Carbohydrate Research, 27 (1973) 303–308
© Elsevier Scientific Publishing Company, Amsterdam – Printed in Belgium

DERIVATIVES OF 2,5-ANHYDROALLITOL AND 2,5-ANHYDROALTRITOL*

JOHN A MONTGOMERY, KATHLEEN HEWSON, AND ANNE G LASETER
Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205 (U S A)

(Received August 9th, 1972, accepted with revisions October 7th, 1972)

ABSTRACT

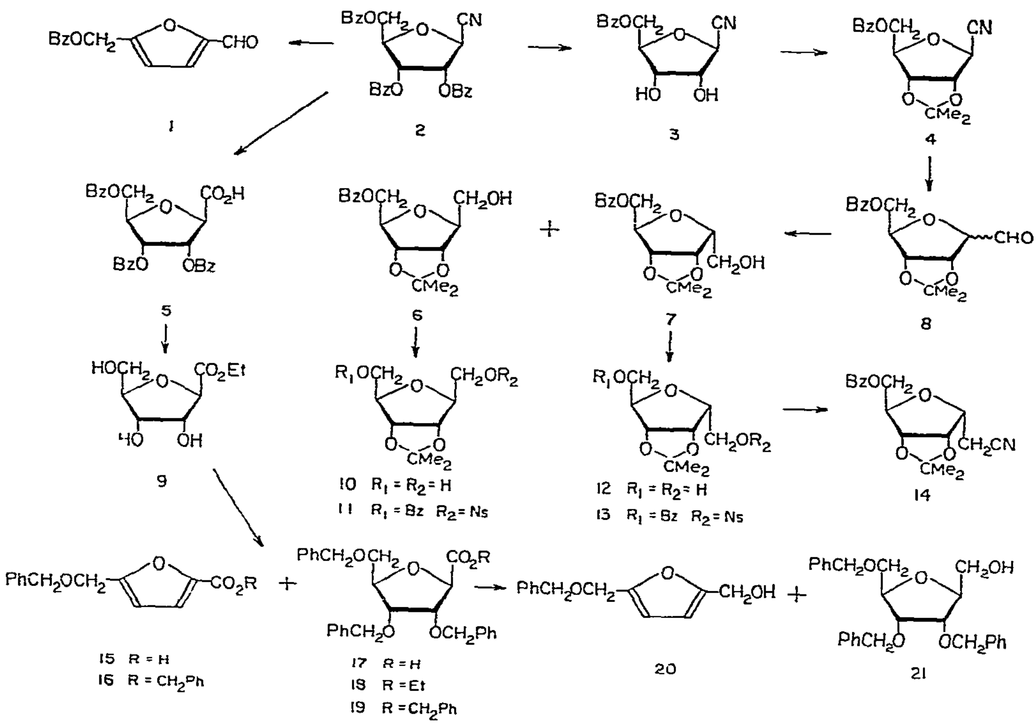
Two routes to protected derivatives of 2,5-anhydroallitol were investigated The first route, involving a two-step reduction of 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allonitrile (**4**), gave a mixture of 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-altritol (**7**) and a lesser amount of the desired 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allitol (**6**) Isomerization was shown to occur in the first reduction step—treatment of the nitrile **4** with Raney nickel, sodium hypophosphite, and acetic acid The second route gave isomerically pure 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allitol (**21**) via reduction of the corresponding ethyl allonate (**18**)

DISCUSSION

Interest in *C*-nucleosides prompted us to investigate the preparation of derivatives of 2,5-anhydroallose, which in fact the naturally occurring *C*-nucleosides are Treatment of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allononitrile[1] (**2**) with Raney nickel and sodium hypophosphite in pyridine and acetic acid, a procedure reported to reduce nitriles to aldehydes[2], gave 5-(benzoyloxymethyl)furaldehyde (**1**), the desired reduction of the nitrile to aldehyde being accompanied by aromatization resulting from the loss of two molecules of benzoic acid As esters are reported to be unaffected if this reduction is carried out in formic acid[3], this modification was also investigated, but it also gave **1** and none of the desired allose The aromatization was avoided by carrying out the reduction with 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allonitrile[1] (**4**) Examination of this reduction product by t l c showed two spots, one traveling directly beneath the other, that charred on heating after spraying with ammonium sulfate solution and that gave positive aldehyde tests with both 2,4-dinitrophenylhydrazine and *p*-rosaniline The p m r spectrum of the mixture showed two aldehyde-proton signals (at 9 65 and 9 75 p p m) As the aldehydes (**8**) could not be reasonably separated, the mixture was further reduced with sodium borohydride at pH 5 to the corresponding alditols Although the p m r spectra of the alditols,

---

*This work was supported by funds from the C F Kettering Foundation, and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract No NIH-71-2021



Ns = *p*-Nitrobenzenesulfonyl

which were separated by column chromatography on silica gel, indicated that one was an allitol and the other an altritol resulting from epimerization at C-2, overlapping of the proton signals prevented the establishment of their identities Debenzoylation of the two compounds gave one optically active compound and an optically inactive one As 2,5-anhydro-3,4-*O*-isopropylidene-D-allitol (**10**) has a plane of symmetry and 2,5-anhydro-3,4-*O*-isopropylidene-D-altritol (**12**) does not, the identities of the alditols **6** and **7** were established by this experiment, and the preponderant isomer was proved to be the altritol (**7**) These compounds were converted into their 1-*O*-(*p*-nitrobenzenesulfonyl) derivatives (**11** and **13**) for analysis Thus, it was established that reduction of the allonitrile was accompanied by epimerization at C-2 to give primarily 2,5-anhydro-3,4-*O*-isopropylidene-*aldehydo*-D-altrose (altro-**8**) and some 2,5-anhydro-3,4-*O*-isopropylidene-*aldehydo*-D-allose (allo-**8**) Reaction of the sulfonate **13** with sodium cyanide gave 3,6-anhydro-7-*O*-benzoyl-2-deoxy-4,5-*O*-isopropylidene-D-*altro*-heptonitrile (**14**)

Another route to a protected 2,5-anhydroallitol that would prevent epimerization was sought 2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allonitrile (**2**) was hydrolyzed to the acid[4] (**5**), which was debenzoylated with methanolic sodium methoxide and then esterified by several evaporations of solutions of the lactone in abs alcohol Benzylation of the ethyl ester **9** with benzyl chloride and sodium hydride in *N*,*N*-dimethylformamide gave a mixture of five products 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allonic acid (**17**), its ethyl ester (**18**), its benzyl ester (**19**), and 5-(benzyloxymethyl)-2-furoic acid (**15**) and its benzyl ester (**16**), which were partially separated and identified Reduction of the principal product, the ethyl ester **18**, with sodium bis(2-methoxyethoxy)aluminum hydride then gave 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allitol (**21**) Later, the mixture was simply reduced to **21** and 5-(benzoyloxymethyl)-2-hydroxymethyl)furan (**20**) The desired tri-*O*-benzylallitol **21**, which should be a valuable intermediate in the preparation of *C*-nucleosides, was readily separated from the furan and obtained in crystalline form

EXPERIMENTAL

General — Melting points were determined with a Mel-Temp apparatus and are not corrected The p m r spectra were determined in $CDCl_3$-(Me_4Si) with a Varian XL-100-15 spectrometer, and the correct integrals were obtained for the assignments indicated, chemical shifts quoted for multiplets were measured from the approximate centers The mass spectra were determined with a Hitachi–Perkin-Elmer RMU-6D-3 spectrometer Chromatographic analyses were carried out on t l c plates of silica gel H (Brinkmann) The spots were detected by u v light after spraying with Ultraphor (WT, highly concentrated) and by charring after spraying with aqueous ammonium sulfate Most of the chromatographic separations were performed on a 43-inch column of SilicAR 7 (Mallinckrodt) under 40 lb in^{-2} at a flow rate of 600 ml/h with the solvents indicated

*Reduction of 2,5-anhydro-3,4,6-tri-O-benzoyl-*D*-allonitrile* (**2**) — A mixture of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonitrile (**2**, 500 mg), sodium hypophosphite (1 g), and Raney nickel (300 mg) in 15 ml of 1 1 2 water–acetic acid–pyridine was stirred for 1 5 h at 50° before the catalyst was removed by filtration and washed with ether, benzene, and water The combined filtrate and washings were separated and the organic phase washed with water and then sodium hydrogen carbonate solution before drying over magnesium sulfate The solution was evaporated to dryness, and the residue chromatographed on a column of silica gel with chloroform as the eluant The eluate gave 198 mg of an oil, which was rechromatographed on silica gel with 19 1 benzene–ethyl acetate as eluant Evaporation gave a solid, which was identified as 5-(benzoyloxymethyl)-2-furaldehyde (**1**) by its p m r spectrum δ 5 48 (s, 2, CH_2), 6 8 and 7 4 (d of d, 2, H-2 and H-3), 7 6 and 8 2 (m, 5, phenyl), and 9 8 (s, 1, CHO)

*Reduction of 2,5-anhydro-6-O-benzoyl-3,4-O-isopropylidene-*D*-allonitrile* (**4**) — Raney nickel (7 5 g wet, suspended in 5 ml of water) was added to a solution of 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allonitrile (7 57 g, 25 mmoles) and sodium hypophosphite hydrate (15 13 g) in 151 ml of 2 1 1 pyridine–acetic acid–water, and the mixture was heated for 1 h at 50° with stirring The procedure was repeated to ensure complete reduction The catalyst was removed by filtration and washed with ethanol and water To the combined filtrate and washings was added portionwise 2 78 g of sodium borohydride, and the mixture was stirred overnight (pH 5) before it was evaporated to dryness *in vacuo* A solution of the residue in water, acidified with concentrated hydrochloric acid to pH 3, was extracted with three 50-ml portions of chloroform The chloroform extract was washed with 5% sodium hydrogen carbonate solution and then with water before drying over magnesium sulfate The dried solution was evaporated to dryness, and the residue (7 06 g) chromatographed in two parts on a column of silica gel (eluant 4 1 benzene–ethyl acetate) A partial separation of the two products was achieved so that 1 18 g of 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-altritol (**7**), 0 570 g of 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allitol (**6**), and 0 703 g of a 1 1 mixture of the two were obtained, making the total yield of the altritol 1 53 g (20%) and of the allitol 0 92 g (12%) (α β ratio 5 3) The mass spectrum of the mixture (mol wt 308) before separation showed the following principal peaks 293 (308 – Me), 277 (308 – CH_2OH), 186 (308 – $C_6H_5CO_2CH_2$, – H), 171 (308 – $C_6H_5CO_2CH_2$, – Me, – H), 122 ($C_6H_5CO_2CH_2$ + H), and 105 (C_6H_5CO) P m r spectra (δ in p p m) **6**—1 36 and 1 54 (s, CH_3), 2 25 (s broad, OH), 3 91 (d, $J_{1\ 2}$ 5 2 Hz, 2H-1), ca 4 2 (m, H-2), 4 3–5 0 (m of m, H-3, H-4, H-5, 2H-6), 7 47 and 8 04 (m, phenyl H), **7**—1 37 and 1 57 (s, CH_3), 2 27 (s broad, OH), 3 74 (m, 2H-1), 4 14 (q, $J_{1\ 2}$ 3 1 Hz, $J'_{1\ 2}$ 3 8 Hz, H-2), 4 2–4 8 (m of m, H-3, H-4, H-5, 2H-6), 7 48 and 8 05 (m, phenyl H) In both cases the assignment of the C-1 protons was confirmed by reaction with trichloroacetyl isocyanate, which caused a downfield shift of the signals from the C-1 protons and H-2 of both **6** and **7** Because of overlapping absorption, it was necessary to locate H-2 of **6** by an INDOR experiment, observing at the frequency of the low-field peak of the H-1 doublet while sweeping the decoupling frequency, The signal from the C-1 protons of **7** indicates that they are magnetically non-equivalent, perhaps because of restricted rotation imposed by the proximity of one of the methyl groups of the isopropylidene moiety Irradiation of the C-1 protons decreased the H-2 signal to a doublet ($J_{2\ 3}$ 3 7 Hz) Attempts to identify **6** and **7** by nuclear Overhauser effect experiments failed because of the overlapping of the signals from H-2, H-3, and H-4 These sugars were further characterized by conversion into their **1**-*O*-(*p*-nitrobenzenesulfonyl) derivatives (**11** and **13**) and by debenzoylation to 2,5-anhydro-3,4-*O*-isopropylidene-D-altritol (**12**) $\{[\alpha]_D^{24\ 5}$ $-9\ 3° \pm 1\ 0°$ (*c* 0 37, ethanol)$\}$ and 2,5-anhydro-3,4-*O*-isopropylidene-D-allitol (**10**) ($[\alpha]_D^{24\ 5}$ 0°)

*2,5-Anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-1-*O*-(*p*-nitrobenzenesulfonyl)-*D*-allitol* (**11**) *and 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-1-*O*-(*p*-nitrobenzenesulfonyl)-*D*-altritol* (**13**) — 2,5-Anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allonitrile (5 g, 16 5 mmoles) was reduced as already described to give, after purification on a column of silica gel, 3 33 g (65% yield) of a mixture of **6** and **7** To a solution of this mixture in dry pyridine (10 ml) was added, in portions with cooling and stirring over a period of 7 h, 3.41 g of *p*-nitrobenzenesulfonyl chloride After two days at 4°, the mixture was poured onto 150 g of ice, and the resultant gum washed well with water before being dissolved in 100 ml of benzene The dried benzene solution was evaporated to dryness, and the residue (3 68 g) chromatographed on a column of silica gel with 9 1 benzene–ethyl acetate as the eluant From this column 1 49 g (28%) of a mixture of the *p*-nitrobenzenesulfonic esters **11** and **13** was obtained These compounds were separated by chromatography on a second column of silica gel with 19 1 benzene–ethyl acetate as eluant· yield of 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-1-*O*-(*p*-nitrobenzenesulfonyl)-D-allitol (**11**), 716 mg (13 5%) A small sample was recrystallized for analysis m p 93–94°, $[\alpha]_D^{25}$ $-9\ 9 \pm 0\ 4°$ (*c* 0 83, *ethanol*), δ in p p m · 1 37 and 1 54 (s, CH_3), 4 2–4 8 (m, H-1, H-2, H-3, H-4, H-5, H-6), 7 48 and 8 05 (phenyl H), and 8 05 and 8 3 (*p*-nitrophenyl H)

Anal Calc for $C_{22}H_{23}NO_{10}S$ C, 53 55, H, 4 70, N, 2 84 Found· C, 53 55, H, 4 84, N, 2 56

The yield of 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-1-*O*-(*p*-nitrobenzenesulfonyl)-D-altritol (**13**), an oil that could not be crystallized, was 335 mg (6 3%), $[\alpha]_D^{24\ 5}$ $-11\ 5 \pm 0\ 3°$ (*c* 0 98, ethanol), δ in p p m 1 3 and 1 4 (s, CH_3), 4 2–5 0 (m, H-1, H-2, H-3, H-4, H-5, H-6), 7 48 and 8 05 (phenyl H), and 8 05 and 8 35 (*p*-nitrophenyl H)

Anal Calc for $C_{22}H_{23}NO_{10}S$ C, 53 55, H, 4.70, N, 2 84 Found C, 53 64, H, 4 47, N, 2 78

*Ethyl 2,5-anhydro-*D*-allonate* (**9**) — A solution of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid[4] (12 26 g, 25 mmoles) and sodium methoxide (2 70 g, 50 mmoles) in 100 ml of methanol was refluxed for 30 min before being diluted with 50 ml of water and neutralized with AG 50W-X4 (H^+) resin The resin was removed by filtration and washed with three 25-ml portions of water The combined filtrate and washings were concentrated *in vacuo* and then extracted with four 25-ml portions of chloroform The residue from evaporation of the water solution was dissolved in 25 ml of M hydrochloric acid and 5 ml of *p*-dioxane, and the solution was diluted with 100 ml of ethanol before evaporation to dryness The residue was dissolved in ethanol and the solution evaporated to dryness five times, converting the allonic acid into its ethyl ester, which was dried overnight *in vacuo*, yield 5 25 g This material was used in the next step without further purification

*3,6-Anhydro-7-*O*-benzoyl-2-deoxy-4,5-*O*-isopropylidene-*D*-altro-heptononitrile* (**14**) — A solution of 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-1-*O*-(*p*-nitrobenzenesulfonyl)-D-altritol (370 mg) and sodium cyanide (50 mg) in *N,N*-dimethylformamide (10 ml) was heated with stirring for 2 h at 40° before evaporation to dryness The residue was partitioned between water and ether, and the ether layer was dried with magnesium sulfate before evaporation to dryness, yield 210 mg This oil was purified by chromatography on a column of silica gel with 9 1 benzene–ethyl acetate as the eluant The yield of crystalline solid was 130 mg (64% based on unrecovered starting material) A small sample was recrystallized for analysis, m p 62–63°, $[\alpha]_D^{26}$ $-28\ 2 \pm 1\ 8°$ (*c* 0 22, ethanol), δ in p p m 1 38 and 1 58 (s, CH_3), 2 73 (d, 2H-1), 4 16 (q, H-2), 4 33 (t, H-5), 4 51 (d, H-6), 4 62 (m, H-3 and H-4), 7 5 and 8 07 (phenyl H)

Anal Calc for $C_{17}H_{19}NO_5$ C, 64 34, H, 6 04, N, 4 41 Found C, 64 42, H, 5 93, N, 4 28

*Ethyl 2,5-anhydro-3,4,6-tri-*O*-benzyl-*D*-allonate* (**18**) — To a stirred solution of ethyl 2,5-anhydro-D-allonate (5 2 g, 25 mmoles) and benzyl chloride (13 9 g, 110 mmoles) in 75 ml of dimethyl sulfoxide was added during 1 h a suspension of sodium hydride (2 64 g, 110 mmoles) in 50 ml of dimethyl sulfoxide The solution was stirred for an additional 22 h before being evaporated to dryness The residue was three times dissolved in ethanol and the solution evaporated to dryness before it was chromatographed on a silica gel column (600 g, 140–200 mesh) with chloroform as the eluant Fractions were eluted that were shown by mass spectrometry to contain benzyl 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allonate (**19**) (447, M$^+$ $-C_6H_5CH_2$) and benzyl 5-(benzyloxymethyl)-2-furoate (**16**) (322, M$^+$, 231, M$^+-C_6H_5CH_2$), followed by ethyl 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allonate (**18**), (5 09 g, 43%) (476, M$^+$, 385, M$^+-C_6H_5CH_2$) Later fractions contained 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allonic acid (**17**), (100 mg) (357, M$^+-C_6H_5CH_2$) and 5-(benzyloxymethyl)-2-furoic acid (**15**), (2 32 g, 40%) (232, M$^+$, 215, M$^+-$OH, 141, M$^+-C_6H_5CH_2$, 125, M$^+-C_6H_5CH_2O$) The product **18** was reduced without further purification

*2,5-Anhydro-3,4,6-tri-O-benzyl-*D*-allitol* (**21**) — A solution of ethyl 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allonate (4 77 g, 10 mmoles) in benzene (50 ml) was added dropwise to a refluxing solution of sodium bis(2-methoxyethoxy)aluminum hydride (190 mmoles) in benzene (79 ml) After the addition was complete, the solution was refluxed for 1 h before being cooled, and 380 ml of 3 6M sulfuric acid was then added dropwise The benzene layer was separated, washed with saturated sodium hydrogen carbonate solution, and then washed with saturated sodium chloride solution before being dried with magnesium sulfate Evaporation of the benzene solution gave a residue that solidified, yield 3 77 g (87%) A small amount of this residue (258 mg) was recrystallized from 50% aqueous ethanol with charcoal treatment, yield 200 mg, m p 58–59°, $[\alpha]_D^{24\ 5}$ +20 5 ±0 9° (*c* 0 51, ethanol), δ in p p m 2 45 (broad, OH), 3 52 (t of d, H-6), 3 62 (d, H-1), 4 1 (m, H-2, H-3, H-4, H-5), 4 52 (m, CH_2 of benzyl), 7 28 (m, phenyl H)

Anal Calc for $C_{27}H_{30}O_5$ C, 74 63, H, 6 96 Found C, 74 47, H, 7 11

ACKNOWLEDGMENTS

The authors are indebted to Dr W C Coburn, Jr , and members of the Molecular Spectroscopy Section of Southern Research Institute for spectral and microanalytical data, and to Mrs Martha Thorpe and Mr Marion Kirk for their help in the interpretation of some of the data

REFERENCES

1 J A Montgomery and K Hewson, *J Heterocycl Chem* , 7 (1970) 443
2 O G Backeberg and B Staskun, *J Chem Soc* , (1962) 3961
3 T Van Es and B Staskun, *J Chem Soc* , (1965) 5775
4 M Bobek and J Farkaš, *Collect Czech Chem Commun* , 34 (1969) 247