution of γ-ethylallyl phenyl ether in mesitylene at 165° for 175 hr. gives *o*-(α-ethylallyl)phenol (b.p. 65° (0.25 mm), $n^{20}D$ 1.5321, ν 915 $cm.^{-1}$). When this phenol is heated in diphenyl ether, diethylaniline or neat at 200–225° it slowly rearranges to give *o*-(α,γ-dimethylallyl)phenol.[3] The earlier data[1] leading to this structure for the abnormal product are bolstered by the synthesis of a phenol with an identical infrared spectrum by the C-alkylation of dry sodium phenoxide with α,γ-dimethylallyl bromide in toluene.[4]

TABLE I

REARRANGEMENT OF γ-ETHYLALLYL PHENYL ETHER IN DIETHYLANILINE AT 195°

Time (hr.)	Ether (Mole/L.)	Normal Product (Mole/L.)	Abnormal Product (Mole/L.)
0	0.50	—	—
6	0.32	0.15	0.00
12	0.20	0.25	0.02
18	0.10	0.32	0.05
36	0.03	0.25	0.16
48	0.00	0.20	0.27

It is significant that the methyl ether of *o*-(α-ethylallyl)phenol [b.p. 80° (0.5 mm.), ν 907,990 $cm.^{-1}$] was recovered unaltered after being heated 13 hr. in diethylaniline at 195° or in diethylaniline containing one molar equivalent of phenol at 230° for 16 hr. Since the ether recovered from a partial rearrangement of γ-ethylallyl phenyl ether at 200° exhibited an unchanged infrared spectrum, α,γ-dimethylallyl phenyl ether is apparently not an intermediate. Furthermore, a sample of 2,6-dimethyl-4-(α-ethylallyl)phenol (undistilled, ν 910,-990 $cm.^{-1}$. Calcd. for $C_{13}H_{18}O$: C, 82.1; H, 9.5. Found: C, 82.8; H, 10.2), obtained by preferential

(1) W. M. Lauer and W. F. Filbert, *J. Am. Chem. Soc.*, **58**, 1388 (1936). C. D. Hurd and M. A. Pollack, *J. Org. Chem.*, **3**, 550 (1939).

(2) *Cf.* for example D. S. Tarbell, *Org. Reactions*, II, 1 (1944). W. M. Lauer, G. A. Douldoras, R. E. Hileman & R. Lupino, *J. Org. Chem.*, 26, 4785 (1961).

(3) E. N. Marvell and J. L. Stephenson, *J. Org. Chem.*, 25, 676 (1960).

(4) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, 81, 2705 (1959).