ISOPROPYLIDENATION OF L-ARABINOSE N,N-DIMETHYLHYDRAZONE

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Direct isopropylidenation of L-arabinose N,N-dimethylhydrazone (*I*) was studied. Four major products whose structures were proven were produced in varying ratios depending upon the conditions. 2,2-Dimethoxypropane and sulfuric acid at 20°C gave a 36% yield of 2,3:4,5-di-O-isopropylidene-L-arabinose N,N-dimethylhydrazone (*II*). Attempted aldol condensations directly on this hydrazone with paraformaldehyde were unsuccessful. This hydrazone was readily hydrolyzed to the corresponding protected aldehyde *VI* which underwent an aldol-Cannizzaro reaction to give the branched chain pentitol *VII* in high yield.

During a study on the synthesis of branched chain sugars we planned to investigate the aldol condensation of formaldehyde directly with 2,3:4,5-di-O-isopropylidene--L-arabinose N,N-dimethylhydrazone (*II*). This protected hydrazone and its D isomer, have been prepared through the corresponding 2,3:4,5-di-O-isopropylidene-aldehydo--arabinose (*VI*, L isomer) which in turn requires a three-step synthesis from arabinose (through the corresponding dithioethylacetal isopropylidenation and dethioacetalation[1-4]. The direct isopropylidenation of the N,N-dimethylhydrazone of arabinose, as shown in Scheme 1, $I \rightarrow II$ for the L isomer, would shorten and simplify this synthesis substantially.

We have now studied the isopropylidenation of L-arabinose N,N-dimethylhydrazone (*I*) under various conditions (Table I). Treatment of *I* with acetone and an equimolar amount of *p*-toluenesulfonic acid hydrate (method *A*) resulted in the loss of the N,N-dimethylhydrazine group and formation of 1,2:3,4-di-O-isopropylidene--β-L-arabinopyranose[5-7] (*III*, 91% yield). This reaction appears to be the simple hydrolysis of *I* and formation of *III*, the known isopropylidenation product of arabinose (Scheme 1). When dry acetone was used with concentrated sulfuric acid (method *B*) three major products were identified: *III* (12%), 2,5-anhydro-3,4-O-isopropylidene--L-arabinose N,N-dimethylhydrazone (*IVa*, 29%), and 2,5-anhydro-3,4-O-isopropylidene-L-ribose N,N-dimethylhydrazone (*Va*, 20%). When this reaction was repeated in the presence of phosphoric anhydride (method *C*), the same products were formed but in different ratios. The use of zinc chloride instead of sulfuric acid (method *D*) was no improvement. The use of 2,2-dimethoxypropane and slightly more than one molar equivalent of anhydrous *p*-toluenesulfonic acid in N,N-dimethylformamide

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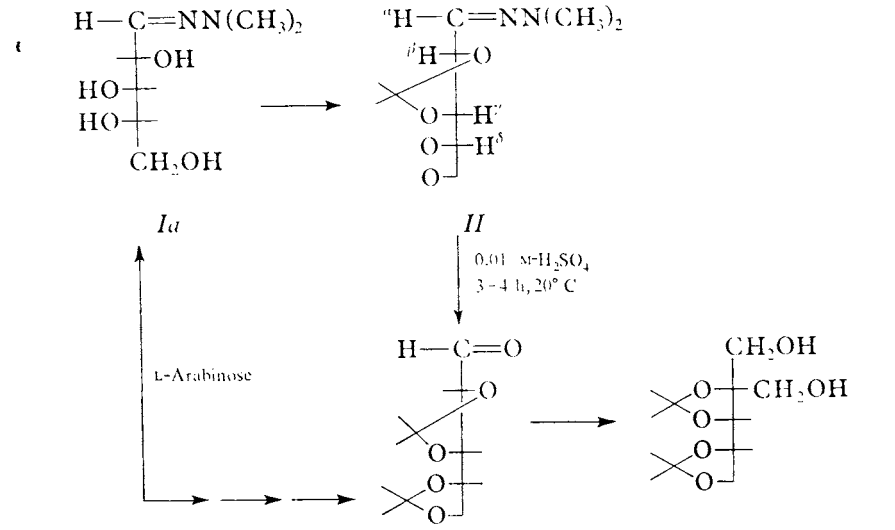
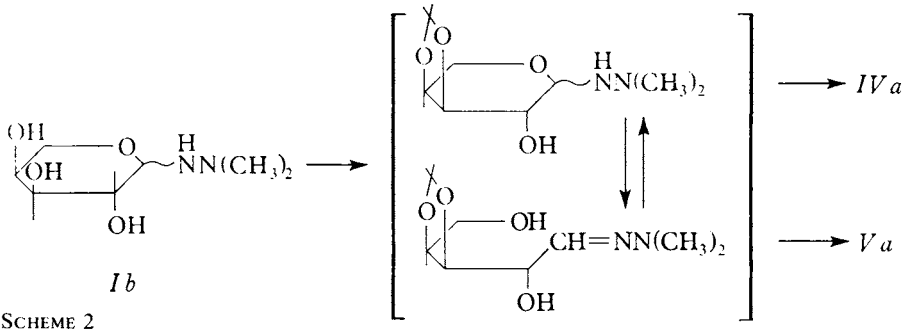
at room temperature (method *E*) gave the highest yield of the two tetrahydrofuranylhydrazones *IVa* (36%) and *Va* (21%), along with a small amount of two unidentified components (slower moving on TLC).



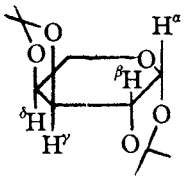
SCHEME 1



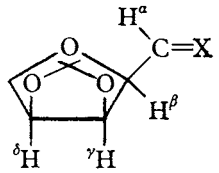
SCHEME 2

The structure of *IVa* was based on its NMR data and that of the aldehyde *IVb* and its dimethylacetal[8] *IVc* prepared from *IVa*. Similarly the structure of *Va* was based on decoupling experiments and by comparison of the NMR data of its free aldehyde[9] *Vb* and its oxime *Vc* to those for the D-isomer reported in the literature[10]. The origins of *IVa* and *Va* can be accounted for as shown in Scheme 2 by assuming the initial formation of the mono-isopropylidenation product (shown in brackets) from the pyranose form of the arabinose hydrazone *Ia*. Tetrahydrofuran ring closure would give the arabinose derivative *IVa*; but inversion at $C_{(2)}$, either by an S_N1, S_N2 of dehydration-addition process, could give the ribose derivative *Va*.

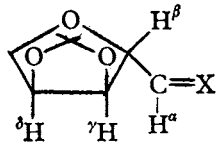
The reaction of 2,2-dimethoxypropane and sulfuric acid with *I* (method *F*) gave the highest yields of the sought for 2,3:4,5-di-O-isopropylidene-L-arabinose N,N-dimethylhydrazone (*II*, 36%) along with some *IVa* (6%), *Va* (5%) and smaller amounts of three unidentified products (slower moving on TLC). It is evident from the NMR data that hydrazone *II* exists as a single isomer. The chemical shift of H_α and H_β



III



IVa, X = $NN(CH_3)_2$
IVb, X = O
IVc, X = $O(CH_3)_2$



Va, X = $NN(CH_3)_2$
Vb, X = O
Vc, X = NOH

protons (δ 6·41 and 4·44 ppm) and coupling constants $J_{\alpha,\beta}$ and $J_{\beta,\gamma}$ (6·1 and 7·6 Hz) are in agreement with a *syn* (*s trans*) configuration of the hydrazone group [$N(CH_3)_2$ *syn* to C—H] in accord with that reported for the D isomer[1] and other N,N-dimethylhydrazones[1,11]. The structure of *II* was confirmed as shown in Scheme 1 by its hydrolysis to the protected aldehyde *VI* followed by treatment with formaldehyde in the presence of base to produce the crystalline branched-chain pentitol *VII* (ref.[12,13]) by a combined aldol-Cannizzaro reaction by the method in the xylose series[14].

TABLE I
Isopropylidenation of L-arabinose N,N-dimethylhydrazone

Method	Reagents[a]	Products, %				Other[b]
		II	*III*	*IVa*	*Va*	
A	Me_2CO, PTSA.H_2O	—	91	—	—	0
B	Me_2CO, H_2SO_4	n	12	3	20	0
C	Me_2CO, H_2SO_4, P_2O_5	n	51	10	7	1
D	Me_2CO, $ZnCl_2$	4	n	26	6	1
E	DMP, PTSA, DMF	n	n	36	21	2
F	DMP, H_2SO_4	36	n	6	5	3
F[c]	DMP, H_2SO_4	31	n	8	n	—

[a] Abbreviations: PTSA.H_2O, *p*-toluenesulfonic acid hydrate; PTSA, anhydrous *p*-toluenesulfonic acid; DMP, 2,2-dimethoxypropane; DMF, N,N-dimethylformamide; n, refers to negligible amount. [b] Number of unidentified compounds detected by TLC. [c] Slightly different conditions, *cf.* Experimental.

Finally, we were unsuccessful in carrying out an aldol condensation directly on the hydrazone *II* using paraformaldehyde and basic catalysts including lithium diethylamide as reported for other hydrazones[15].

EXPERIMENTAL

Melting points were determined in capillary on an aluminum block. ^{1}H NMR spectra (100 MHz) were determined on a Varian XL-100 Fourier Transform instrument with C^2HCl_3 as solvent and tetramethylsilane as internal standard and lock signal. Chemical shifts, δ, are given in ppm downfield from tetramethylsilane, and coupling constants, J, in Hz. Abbreviations for signal multiplicity are: s, singlet, d, doublet, t, triplet, m, multiplet. Decoupled ^{1}H NMR spectra were taken on a Nicolet NMC-300 instrument. Optical rotations were determined on an Autopol III (Rudolf Research Company) electronic polarimeter with a reproducibility of $\pm 0{\cdot}002°$. Mass spectra were measured on a quadrupole R 10-10C Ribermag instrument with 70 eV ionizing voltage. Reactions were followed by thin layer chromatography (TLC) on 10 × 2·5 cm silica gel GF Uniplates (Analtech Company). Visualization was by spraying with 20% H_2SO_4 and heating to 150°C. Column chromatography was with silica gel (Davidson, Daniel G2) using 3 : 2 v/v ethyl acetate–hexane as solvent system. The starting material, L-arabinose N,N-dimethylhydrazine (*I*), was prepared from L-arabinose and 1,1-dimethylhydrazine in 80% yield according to method reported[16].

Isopropylidenation of L-Arabinose N,N-dimethylhydrazone (*I*)

A) *p*-Toluenesulfonic acid hydrate (7·1 g, 37·5 mmol) was added to a stirred mixture of *I* (0·72 g, 3·75 mmol) in dry acetone (200 ml); after 2·5 h all the solid had dissolved. The mixture was then poured into a stirred solution of $NaHCO_3$ (6·7 g, 80 mmol) in ice and water (80 ml). The volume was reduced under vacuum to *c.* 50 ml and the product was extracted with $CHCl_3$ (4 × 30 ml); TLC showed only one spot (R_F 0·68). The solution was dried ($MgSO_4$) and the solvent evaporated. The residue was recrystallized from n-hexane to give 0·69 g (91%) of *III*; physical properties and analytical data were in full accord with those previously reported[5–7].

B) Sulfuric acid (1·0 ml, 98%, 20 mmol) was added dropwise in the course of 5 min to a stirred suspension of *I* (1·92 g, 10 mmol) in dry acetone (125 ml) at 20°C. During the addition, precipitation occurred. The mixture was stirred for 6 h at room temperature. Solid Na_2CO_3 (3 g) was then added and stirring was continued for 1·5 h. The acetone was evaporated under vacuum and the heterogeneous residue dissolved in water and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and vacuum evaporated, to give a brown residue which contained three major products as determined by TLC. Column chromatography gave the following: 1,2:3,4-Di-O-isopropylidene-β-L-arabinopyranose (*III*, R_F 0·68, 0·27 g, 12%, see method *A*); 2,5-anhydro-3,4--O-isopropylidene-L-ribose N,N-dimethylhydrazone (*Va*, R_F 0·54, 0·43 g, 20%); for $C_{10}H_{18}N_2O_3$ (214·1) calculated: 56·09% C, 8·40% N, 13·07% N; found: 56·17% C, 8·51% H, 13·01% N; $[\alpha]_D^{20}$ +107·3° (*c* 1, CH_3OH); ^{1}H NMR: δ 1·35, 1·52 (2 s, $(CH_3)_2C$), 2·78 (s, $(CH_3)_2N$), 3·71 (dd, J_{gem} 10·5, $J_{4,5}$ 3·9, H-5), 3·95 (d, H-5′), 4·65 (d, $J_{1,2}$ 3·5, H-2), 4·77 (dd, $J_{3,4}$ 6·3, H-4), 5·08 (d, H-3), 6·42 (d, H-1); 2,5-anhydro-3,4-O-isopropylidene-L-arabinose N,N-dimethylhydrazone (*IVa*, R_F 0·38, 0·62 g, 29%); for $C_{10}H_{18}N_2O_3$ (214·1) calculated: 56·09% C, 8·40% H, 13·07% N; found: 56·04% C, 8·39% H, 12·99% N; m.p. 60–60·5°C, $[\alpha]_D^{20}$ +203·3° (*c* 1, CH_3OH); ^{1}H NMR: δ 1·33, 1·51 (2 s, $(CH_3)_2C$), 2·86 (s, $(CH_3)_2N$), 3·51 (dd, J_{gem} 10·7, $J_{4,5}$ 3·6, H-5), 4·01 (dd, $J_{1,2}$ 6·7, $J_{2,3}$ 3·5, H-2), 4·05 (d, H-5′), 4·67 (dd, $J_{3,4}$ 6·0, H-3), 4·72 (dd, H-4), 6·55 (d, H-1); mass spectrum, *m/z* (rel. intensity, %): 215 (20, $M^{+\cdot}+1$), 214 (65, $M^{+\cdot}$), 200 (4), 199 (35, $M^{+\cdot}$–

$-CH_3^{\bullet}$), 186 (11), 172 (14), 170 (11), 142 (6), 139 (19), 127 (7), 101 (10), 100 (12), 85 (19), 71 (36), 70 (10), 69 (16), 68 (13), 59 (47), 58 (57), 57 (34), 55 (28), 46 (68), 45 (100), 44 (67), 43 (73), 42 (62), 41 (35).

C) At room temperature conc. H_2SO_3 (0·4 ml) was added to a stirred suspension of *I* (0·96 g, 5·0 mmol) in dry acetone (70 ml) followed by addition of P_2O_5 (50 mg). During addition, precipitation occurred. The mixture was stirred overnight at room temperature and worked up as in method *B* to give *III* (0·58 g, 51%), *Va* (75 mg, 7%), *IVa* (0·1 g, 10%), and 61 mg of unidentified compound (R_F 0·26).

D) Dry acetone (50 ml) and anhydrous $ZnCl_2$ (10 g) were stirred for 2 h and the mixture filtered to remove excess $ZnCl_2$. The clear acetone solution was added to *I* (0·96 g, 5·0 mmol) and the mixture was stirred for 17 h at room temperature. Powdered Na_2CO_3 (1 g) was added and stirring continued for 24 h. Filtration and concentration of the filtrate under vacuum gave an oil. TLC showed two major products (R_F 0·38 and 0·21) plus two minor ones (R_F 0·63 and 0·54). The predominant component (R_F 0·38) was identified as *IVa* (0·28 g, 26% after column chromatography) and the minor components were identified as *Va* (64 mg, 6%) and *II* (54 mg, 4%); for $C_{13}H_{24}N_2O_4$ (272·1) calculated: 57·37% C, 8·82% H, 10·29% N; found: 57·29% C, 8·90% H, 10·20% N; ^{1}H NMR spectrum: δ 1·34, 1·40, 1·42 (3 s, $2(CH_3)_2C$), 2·83 (s, $(CH_3)_2N$), 3·95–4·23 (m, 4 protons, H-3, 4 and 5), 4·44 (dd, $J_{1,2}$ 6·1, $J_{2,3}$ 7·6, H-β), 6·41 (d, H-α).

E) 2,2-Dimethoxypropane (4·16 g, 40 mmol) was added at room temperature to a stirred solution of *I* (2·26 g, 13 mmol) in dimethylformamide (30 ml), followed by addition of anhydrous *p*-toluenesulfonic acid (2·29 g, 13·2 mmol). The color of the solution changed from yellow through yellow-greenish to dark green during the first hour. After 8 h, the acid was neutralized with Amberlite IRA-400 (OH^-) resin. The resin was removed and washed with dimethylformamide and CH_3OH. Evaporation of the combined washings and reaction mixture (down to 1 mm press below 40°C) afforded an oil which was dissolved in CH_2Cl_2 and filtered through Celite and twice through Florisil. The filtrate was concentrated to an oil which by TLC showed the presence of four compounds. Column chromatographic separation gave: *Va* (R_F 0·54, 0·58 g, 21%), *IVa* (R_F 0·38, 1·0 g, 36%) and two unidentified compounds (R_F 0·22 and 0·10, 160 mg and 43 mg respectively).

F) To 2,2-dimethoxypropane (50 ml) H_2SO_4 (3 ml, 98%) was added slowly with stirring at room temperature. A gum separated. The supernatant solution was added to *I* (3·84 g, 20 mmol) at room temperature and stirring continued for 2 h, during which time solid slowly dissolved. The excess 2,2-dimethoxypropane was vacuum evaporated, the resulting oil taken up in $CHCl_3$ (50 ml) and the solution washed with aq. K_2CO_3 solution. The organic layer was dried ($MgSO_4$), and the solvent vacuum evaporated to give a mixture of six components (as seen from TLC). Column chromatography gave *II* (R_F 0·63, 1·96 g, 36%), *Va* (R_F 0·54, 0·2 g, 5%), *IVa* (R_F 0·38, 0·25 g, 6%), and three unidentified slower moving components (R_F 0·23, 0·16, and 0·09).

In a slightly modified procedure a solution of 2,2-dimethoxypropane (30 ml) and conc. H_2SO_4 (0·4 ml) was prepared as above and added to *I* (0·96 g, 5 mmol). The mixture was stirred for 17 h at room temperature, and then processed as described above to give the same six components, but in this case, compounds *II* (31%) and *IVa* (18%) were the major products isolated by column chromatography.

In small scale (<1 g of *I*) experiments, the slower moving components (R_F <0·25) can be removed by a simple filtration of a CH_2Cl_2 solution of the crude reaction product through a pad of Florisil.

2-C-(Hydroxymethyl)-2,3:4,5-di-O-isopropylidene-3,4-L-*erythro*-pentitol (*VII*)

A solution of hydrazone *II* (68 mg, 0·25 mmol) in 0·01M-H_2SO_4 (20 ml) was stirred at room temperature for 3—4 h. TLC showed that all the hydrazone (R_F 0·63) was hydrolyzed to aldehyde (R_F 0·49). The product was extracted into CH_2Cl_2, dried ($MgSO_4$) and the solvent evaporated under vacuum to give aldehyde *VI* (57 mg, 100%, oil). To a stirred solution of the above aldehyde in C_2H_5OH (2 ml), formaldehyde (37% aq. solution, 0·3 ml) was added followed by an aq. solution of NaOH (2 ml of 2·5% solution). After 24 h of stirring at room temperature, TLC revealed that all the starting aldehyde had been converted into product (R_F 0·34). The base was neutralized with 96% HCOOH, the mixture extracted into $CHCl_3$, the organic layer dried ($MgSO_4$), and the solvent vacuum evaporated, leaving an oily product which crystallized on addition of small amount of *n*-hexane. Recrystallization from hexane gave *VII* as white needles, 54·4 mg, 83% yield, having m.p. of 90—91°C, $[\alpha]_D^{20}$ +13·4° (*c* 2, CH_3OH); ref.[12] m.p. 91—92°C, $[\alpha]_D$ +14°; for $C_{12}H_{22}O_6$ (262·1) calculated: 54·98% C, 8·39% H; found: 54·92 C, 8·47% H. ^1H NMR spectrum: δ 1·36, 1·40, 1·44 (3 s, 2 $(CH_3)_2C$), 2·30 (dd, J = 7·9 and 5·4, OH), 2·39 (t, J = 6·7, OH), 3·69—4·05 (m, 6 protons, 3 CH_2), 4·12—4·29 (m, 2 protons, H-3 and H-4).

Hydrolysis of Hydrazones *IVa* and *Va*

A solution of either hydrazone *IVa* or *Va* (0·21 g, 1·0 mmol) in 0·01M-H_2SO_4 (50 ml) was stirred at room temperature for 6 h. Extraction by $CHCl_3$ and evaporation of the dried ($MgSO_4$) extracts gave the corresponding aldehyde *IVb* (ref.[9] for D enantiomer) or *Vb*. These were converted into the corresponding oximes *Vc* and dimethylacetal *IVc* according to procedures previously reported[8,10]. Analytical data were in accordance with those described.

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