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2-β-D-RIBOFURANOSYLBENZOXAZOLE FROM 2,5-ANHYDRO-D-ALLONOIMIDATE, AND 1,3-DIMETHYL-8-β-D-RIBOFURANOSYLXANTHINE FROM 2,5-ANHYDRO-D-ALLONO-THIOIMIDATES AND -DITHIOATES

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ABSTRACT

The ability of imidates, thioimidates, and dithioates to react with *o*-aminophenol (**2**) and 5,6-diamino-1,3-dimethyluracil (**6**) was studied, using non-saccharide model compounds, as well as saccharide derivatives. All of the model compounds gave 2-methylbenzoxazole, but only ethyl dithioacetate gave a purine derivative with **6**. Methyl 2,5-anhydro-D-allonoimidate hydrochloride reacted with **2** to yield 2-β-D-ribofuranosylbenzoxazole, but failed to react with compound **6**. On reaction with compound **6** such fully acylated thioimidates as ethyl and benzyl 2,5-anhydrotri-*O*-benzoyl- or tri-*O*-*p*-toluoyl-D-allonothioimidate hydrochloride yielded amidines that underwent aromatization of the furanose ring. Such monoacylated thioimidates as ethyl or benzyl 2,5-anhydro-6-*O*-benzoyl-D-allonothioimidate hydrochloride yielded, with compound **6**, 8-(5-*O*-benzoyl-β-D-ribofuranosyl)-1,3-dimethylxanthine, without aromatization. Such dithioates as benzyl 2,5-anhydro-6-*O*-benzoyl-D-allonodithioate and ethyl 2,5-anhydrotri-*O*-benzoyl-D-allonodithioate were obtained by treating the corresponding thioimidate with H_2S in pyridine. With compound **6**, the first yielded 8-(5-*O*-benzoyl-β-D-ribofuranosyl)-1,3-dimethylxanthine, which afforded the free *C*-nucleoside 1,3-dimethyl-8-β-D-ribofuranosylxanthine on treatment with methanolic ammonia.

INTRODUCTION

A number of 8-substituted purine nucleosides have been synthesized by treating aldonic acids with 4,5-diaminopyrimidines. Thus, for example, 8-β-D-ribofuranosyladenine and 8-(3-deoxy-β-D-ribofuranosyl)adenine have been prepared by treating 4,5,6-triaminopyrimidine with 2,5-anhydro-D-allonic acid and 2,5-anhydro-4-deoxy-D-*ribo*-hexonic acid, respectively. The acids afforded amides which were cyclized by pyrolysis, to give the desired nucleosides[1,2]. Because the conditions needed for cyclization often caused partial anomerization of the resulting nucleosides, or aromatization of their sugar moiety, other routes were tried. Igolen *et al.*[3–5] treated benzyl 2,5-anhydro-6-*O*-benzoyl-D-allonothioimidate hydro-

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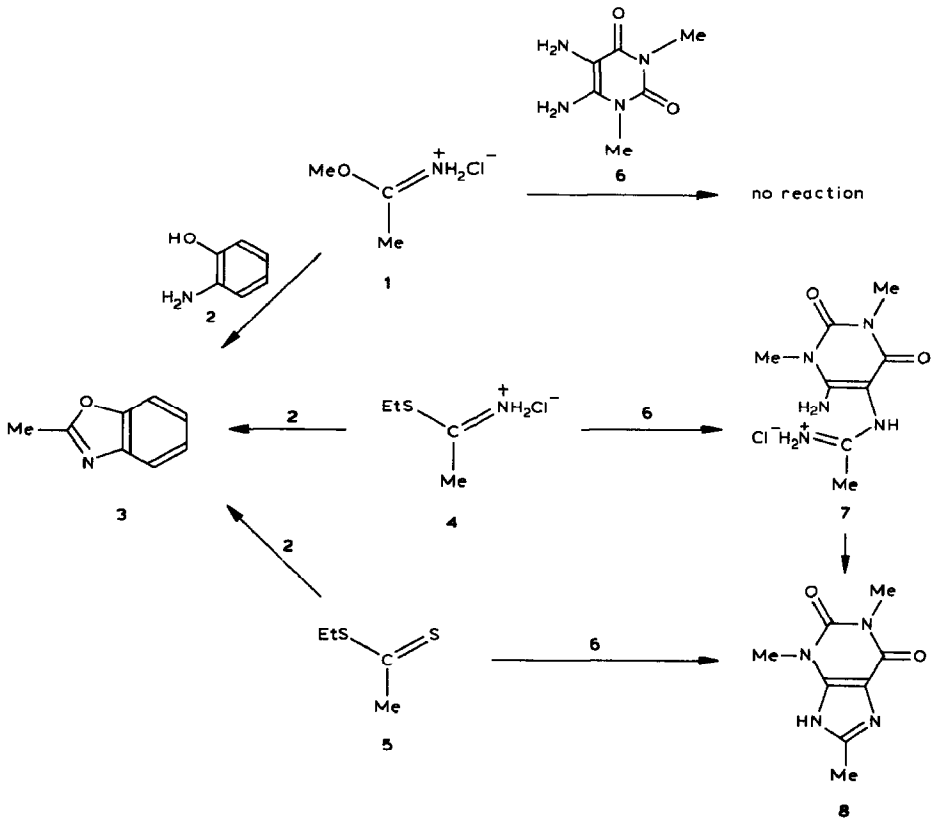
chloride with 2-aminomalononitrile, and converted the resulting pyrazole into 8-β-D-ribofuranosylpurine (a *C*-nucleoside). Poonian and Nowoswiat[6] used a base, namely, methyl 2,5-anhydro-D-allonoimidate, to obtain a structurally related, triazole *C*-nucleoside.

The purpose of this work was to explore the ability of saccharide imidates, thioimidates, and dithioates to form heterocycles by reaction with such nucleophiles as *o*-aminophenol (**2**) and 5,6-diamino-1,3-dimethyluracil (**6**). Methyl acetimidate hydrochloride, ethyl acetothioimidate hydrochloride, and ethyl dithioacetate were found to be useful as model compounds, as they duplicated the reactions of the corresponding saccharide derivatives.

DISCUSSION

When the model compounds methyl acetimidate hydrochloride (**1**), ethyl acetothioimidate hydrochloride (**4**), and ethyl dithioacetate (**5**) were treated with *o*-aminophenol (**2**), they all yielded 2-methylbenzoxazole (**3**). However, when they were treated with the weaker nucleophile 5,6-diamino-1,3-dimethyluracil (**6**), each compound behaved differently: methyl acetimidate (**1**) did not react; ethyl acetothioimidate (**4**) afforded an amidine (**7**), which upon pyrolysis yielded 1,3,8-trimethylxanthine (**8**); and ethyl dithioacetate (**5**) afforded purine **8** directly. The saccharide derivatives studied behaved similarly, as will be shown later.

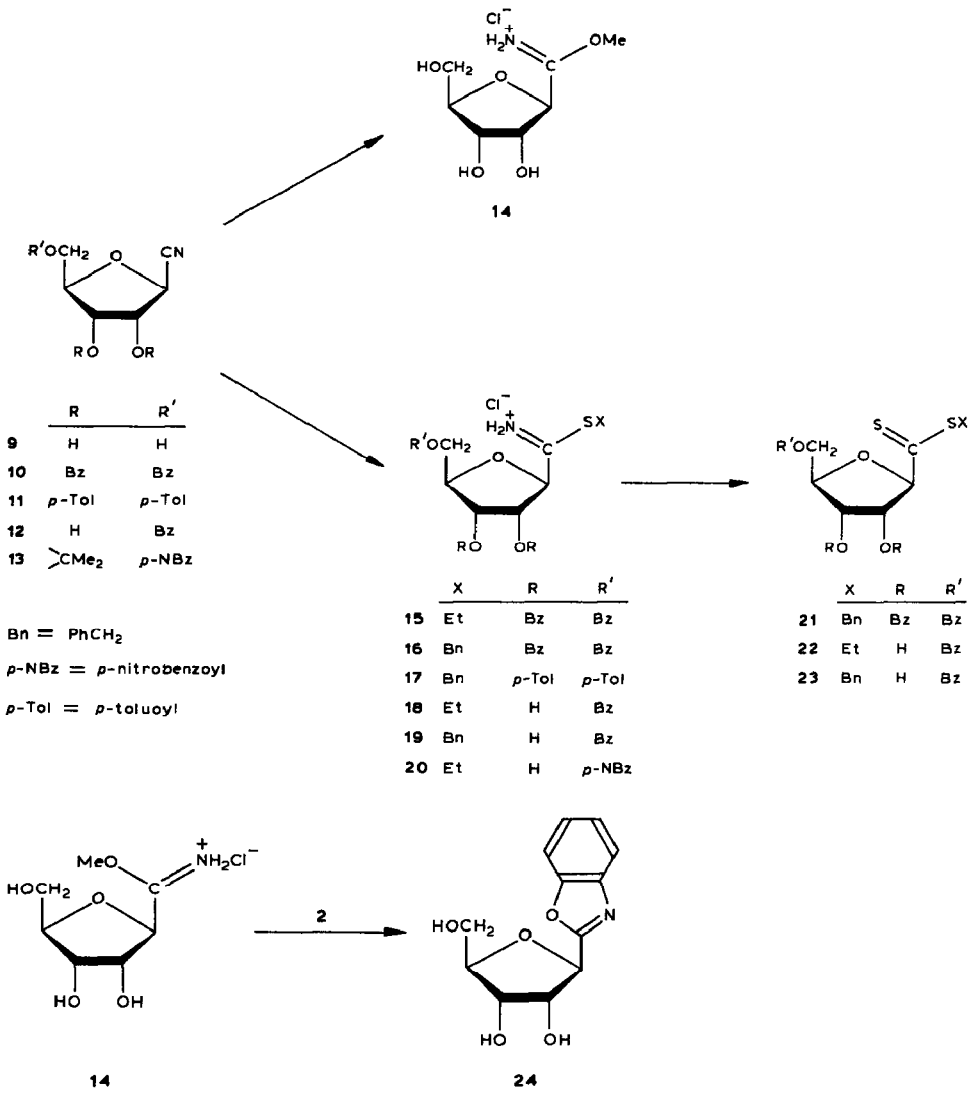


Preparation of imidates, thioimidates, and dithioates. The model compounds (**1**, **4**, and **5**) were obtained by methods described in the literature, whereas new saccharide derivatives were synthesized by modifying the procedures developed for the preparation of the non-carbohydrate derivatives. Methyl 2,5-anhydro-D-allonoimidate hydrochloride (**14**) was prepared from a base obtained by the action of sodium methoxide on 2,5-anhydro-D-allononitrile[6] (**9**). To prepare ethyl and benzyl thioimidate hydrochlorides, esters of 2,5-anhydro-D-allononitrile were treated with ethanethiol or α-toluenethiol in the presence of HCl, according to a procedure[7,8] first developed by Pinner and Klein[7]. Two types of 2,5-anhydro-D-allononitrile esters were used as starting materials. The first comprised tri-*O*-acylated (tri-*O*-benzoyl or tri-*O*-*p*-toluoyl) derivatives, whereas the second included monoacylated (6-*O*-benzoyl or 6-*O*-*p*-nitrobenzoyl) derivatives. Thus, with ethanethiol in HCl, 2,5-anhydrotri-*O*-benzoyl-D-allononitrile (**10**) afforded ethyl 2,5-anhydro-tri-*O*-benzoyl-D-allonothioimidate hydrochloride (**15**), and, with α-toluenethiol, benzyl 2,5-anhydrotri-*O*-benzoyl-D-allonothioimidate hydrochloride (**16**). Similarly, the readily accessible 2,5-anhydrotri-*O*-*p*-toluoyl-D-allononitrile[9] (**11**) afforded, with α-toluenethiol, benzyl 2,5-anhydrotri-*O*-*p*-toluoyl-D-allonothioimidate hydrochloride (**17**). To prepare the monoacylated thioimidates, 2,5-anhydro-6-*O*-benzoyl-D-allononitrile (**12**) and *p*-nitrobenzoyl derivative **13** were converted by the same procedure into the corresponding ethyl and benzyl 2,5-anhydro-6-*O*-aroyl-D-allonothioimidate hydrochlorides (**18** and **19**) and into ethyl 2,5-anhydro-6-*O*-*p*-nitrobenzoyl-D-allonothioimidate hydrochloride (**20**). The analogous 2,5-anhydro-6-*O*-*p*-toluoyl-D-allononitrile was not used, because it was not readily accessible.

After testing various procedures, it was found that good yields of the 2,5-anhydro-D-allonodithioates needed for the study could be obtained by bubbling H_2S into thioimidate solutions in pyridine. Using this procedure, benzyl 2,5-anhydrotri-*O*-benzoyl-D-allonothioimidate[3] (**16**), ethyl 2,5-anhydro-6-*O*-benzoyl-D-allonothioimidate hydrochloride (**18**), and its known[5] benzyl derivative (**19**) were converted into benzyl 2,5-anhydrotri-*O*-benzoyl-D-allonodithioate (**21**) and ethyl and benzyl 2,5-anhydro-6-*O*-benzoyl-D-allonodithioates (**22** and **23**), respectively.

Cyclization reactions. — a. Imidates. To test the ability of imidate salts to form heterocycles, the hydrochlorides of a model imidate and of a saccharide imidate were refluxed with *o*-aminophenol (**2**) and with 5,6-diamino-1,3-dimethyluracil (**6**). With **2**, methyl acetimidate hydrochloride (**1**) afforded 2-methylbenzoxazole (**3**). Similarly, the saccharide derivative, methyl 2,5-anhydro-D-allonoimidate hydrochloride (**14**) yielded an anomeric mixture of 2-D-ribofuranosylbenzoxazoles (*e.g.*, **24**). However, neither of the two imidate hydrochlorides (**1** and **14**) nor their free bases could be made to react with 5,6-diamino-1,3-dimethyluracil (**6**). It seems that the amino groups of this diamine are weak nucleophiles that are incapable of displacing the MeO group of methyl imidates or their salts.

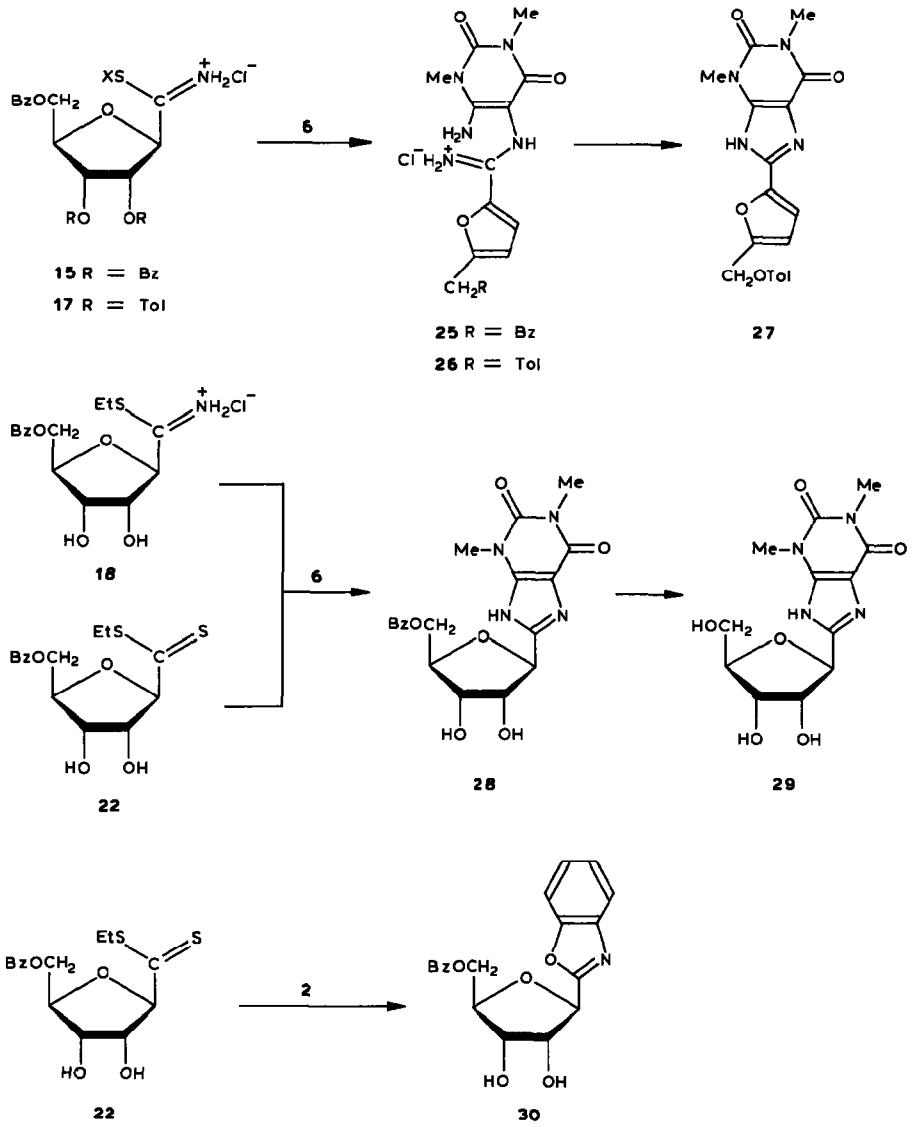
b. Thioimidates. The model ethyl acetothioimidate hydrochloride (**4**) reacted with *o*-aminophenol (**2**) to afford 2-methylbenzoxazole (**3**), resembling in this respect imidate **1**. However, unlike the latter compound, which failed to react with



6, hydrochloride **4** was able to do so, and yielded an amidine (**7**), which could be converted into 1,3,8-trimethylxanthine (**8**) by pyrolysis. The fully acylated sugar thioimidates also reacted with **6**, and gave amidines which, on pyrolysis, afforded 8-substituted xanthines. Thus, ethyl 2,5-anhydrotri-*O*-benzoyl-D-allonothioimidate hydrochloride (**15**) and 2,5-anhydrotri-*O*-*p*-toluoyl-D-allonothioimidate (**17**) respectively afforded amidines **25** and **26**. Unfortunately, aromatization of the furanose ring occurred during their formation, rendering the reaction useless for the preparation of *C*-nucleosides. Aromatization did not take place when the monobenzoylated derivatives were used, presumably because elimination of hydroxyl groups is more difficult than that of benzoxy groups. One monoacylated

thioimidate that resisted aromatization and cyclized to give the blocked nucleoside in small yield was ethyl 2,5-anhydro-6-*O*-benzoyl-D-allonothioimidate hydrochloride (**18**), which, with **6**, afforded 8-(5-*O*-benzoyl-β-D-ribofuranosyl)-1,3-dimethylxanthine (**28**).

c. Dithioates. Two dithioates were investigated, a model compound, ethyl dithioacetate (**5**), and a monoacylated sugar derivative, ethyl 2,5-anhydro-6-*O*-benzoyl-D-allonodithioate (**22**). Both compounds reacted with **2** and with **6**, to afford the corresponding benzoxazole and xanthine derivatives. The model dithioate **5** afforded 2-methylbenzoxazole (**3**) and 1,3,8-trimethylxanthine (**8**), and the



monoacylated saccharide dithioate **22** afforded the partly blocked *C*-nucleosides 2-(5-*O*-benzoyl-β-D-ribofuranosyl)benzoxazole (**30**) and 8-(5-*O*-benzoyl-β-D-ribofuranosyl)-1,3-dimethylxanthine (**28**), respectively. The latter gave the unblocked *C*-nucleoside, 1,3-dimethyl-8-β-D-ribofuranosylxanthine (**29**) on treatment with methanolic ammonia. It seems that saccharide dithioates require longer reaction times than do thioimidates, but afford better yields of 8-substituted xanthine nucleosides. For this reason, it is worthwhile to convert saccharide thioimidates into dithioates before carrying out the cyclization reaction.

The ultraviolet absorption spectra of 2-methylbenzoxazole and 2-D-ribofuranosylbenzoxazole, as well as of 1,3,8-trimethylxanthine and the various 1,3-dimethyl-8-β-D-ribofuranosylxanthine's prepared, showed characteristic absorptions at 274–281 nm (see Table I).

EXPERIMENTAL

General. — The uncorrected melting-points reported here were determined on a Kofler-block apparatus preheated to 10° below the actual melting-point and then heated at the rate of 2°/min. Optical rotations were measured in 0.2-dm tubes with a Bendix NPL 1100 or in 1.0-dm tubes with a Perkin–Elmer 141 polarimeter. Mass spectra were recorded with a Hewlett–Packard 5995 GC/MS spectrometer,

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

Compounds	λ_{max} *(log ε) in EtOH*
2-Methylbenzoxazole (**3**)	276 (3.64)[a] 270 (3.61) 264 (3.43) 231 (3.97)
2-D-Ribofuranosylbenzoxazole (**24**)	280 (3.75) 273 (3.82) 265 (3.70) 236 (4.13)
2-(5-*O*-Benzoyl-β-D-ribofuranosyl)benzoxazole (**30**)	281 (3.81) 273 (3.87) 232 (4.40)
1,3,8-Trimethylxanthine (**8**)	274 (4.10) in H_2O[b]
8-(5-*O*-Benzoyl-β-D-ribofuranosyl)-1,3-dimethylxanthine (**28**)	277 (3.91) 230 (4.00) 214 (4.07)
1,3-Dimethyl-8-β-D-ribofuranosylxanthine (**29**)	277 (4.67)

[a]Ref. 16. [b]Ref. 23.

and i.r. spectra with a Perkin–Elmer 735 spectrophotometer calibrated with polystyrene. U.V. spectra were recorded with a Perkin–Elmer 323 spectrophotometer. ^{1}H-N.m.r. spectra were recorded at 200 MHz with a Nicolet spectrometer interfaced with a 1180 data system and a 293A pulser, and at 60 MHz with a Varian EM-360 spectrometer, with tetramethylsilane or sodium 4,4-dimethyl-4-silapentane-1-sulfonate as the internal standard. ^{1}H-N.m.r. data are described as br, broad; d, doublet; dd, doublet of doublets; m, multiplet; q, quartet; s, singlet; t, triplet; followed by the coupling constant (J, in Hz) or the number of protons from the integrated peak area and the chemical identification of the protons described. ^{13}C-N.m.r. spectra were recorded with a Bruker WP-80 spectrometer at 20.1 MHz in the F.t. mode at 32°. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Pyridine, tetrahydrofuran (THF), and MeOH were distilled over calcium hydride, and kept over molecular sieves. Acetonitrile, ethanethiol, and α-toluenethiol were dried over molecular sieves. *o*-Aminophenol was recrystallized from ether before use. HCl gas was dried with anhydrous calcium chloride. Column chromatography was performed on Merck silica gel 60 (0.063–0.200 mm).

Methyl acetimidate hydrochloride[7,8] (**1**) and ethyl acetothioimidate hydrochloride[10,11] (**4**) were prepared by bubbling HCl into an ether solution of acetonitrile and MeOH or ethanethiol, respectively. Ethyl dithioacetate[11–13] (**5**) was prepared by bubbling H_2S into a solution of compound **4** in pyridine. To prepare 5,6-diamino-1,3-dimethyluracil monotosylate, equimolar amounts of 5,6-diamino-1,3-dimethyluracil and *p*-toluenesulfonic acid were warmed in water, and the hydrated crystals filtered off and dried; m.p. 255–257°.

2-Methylbenzoxazole[14–18] (**3**). — Equimolar amounts of *o*-aminophenol and of compound **1**, **4**, or **5** were refluxed in MeOH for 30 min, 40 min, and 18 h, respectively, the mixture was cooled and evaporated, the residue dissolved in ether (15 mL), and the solution washed with water, dried (Na_2SO_4), and evaporated to dryness; yields 38, 66, and 70%, respectively. The u.v. spectra were identical with those reported in the literature[16]; ν_{max}^{neat} 3385, 3312, 3070 (Ar-H), 2980 (C–H), 2930 (C–H), and 1390 cm^{-1} (CH_3); ^{1}H-n.m.r. (CCl_4): δ 7.75–7.10 (m, 4 H, Ar) and 2.50 (s, 3 H, Me).

N^1-*(6-Amino-1,3-dimethyluracil-5-yl) acetamidine hydrochloride* (**7**). — A solution of compound **4** (420 mg, 3 mmol) and 5,6-diamino-1,3-dimethyluracil hydrate (**6**; 564 mg, 3 mmol) in abs. EtOH (50 mL) was boiled under reflux for 10 h. The hot suspension was filtered to remove the precipitate, and the filtrate concentrated to ~10 mL. The yellow oil that separated crystallized after some time, and was recrystallized from EtOH–$CHCl_3$, plates, m.p. 295° (dec.); yield 391 mg (62%); ν_{max}^{Nujol} 2960, 2930, and 2860 (C–H), 2730 (N–Me), and 1700 cm^{-1} (C=O); ^{1}H-n.m.r. (CD_3SOCD_3): δ 9.80 (b, 2 H, C=NH_2), 8.55 (b, 1 H, 5–N*H*), 7.30 (b, 2 H, 6-NH_2), 3.40 (s, 3 H, 3-Me), 3.20 (s, 3 H, 1-Me), and 2.30 (s, 3 H, N=C–Me).

Anal. Calc. for $C_8H_{14}ClN_5O_2 \cdot 0.5\ H_2O$: C, 37.43; H, 5.89; Cl, 13.81; N, 27.28. Found: C, 37.46; H, 5.92; Cl, 13.80; N, 27.21.

1,3,8-Trimethylxanthine[19] (**8**). — *Method (a).* Compound **7** (179 mg, 0.84 mmol) was heated for 10 min in a metal bath at 260°. The orange melt was mixed with 70% EtOH, the suspension filtered from an insoluble residue, and the filtrate concentrated to ~7 mL. The yellow crystals obtained (yield 85 mg; 52%) had m.p. 330° (lit.[19] m.p. 325°) alone or on admixture with an authentic specimen. The u.v. spectra were identical with those reported in the literature[20]; ν_{max}^{KBr} 2955 and 2820 (C–H), 2780 (N–Me), and 1710 cm^{-1} (C=O).

Method (b). A solution of compound **5** (460 mg, 3.8 mmol), 5,6-diamino-1,3-dimethyluracil (714 mg, 3.8 mmol), and *p*-toluenesulfonic acid (100 mg, 0.6 mmol) in abs. EtOH (40 mL) was boiled under reflux for 10 h, and treated as in (*a*); yield, 244 mg (33%).

*Methyl 2,5-anhydro-*D*-allonoimidate hydrochloride* (**14**). — Because this product is highly hygroscopic, its synhesis was conducted in a dry glove-box. Methyl 2,5-anhydro-D-allonoimidate[6] (194 mg, mmol) was mixed with THF (100 mL), the suspension filtered from some insoluble matter, and the filtrate treated with a solution of dry HCl (106 mg) in THF (15 mL, 3 mmol) at room temperature. The salt that precipitated was quickly filtered off by suction, dissolved in MeOH (10 mL), and the solution used in the next reaction.

*Ethyl 2,5-anhydro-3,4,6-tri-*O*-benzoyl-*D*-allonothioimidate hydrochloride* (**15**). — Dry HCl gas was passed for 1 h into a solution of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allononitrile[1] (**10**) (12.4 g, 26 mmol) and ethanethiol (3.9 mL, 52 mmol) in anhydrous ethyl ether (300 mL) cooled to 0°, and the container was sealed and kept for 2 days in a refrigerator. The white crystalline mass that separated was filtered off in a dry glove-box by suction; yield, 3.05 g; m.p. 99–104° (dec.), $[\alpha]_D^{24}$ −35.2° (*c* 0.24, $CHCl_3$); ν_{max}^{Nujol} 1735 (C=O) and 1190 cm^{-1} (C=S)[12]; ^{1}H-n.m.r. (CD_3SOCD_3): δ 8.18–7.26 (m, 15 H, Ar), 3.34 (q, *J* 3.2 Hz, SCH_2), and 1.20 (t, *J* 3 Hz, Me). On concentration the mother liquor afforded another 0.66 g of product, which brought the overall yield to 25%.

Anal. Calc. for $C_{29}H_{27}NO_7S \cdot HCl$: C, 61.10; H, 4.95; Cl, 6.22; N, 2.46; S, 5.62. Found: C, 61.14; H, 4.90; Cl, 6.25; N, 2.55; S, 5.78.

*Benzyl 2,5-anhydro-3,4,6-tri-*O*-benzoyl-*D*-allonothioimidate hydrochloride*[5] (**16**). — Gaseous HCl was passed through a solution of nitrile **10** (37.7 g, 80 mmol) and ethanethiol (18.9 mL, 160 mmol) in ethyl ether (1500 L) for 6 h at 0°. The salt (31.4 g, 62%); was isolated as already described; m.p. 83–85°, $[\alpha]_D^{24}$ −168° (*c* 0.45, $CHCl_3$); ν_{max}^{Nujol} 1720 (C=O) and 1180 cm^{-1} (C=S); ^{1}H-n.m.r. (CD_3SOCD_3): δ 9.25 (b, 2 H, C=NH_2^+), 8.05–7.28 (m, 20 H, Ar), 6.65 (d, $J_{2,3}$ 3.5 Hz, 1 H, H-2), and 4.68 (s, 2 H, S-CH_2).

Anal. Calc. for $C_{34}H_{29}NO_7S \cdot HCl$: C, 64.60; H, 4.78; N, 2.22. Found: C, 64.61; H, 4.79; N, 2.11.

*Benzyl 2,5-anhydro-3,4,6-tri-*O*-p-toluoyl-*D*-allonothioimidate hydrochloride* (**17**). — Dry HCl gas was passed through a solution of 2,5-anhydro-3,4,6-tri-*O*-*p*-toluoyl-D-allononitrile (**11**)[9] (1.42 g, 2 mmol) and α-toluenethiol (0.5 mL, 4 mmol) in ethyl ether (50 mL) cooled at 0°. After 2 d in a refrigerator, the salt was filtered

off, and dried as before; yield, 1.06 g; m.p. 92–94°, $[\alpha]_D^{24}$ −31.9° (*c* 0.91, $CHCl_3$); ν_{max}^{Nujol} 1732 and 1720 (C=O) and 1180 cm^{-1} (C=S); ^{1}H-n.m.r. (CD_3SOCD_3): δ 7.90 (dd, 6 H, *o*-Ar), 7.30 (m, 11 H, Ar), 6.75 (d, $J_{2,3}$ 4.0 Hz, 1 H, H-2), 3.78 (s, 2 H, S–CH_2), and 2.35 (s, 9 H, 3 Me). On concentration, the mother liquor afforded another crop (0.06 g), which brought the overall yield to 83%.

Anal. Calc. for $C_{37}H_{35}NSO_7$ · HCl: C, 65.91; H, 5.38; Cl, 5.26; N, 2.08; S, 4.76. Found: C, 65.98; H, 5.31; Cl, 5.18; N, 2.05; S, 4.80.

*Ethyl 2,5-anhydro-6-*O*-benzoyl-*D*-allonothioimidate hydrochloride* (**18**). — Dry HCl gas was passed through a solution of 2,5-anhydro-6-*O*-benzoyl-D-allononitrile (**12**)[20,21] (14 g, 53 mmol) and ethanethiol (7.7 mL, 111 mmol) in ethyl ether (1300 L) cooled to 0° in an ice bath. After 1 h at 0°, the container was sealed, and kept in a refrigerator for 4 days. The colorless, hygroscopic, amorphous solid obtained by evaporating the solution under diminished pressure (yield 15 g, 79%) had $[\alpha]_D^{24}$ +35.7° (*c* 0.17, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 8.12 (dd, 2 H, *o*-Ar), 7.50 (m, 3 H, *m*- and *p*-Ar), 5.15 (b, 1 H, H-2), 4.40 (b, 5 H, H-3,4,5,6a,6b), 3.25 (q, 2 H, SCH_2), and 1.20 (t, 3 H, Me).

Anal. Calc. for $C_{15}H_{19}NO_5S$ · HCl: C, 49.79; H, 5.57; N, 3.87. Found: C, 49.71; H, 5.70; N, 3.98.

*Benzyl 2,5-anhydro-6-*O*-benzoyl-*D*-allonothioimidate hydrochloride*[5] (**19**). — A solution of compound **12** (2.15 g, 8.2 mmol) and α-toluenethiol (1.94 mL, 16.4 mmol) in ether (300 mL) was treated with HCl gas as already described, affording a hygroscopic, pinkish-white, amorphous solid (yield 1.55 g, 45%), which was used immediately to prepare compound **23**.

*Ethyl 2,5-anhydro-6-*O*-p-nitrobenzoyl-*D*-allonothioimidate hydrochloride* (**20**). — Dry HCl gas was passed through a solution of 2,5-anhydro-3,5-*O*-isopropylidene-6-*O*-*p*-(nitrobenzoyl)-D-allononitrile (**13**)[22] (1.40 g, 4 mmol) and ethanethiol (0.6 mL, 8 mmol) in a mixture of ethyl ether (700 mL) and CH_2Cl_2 (150 mL). The bubbling was continued for 1 h at 0°, and the vessel was sealed, and kept in a refrigerator for a week. The colorless, crystalline mass that separated was collected by filtration in a dry glove-box; yield, 416 mg (26%); m.p. 128–132° (dec.), $[\alpha]_D^{24}$ −0.88° (*c* 0.02, $CHCl_3$); ν_{max}^{KBr} 1725 (C=O) and 1160 cm^{-1} (C=S); ^{1}H-n.m.r. (CD_3SOCD_3): δ 8.55–8.10 (m, 4 H, Ar), 4.85 (d, $J_{2,3}$ 5 Hz, 1 H, H-2), 4.55 (m, 2 H, H-3,4), 4.15 (m, 3 H, H-5,6a,6b), 3.20 (q, 2 H, SCH_2), and 1.15 (t, 3 H, Me).

Anal. Calc. for $C_{15}H_{18}N_2O_7S$ · HCl: C, 44.28; H, 4.71; N, 6.89. Found: C, 44.31; H, 4.69; N, 6.89.

*Benzyl 2,5-anhydro-3,4,6-tri-*O*-benzoyl-*D*-allonodithioate* (**21**). — Dry H_2S was passed for 4 h into a solution of compound **16** (8.96 g, 14 mmol) in pyridine (30 mL) presaturated with H_2S at 0°. The mixture was diluted with ice–water (10 mL), poured into a mixture of conc. HCl (30 mL) and ice (30 mL), extracted twice with ethyl ether (70 mL each), and the aqueous layers combined, and extracted with ether (30 mL). The extracts were combined, successively washed with 5M HCl and water, dried (Na_2SO_4), and evaporated. The residue (8.40 g) was purified by chromatography on a column (2 × 20 cm) of silica gel eluted with 200 mL each of

toluene, 1:1 toluene–ethyl acetate, and ethyl acetate, and the eluate collected in 15-mL fractions. Thin-layer chromatography showed that the last four fractions eluted with toluene–ethyl acetate, and the first two fractions eluted with ethyl acetate, contained the desired product (**21**). The chromatographically pure syrup obtained by evaporation had $[\alpha]_D^{24}$ +3.5° (*c* 1.14, $CHCl_3$); $\nu_{max}^{CCl_4}$ 1715 (C=O) and 1162 cm^{-1} (C=S); ^{1}H-n.m.r. ($CDCl_3$): δ 8.25–7.25 (m, 20 H, Ar) and 3.62 (s, 2 H, SCH_2).

Anal. Calc. for $C_{34}H_{28}O_7S_2 \cdot H_2O$: C, 64.75; H, 4.79. Found: C, 64.70; H, 5.08.

*Ethyl 2,5-anhydro-6-*O*-benzoyl-*D*-allonodithioate* (**22**). — When compound **18** (5.06 g, 14 mmol) was treated with H_2S in the same way, it yielded 3.91 g (82%) of product, which was purified by chromatography on a column (1 × 16 cm) of silica gel eluted with 1:1 benzene–ethyl acetate (500 mL) and collected in 15-mL fractions. Compound **22** was isolated from fractions 4–6 as yellow crystals which, after recrystallization from CCl_4, had m.p. 67–72°, $[\alpha]_D^{24}$ +157° (*c* 0.1, $CHCl_3$); ν_{max}^{KBr} 3450 (OH), 1710 (C=O), and 1175 cm^{-1} (C=S); ^{1}H-n.m.r. ($CDCl_3$): δ 8.20–7.20 (m, 6 H, Ar), 4.80 (d, $J_{2,3}$ 5.8 Hz, 1 H, H-2), 4.70–3.90 (m, 5 H, H-3,4,5,6a,6b), 3.00 (q, 2 H, SCH_2), and 1.20 (t, 3 H, Me).

Anal. Calc. for $C_{15}H_{18}O_5S_2$: C, 52.61; H, 5.36. Found: C, 52.67; H, 5.36.

*Benzyl 2,5-anhydro-6-*O*-benzoyl-*D*-allonodithioate* (**23**). — Compound **19** (1.55 g, 3.7 mmol) was treated with H_2S, and the product purified as for compound **21**. After column chromatography, the product (1.64 g, 93%) crystallized from EtOH in needles; m.p. 109.0–113.5°, $[\alpha]_D^{24}$ +142° (*c* 0.1, $CHCl_3$); ν_{max}^{KBr} 3420 (OH), 1701 (C=O), and 1160 cm^{-1} (C=S); ^{1}H-n.m.r. ($CDCl_3$): δ 8.20–7.25 (m, 10 H, Ar), and 4.90 (d, $J_{2,3}$ 5.8 Hz, 1 H, H-2).

Anal. Calc. for $C_{28}H_{20}O_5S_2$: C, 59.39; H, 4.95. Found: C, 59.42; H, 4.95.

*2-*D*-Ribofuranosylbenzoxazole* (**24**). — A methanolic solution of **14** was treated with *o*-aminophenol (109 mg, 1 mmol) and boiled for 2 h under reflux. The solution was concentrated, and treated with a small quantity of $CHCl_3$ to crystallize the product. This was filtered off, and purified by chromatography on a column (2.5 × 25 cm) of silica gel eluted with ethyl acetate. Crystallization from EtOH afforded colorless, hygroscopic needles, which darkened in air; yield 50 mg (20%); m.p. 157.8–158.3° (dec.); ν_{max}^{KBr} 3065 (Ar–H) and 2940–2874 cm^{-1}; ^{1}H-n.m.r. (CD_3SOCD_3): δ 7.70 (m, 2 H, H-4,7), 7.50 (m, 2 H, H-5,6), 5.40 (d, *J* 5.7 Hz, 1 H, O*H*-2′), 5.15 (d, *J* 5.0 Hz, 1 H, O*H*-3′), and 4.85–3.35 (m, 6 H, H-1′,2′,3′,4′,5′a,5′b).

Anal. Calc. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.49; H, 5.34; N, 5.55.

*N^1-(6-Amino-1,3-dimethyluracil-5-yl)-5-*O*-(benzyloxymethyl)-2-furamidine hydrochloride* (**25**). — A solution of compound **15** (13.76 g, 21.8 mmol) and 5,6-diamino-1,3-dimethyluracil monotosylate (7.42 g, 20.6 mmol) in pyridine (110 mL) was boiled under reflux for 5 min, and the precipitate was collected, and recrystallized from EtOH; yield 3.64 g (41%); m.p. 265–270°; ν_{max}^{Nujol} 1726 and 1710 cm^{-1}

(C=O); ^{1}H-n.m.r. (CD_3SOCD_3): δ 10.45 and 10.00 (b, 2 H, C=NH_2^+), 9.00 (b, 1 H, N*H*-5), 7.83 (d, $J_{2',3'}$ 3.5 Hz, 1 H, H-2'), 7.38 (b, 2 H, NH_2-6), 7.14 (d, $J_{2',3'}$ 3.5 Hz, 1 H, H-3'), 5.50 (s, 2 H, H-5'), 3.30 (s, 3 H, Me-3), and 3.18 (s, 3 H, Me-1); ^{13}C-n.m.r. (CD_3SOCD_3): δ 193.71 (*C*=NH$_2^+$), 186.68 (*C*=O at 2), 56.95 (Me at N-3), and 54.25 (Me at N-1).

Anal. Calc. for $C_{19}H_{19}N_5O_5 \cdot HCl$: C, 52.60; H, 4.65; Cl, 8.17; N, 16.14. Found: C, 52.26; H, 4.81; Cl, 8.55; N, 15.98.

N^1-*(6-Amino-1,3-dimethyluracil-5-yl)-5-O-(p-toluyloxymethyl)-2-furamidine hydrochloride* (**26**). — A solution of compound **17** (3.37 g, 5 mmol) and 5,6-diamino-1,3-dimethyluracil tosylate (1.71 g, 5 mmol) in pyridine (25 mL) was boiled under reflux as for compound **25**, affording, after crystallization from EtOH, colorless plates; yield 1.73 g (77%); m.p. 255–265° (dec.); *m/z* 311 (4%, M − HCl) and 394 (100%, M − HCl − NH_3); ν_{max}^{KBr} 1720 and 1705 cm^{-1} (C=O); ^{1}H-n.m.r. (CD_3SOCD_3): δ 11.35 and 10.45 (b, 2 H, C=NH_2^+), 9.50 (b, 1 H, NH_2-6), 7.07 (d, $J_{2',3'}$ 3.5 Hz, 1 H, H-2'), 5.45 (s, 2 H, H-5'), 3.32 (s, 3 H, Me-3), 3.15 (s, 3 H, Me-1), and 2.38 (s, 3 H, toluyl Me).

Anal. Calc. for $C_{20}H_{21}N_5O_5 \cdot HCl$: C, 53.64; H, 4.95; N, 15.64. Found: C, 53.64; H, 5.14; N, 15.57.

1,3-Dimethyl-8-[5-O-(p-toluoyloxymethyl)-2-furyl]xanthine (**27**). — Compound **26** (315 mg, 0.7 mmol) was ground with $ZnCl_2$ (1 g, 7.3 mmol) and heated for 20 min in a metal bath at 180°. Upon cooling to room temperature, the solid resulting was mixed with 1:4 EtOH–H_2O (0.2 L), the suspension filtered, and the filtrate passed through a column of Amberlite IRA-118H (H^+) cation-exchange resin, which was washed with H_2O until the eluate became neutral, and then eluted with 3% NH_4OH. The basic, yellow eluate (80 mL) was treated with charcoal, and concentrated. Two crops of crystals were collected (17 and 33 mg), and recrystallized from DMF-H_2O; m.p. 337–340°; ν_{max}^{KBr} 1705 cm^{-1} (C=O); ^{1}H-n.m.r. (CD_3SOCD_3): δ 7.80 (m, 2 H, *o*-Ar), 7.22 (d, $J_{2',3'}$ 3.4 Hz, 1 H, H-2'), 6.33 (d, $J_{3',2'}$ 3.4 Hz, 1 H, H-3'), 4.18 (s, 2 H, H-5'), 3.48 (s, 3 H, Me-1), 3.25 (s, 3 H, Me-3), and 2.40 (s, 3 H, toluyl Me).

Anal. Calc. for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 60.71; H, 4.66; N, 14.41.

8-(5-O-Benzoyl-β-D-ribofuranosyl)-1,3-dimethylxanthine (**28**). — *Method (a).* A solution of compound **18** (1.81 g, 5 mmol) and 5,6-diamino-1,3-dimethyluracil (0.94 g, 5 mmol) in pyridine (25 mL) was boiled under reflux for 2 h, cooled, and evaporated to dryness *in vacuo*. The residue was dissolved in 3:1 ethyl acetate–pyridine and chromatographed on a column (2.5 × 29 cm) of silica gel eluted with the same solvent system. The first 100 mL of eluate contained the desired product, which crystallized from EtOH in colorless needles, m.p. 219°; yield 180 mg (9%).

Method (b). A solution of compound **22** (1.72 g, 5 mmol) and 5,6-diamino-1,3-dimethyluracil (0.94 g, 5 mmol) in abs. EtOH (75 mL) was boiled under reflux for 30 h, and then concentrated to 10 mL. The crystalline product was collected, washed with a small volume of ether, and recrystallized from EtOH. It had m.p.

220°, $[\alpha]_D^{24}$ −79.2° (*c* 0.05, MeOH); ν_{max}^{KBr} 3400 (OH), 2960, 2920, and 2880 (C–H), 2790 (N–Me), 1730, and 1710 cm^{-1} (C=O); ^{1}H-n.m.r. (CD_3SOCD_3): δ 7.98 (dd, *J* 8 Hz, 2 H, *o*-Ar), 7.55 (m, 3 H, Ar), 5.30 (m, 2 H, O*H*), 4.80 (d, $J_{1',2'}$ 4.0 Hz, 1 H, H-1'), 4.50–4.00 (m, 5 H, H-2',3',4',5'a,5'b), 3.33 (s, 3 H, Me-1), and 3.27 (s, 3 H, Me-3).

Anal. Calc. for $C_{19}H_{20}N_4O_7$: C, 54.81; H, 4.84; N, 13.46. Found: C, 54.58; H, 4.88; N, 13.29.

*1,3-Dimethyl-8-β-*D*-ribofuranosylxanthine* (**29**). — A solution of compound **28** (494 mg, 1.2 mmol) in methanolic ammonia (25 mL) was kept for 19 h at room temperature, and then evaporated to dryness at 40° *in vacuo*. The solid obtained was ground in a small, glass morter, washed successively with ether (2 × 20 mL) and hot benzene (25 mL), and then recrystallized from EtOH, to give colorless prisms; yield 337 mg (91%); m.p. 221–223°, $[\alpha]_D^{24}$ −38.0° (*c* 0.28, H_2O); ν_{max}^{KBr} 3400 (OH), 2920 and 2860 (C–H), 2770 and 2755 (N–Me), and 1705 cm^{-1} (C=O); ^{1}H-n.m.r. (CD_3SOCD_3): δ 5.26 (d, *J* 5.0 Hz, 1 H, OH-2'), 5.00 (d, *J* 4.0 Hz, 1 H, OH-3'), 4.75 (d, $J_{1',2'}$ 4.5 Hz, 1 H, H-1'), 4.20–3.50 (m, 5 H, H-2',3',4',5'a,5'b), 3.43 (s, 3 H, Me-1), and 3.26 (s, 3 H, Me-3).

Anal. Calc. for $C_{12}H_{16}N_4O_6 \cdot 0.5\ H_2O$: C, 43.77; H, 5.20; N, 17.01. Found: C, 44.36; H, 5.49; N, 17.01.

*2-(5-*O*-Benzoyl-β-*D*-ribofuranosyl)benzoxazole* (**30**). — A solution of compound **22** (1.03 g, 3 mmol) and *o*-aminophenol (0.238 g, 2.18 mmol) in abs. EtOH (25 mL) was boiled under reflux for 36 h, cooled to room temperature, evaporated to dryness *in vacuo*, the residue mixed with $CHCl_3$ (10 mL), the suspension filtered, the filtrate evaporated to dryness *in vacuo*, the residue dissolved in ethyl ether, and the solution applied to a column (2 × 15 mL) of silica gel, and eluted with ethyl ether. The yellow crystals obtained were twice recrystallized from EtOH, to give yellow crystals; yield 189 mg (24%); m.p. 154.0–154.8°; ν_{max}^{KBr} 3471, 3200 (OH), 3060 (Ar–H), 2970 (C–H), 2940 (C–H), 2918 (C–H), 2870 (C–H), 1715 (C=O), and 1380 cm^{-1} (CH_3); ^{1}H-n.m.r. (CD_3SOCD_3): δ 8.10–7.20 (m, 9 H, Ar), 5.63 (dd, *J* 4.5 Hz, 1 H, OH-2'), 5.40 (dd, *J* 4.5 Hz, 1 H, OH-3'), 5.05 (d, $J_{1',2'}$ 4 Hz, 1 H, H-1'), and 4.65–4.15 (m, 5 H, H-2',3',4',5'a,5'b).

Anal. Calc. for $C_{19}H_{19}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.20; H, 4.90; N, 3.83.

REFERENCES

1 M. Bobek and J. Farkaš, *Collect. Czech. Chem. Commun.*, 34 (1969) 247–252.
2 H. S. El Khadem and E. S. H. El Ashry, *Carbohydr. Res.*, 32 (1974) 339–348.
3 J. Igolen and T. Huynh-Dinh, *J. Chem. Soc., Chem. Commun.*, (1971) 1267.
4 T. Huynh-Dihn, A. Kolb, G. Barnathan, and J. Igolen, *J. Chem. Soc., Chem. Commun.*, (1973) 680–681.
5 T. Huynh-Dinh, A. Kolb, C. Gouyette, and J. Igolen, *J. Heterocycl. Chem.*, 12 (1975) 111–117.
6 M. S. Poonian and E. F. Nowoswiat, *J. Org. Chem.*, 45 (1980) 203–208.
7 A. Pincer and T. Klein, *Ber.*, 11 (1878) 1825.
8 W. H. Prichard and W. J. Orville-Thomas, *J. Chem. Soc., A*, (1967) 1102–1105.
9 H. S. El Khadem and J. Kawai, *Carbohydr. Res.*, 115 (1983) 131–138.

10 E. SCHMIDT, *Ber.*, 47 (1914) 2545–2550.
11 Y. SAKURADA, *Mem. Coll. Sci. Eng. Kyoto*, 10 (1926) 79–80.
12 C. S. MARVEL, P. DE RADZITZKY, AND J. J. BRADER, *J. Am. Chem. Soc.*, 77 (1955) 5997–5999.
13 J. HOUBEN AND K. M. L. SCHULTZE, *Ber.*, 44 (1911) 3226.
14 A. LADENBURG, *Ber.*, 9 (1876) 1524.
15 F. E. KING AND R. M. ACHESON, *J. Chem. Soc.*, (1949) 1396–1400.
16 R. PASSERINI, *J. Chem. Soc.*, (1954) 2256–2261.
17 W. REID AND E. SCHMIDT, *Justus Liebigs Ann. Chem.*, 676 (1964) 114–120.
18 C. I. BRAZ, G. V. MYASNIKOVA, AND A. YA. YAKUBOVICH, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR*, 1 (1965) 147.
19 J. H. SPEER AND A. L. RAYMOND, *J. Am. Chem. Soc.*, 75 (1953) 114–115.
20 J. A. MONTOGOMERY AND K. HEWSON, *J. Heterocycl. Chem.*, 7 (1970) 443–445.
21 H. P. ALBRECHT, D. B. REPKE, AND J. G. MOFFATT, *J. Org. Chem.*, 38 (1973) 1836–1845.
22 G. JUST, A. MAAYMOND, A. MARTEL, K. GROZINGER, AND M. RAMFEESINGH, *Can. J. Chem.*, 53 (1975) 131–137.
23 E. B. GOODSELL, H. N. STEIN, AND K. J. WENZKE, *J. Med. Chem.*, 14 (1971) 1202–1205.