The Platinum-Catalyzed Hydrogenation and Hydrogenolysis of Acylated Pyranosyl Halides, Tetra-*O*-acetyl-2-hydroxy-D-glucal and Tri-*O*-acetyl-D-glucal[1]

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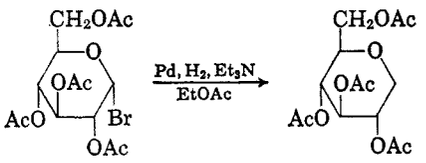
The reduction of acylglycosyl halides using platinum and palladium has been examined. For the preparation of 1,5-anhydroalditols, the platinum-catalyzed reduction in dry ethyl acetate containing diethylamine gives the best yields. The major side reaction involves the formation of 2-hydroxyglycals. The platinum-catalyzed reduction of tetra-*O*-acetyl-2-hydroxy-D-glucal (III) has been shown to give primarily di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (V) and tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hexitol (VI) which are formed through the intermediates tri-*O*-acetyl-D-glucal (IX) and tri-*O*-acetyl-3-deoxy-2-hydroxy-D-glucal (VII). The reduction of III and IX has been examined in a variety of solvents using platinum and palladium catalysts. The nmr spectra of the tritylacetyl derivatives of 1,5-anhydro-D-glucitol, 1,5-anhydro-2-deoxy-D-*arabino*-hexitol, and 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol show that the methyl protons of the 4-*O*-acetyl groups in these compounds are strongly shielded. They have a chemical shift of τ 8.33 ppm.

The reductive dehalogenation of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (I) by palladium and hydrogen



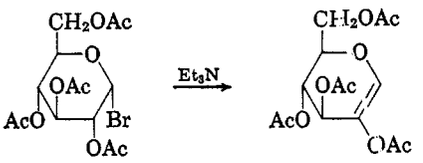
I II

in the presence of triethylamine was reported by Zervas and Zioudrou[2] to give a high yield of the corresponding acetylated 1,5-anhydroalditol (II). Since the acetylated pyranosyl halide derivatives of many sugars are easily prepared, it was felt that this might serve as a general method for the preparation of 1,5-anhydroalditols. To explore this possibility, the conversion of I to II has been examined in order to ascertain the optimum conditions for the production of the 1,5-anhydroalditol.

In our hands the best yields of 1,5-anhydroalditols were obtained by conducting the hydrogenolysis reaction in dry ethyl acetate at room temperature and higher pressure (about 50 psi) using platinum rather than palladium as the catalyst in the presence of diethylamine. As shown in Table I, the yields of 1,5-anhydroalditols from the free sugars vary from 60 to 90%. The yields are based on the weight and gas chromatographic analysis of the material obtained after removal of reducing sugar contaminants. In no case did the amount of impurity exceed 5% and in most cases it was negligible. Pure material was obtained by crystallization from a suitable solvent, usually ethanol. The amount of material isolated was considerably less than the amount present (60–70%), as is usual with this type of compound.

Acetylated intermediates were used except for the preparation of 1,5-anhydroribitol. Owing to the instability of triacetylribopyranosyl bromide[3] and to the relatively high water solubility of the acetylated product which complicated its isolation, benzoylated intermediates[4] were used.

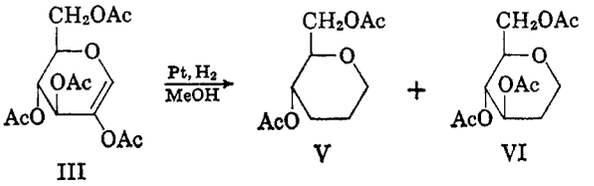
As mentioned above, gas chromatographic analysis of the products after the removal of reducing sugar revealed a small proportion of an impurity. This material had a very short retention time, relative to that of the main product, indicating that it probably contained fewer acetoxy groups. Of the side reactions considered by Zervas and Zioudrou[2] to be important in this preparation, that involving the production of tetra-*O*-acetyl-2-hydroxy-D-glucal (III) seemed most likely to give rise to a product of this type.



I III

There have been several reports of hydrogenolysis occurring in compounds related to III;[5,6] however, the only report of the platinum-catalyzed hydrogenation of tetra-*O*-acetyl-2-hydroxy-D-glucal (III) itself[7] indicates that the major product is probably tetra-*O*-acetyl-1,5-anhydro-D-glucitol (II). This conclusion was based only on the specific rotation of the syrupy product which had a value similar to that of the anhydride II. Since it was felt that this identification may have been in error, the platinum- and palladium-catalyzed reductions of tetra-*O*-acetyl-2-hydroxy-D-glucal (III) were examined. The products obtained are listed in Table II.

The palladium-catalyzed reaction gives primarily tetra-*O*-acetyl-1,5-anhydro-D-mannitol (IV) as reported by Zervas.[8] However, in the platinum-catalyzed reduction of III, no tetra-*O*-acetyl-1,5-anhydro-D-glucitol is produced. The only products are di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (V) and tri-*O*-



III V VI

(1) Supported in part by Public Health Service Grant GM 11,963 and Public Health Service Research Career Program Award GM 24,808 to Robert Barker from the Institute of General Medical Sciences.

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TABLE I

1,5-ANHYDROALDITOLS OBTAINED FROM PLATINUM-CATALYZED HYDROGENOLYSIS OF ACYLATED PYRANOSYL HALIDES

1,5-Anhydroalditol	Yield, %	Mp,[a] °C Obsd	Mp,[a] °C Reptd	$[\alpha]^{25}D$ Obsd	$[\alpha]^{25}D$ Reptd	Footnote
1,5-D-Glucitol[b]	90	142–143	141–142	+41.7	+42.5	*d*
1,5-D-Mannitol	73	154–155	155–156	−49.5	−50.0	*e*
1,5-D-Galactitol	75	113–114	114–115	+77.0	+76.6	*f*
1,5-Ribitol[c]	78	128–129	128–129	0	0	*g*
1,5-Xylitol	70	114–115	116–117	0	0	*h*
1,5-D-Arabinitol	65	94–96	96–97	−97.8	−98.6	*i*
1,5-L-Rhamnitol	63	123–124	123–124	+85.0	+83.0	*j*

[a] Melting points are corrected. [b] Glucose pentaacetate starting material. [c] Prepared from benzoylated intermediates; all others prepared from acetylated intermediates. [d] N. K. Richtmyer and C. S. Hudson, *J. Am. Chem. Soc.*, **65**, 64 (1943). [e] J. Fried and D. E. Walz, *ibid.*, **71**, 140 (1949). [f] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **70**, 310 (1948). [g] See ref 4. [h] H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **69**, 921 (1947). [i] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **69**, 1672 (1947). [j] R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 4547 (1950).

TABLE II

THE YIELDS OF VARIOUS PRODUCTS OBTAINED IN THE CATALYTIC REDUCTION OF TETRA-*O*-ACETYL-2-HYDROXY-D-GLUCAL (III) USING VARIOUS CATALYSTS AND SOLVENTS

Conditions	Di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (V), %	Tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hexitol (VI), %	Tetra-*O*-acetyl-1,5-anhydro-D-mannitol (IV), %	Tetra-*O*-acetyl-1,5-anhydro-D-glucitol (II), %
H_2, Pt,[a] MeOH	67	33	0	0
H_2, Pd,[b] MeOH	Trace	6	75	19
H_2, Pd Blk,[c] MeOH	3	14	72	11
H_2, Pt,[a] HOAc	16	78	0	0
H_2, Pd,[b] HOAc	2	10	71	14
H_2, Pt,[a] EtOAc	67	33	0	0
H_2, Pt[a,d] EtOAc	48	52	0	0
H_2, Pd,[b] EtOAc	0	4	89	7
H_2, Pt,[a] EtOAc, Et_2NH	100	0	0	0

[a] Pt = PtO_2 reduced prior to the addition of substrate. [b] Pd = 10% palladium chloride on charcoal freshly reduced, filtered, and washed to remove hydrochloric acid. [c] Pd Blk = palladium chloride reduced, filtered, and washed to remove hydrochloric acid. [d] Different sample of PtO_2.

acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hexitol (VI) formed in proportions that depend upon the conditions of the reaction.

The results reported here for the platinum-catalyzed reduction of III in methanol are in reasonable agreement with the report by Hockett and Conley[7] with respect to the rotation of the product of the reaction. The acetates V and VI have rotations of +34.0 and +34.7°, respectively, in ethanol. Therefore, a mixture of these two in any proportion would have a rotation of approximately +34° in reasonable agreement with the reported value of +37.1°. However, we did not observe the formation of any 1,5-anhydro-D-mannitol which Hockett and Conley were able to isolate in low yield. The probability that differences between batches of catalyst will produce differences of this nature is quite high. For example, in the present work we observed a significant difference in the proportions of V and VI when different samples of platinum oxide were used (Table II).

If the reduction of tetra-*O*-acetyl-2-hydroxy-D-glucal (III) is carried out under the conditions required for the hydrogenolysis of a glycosyl halide, *i.e.*, in the presence of diethylamine, only V is formed (Table II). Compound V and the silyl derivative obtained from it have the same retention times as the acetate and silyl derivatives of the impurity formed in the platinum-catalyzed hydrogenolysis of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (I). Assuming that the compounds are identical, it appears that the impurity is due to the intermediate formation of tetra-*O*-acetyl-2-hydroxy-D-glucal (III).

The stoichiometry of the platinum-catalyzed hydrogenolysis of III to produce V has been examined; 3 moles of hydrogen are consumed per mole of III and 2 moles of acetic acid are formed. Diethylamine is not required in molar proportions with respect to either III or the acetic acid released; it serves to modify the catalyst and is required only in an amount sufficient to saturate the catalyst (Table III). In the platinum-catalyzed reduction of III, hydrogenolysis of acetoxy functions must precede hydrogenation of the double bond since the products which would be formed in the latter reaction, 1,5-anhydroalditol tetraacetates, are stable under the conditions of the reaction and are not observed. The proportion of products formed probably depends upon changes in the rates of hydrogenolysis at C-2 and C-3 with changes in the catalyst. Possible routes to the products V and VI are indicated in Scheme I.

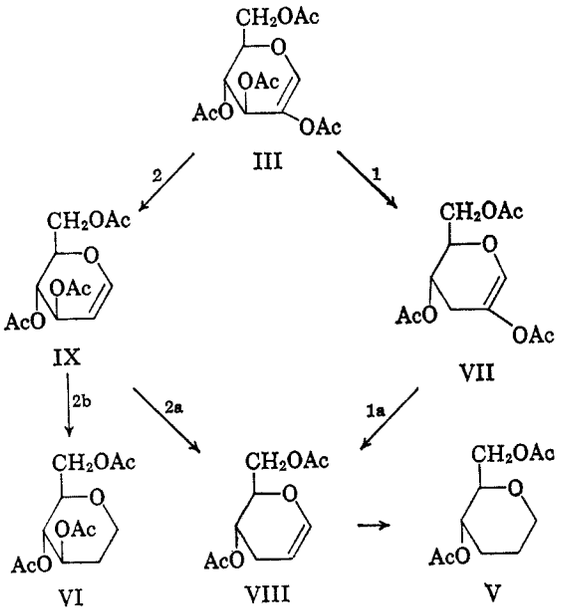
TABLE III

PRODUCTS FORMED IN THE PLATINUM-CATALYZED REDUCTION OF TETRA-*O*-ACETYL-2-HYDROXY-D-GLUCAL (III) USING VARYING PROPORTIONS OF DIETHYLAMINE

Tetra-*O*-acetyl-2-hydroxy-D-glucal (III)–Et_2NH–Pt, Mole:mole:mole	Di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (V), %	Tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hexitol (VI), %
1.37:0.00:1.00	48	52
11.7:4.08:1.00	100	0
5.8:1.00:3.04	95	5

Route 1. Hydrogenolysis of the allylic acetoxyl at

SCHEME I



C-3 produces VII (step 1) which must undergo further hydrogenolysis to give VIII (step 1a) since neither of the products which would be formed if hydrogenation of VII occurred are observed. This route can only produce the dideoxy compound (V).

Route 2. Hydrogenolysis of the vinylic acetoxy group produces tri-*O*-acetyl-D-glucal (IX) which can either undergo further hydrogenolysis to form VIII (step 2a) or can hydrogenate to form the monodeoxy compound (VI) (step 2b). The latter can only form by this route.

Since the intermediate IX can give rise to both of the products observed in the reaction, it is possible that modification of the catalyst serves only to alter the proportion of the reaction proceeding through steps 2a and 2b and that regardless of the catalyst all of the products are formed from the intermediate IX. To test this hypothesis, the reduction of tri-*O*-acetyl-D-glucal (IX) was examined. The results are summarized in Table IV.

TABLE IV

THE PRODUCTS FORMED IN THE PLATINUM AND PALLADIUM-CATALYZED REDUCTION OF TRI-*O*-ACETYL-D-GLUCAL (IX)

Conditions[a]	Di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (V), %	Tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hexitol (VI), %
IX, Pt (EtOAc)	16	84
IX, Pt (HOAc)	15	85
IX–Pt–Et_2NH (5.47:1.00:15.6) (EtOAc)	94	6
IX–Pt–Et_2NH (4.36:1.00:1.03) (EtOAc)	91	9
IX, Pt, Et_2NH_2OAc (EtOAc)	95	5
IX, Pd, Et_2NH (EtOAc)	69	31

[a] Pt = platinum oxide reduced before addition of substrate; the solvent is given in parentheses; where a catalyst modifier was used, the molar proportions of substrate, catalyst, and modifier are given.

According to Scheme I, compound VI can *only* be formed from IX. The proportions of V and VI formed from IX are known under the conditions used in the reduction of tetra-*O*-acetyl-2-hydroxy-D-glucal (III) and it is possible, therefore, to assess the relative importance of IX as an intermediate in the reduction of III. When III is reduced with platinum in ethyl acetate, V and VI are produced in 67 and 33% yields, respectively. When tri-*O*-acetyl-D-glucal (IX) is reduced under the same conditions, V and VI are produced in 16 and 84% yields, respectively. Now, since VI can only form from IX, the 33% of VI formed in the reduction of the tetra-*O*-acetyl-2-hydroxy-D-glucal (III) corresponds to the formation of 39% of IX in the reaction (100/84 × 33). Under these conditions, 39% of the reaction proceeds *via* route 2 and it seems reasonable to assume that the other 61% proceeds *via* the intermediates VII and VIII with the ultimate formation of the dideoxy compound V. The effect of changes in the reaction conditions on the reduction of III can be expressed in terms of the percentage of the reaction which proceeds through the intermediates VII, VIII, and IX. These values are given in Table V.

TABLE V

PLATINUM-CATALYZED REDUCTION OF TETRA-*O*-ACETYL-2-HYDROXY-D-GLUCAL (III) SHOWING PERCENTAGE CONVERSION THROUGH INTERMEDIATES VII, VIII, AND IX OF SCHEME I

	Conversion, %		
Conditions	IX	VII	VIII
III, EtOAc[a]	62	38	48
III, EtOAc[b]	39	61	67
III, EtOAc, Et_2NH	0	100	100
III, HOAc	92	8	16

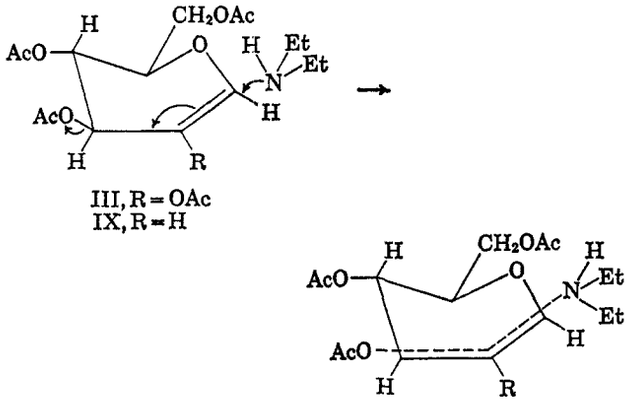
[a] V = 48%, VI = 52%. [b] V = 67%, VI = 33%.

It is apparent that the reductions of both tetra-*O*-acetyl-2-hydroxy-D-glucal and tri-*O*-acetyl-D-glucal are sensitive to the presence of the catalyst–modifier diethylamine. The amine has a high affinity for the catalyst; approximately 0.4 moles of amine per mole of catalyst is bound and it does not appear to be removed by the acetic acid formed in the hydrogenolysis. In fact, diethylammonium acetate serves equally well to modify the catalyst. The amine functions to increase the hydrogenolysis of the allylic acetoxy group of both III and IX, producing the intermediates VII and VIII, respectively. In the case of the glucal (IX), this action is not so complete (95%) as it is in the case of the acetoxyglucal, III (100%). The mechanism by which diethylamine promotes hydrogenolysis is not known. It may participate in an SN2′ displacement on the surface of the catalyst with the formation of a bound species with partial unsaturation over C-1, C-2, and C-3 (Scheme II) which would be expected to promote hydrogenolysis at both C-2 and C-3. Platinum catalyst alone has some ability to produce hydrogenolysis at both C-2 and C-3 and it is the tendency for the latter to occur that is influenced by diethylamine. The hydrogenolysis capability of the unmodified catalyst was found to vary with various batches used (Tables II and V).

In no case were products due solely to saturation of the double bond of III observed, although the majority of the reductions of IX took place at the double bond. The effect of solvent was pronounced in the hydrogenolysis of III where acetic acid was found to suppress hydrogenolysis of the 3-acetoxy group. No such effect of solvent on the reduction of IX was observed.

When tetra-*O*-acetyl-2-hydroxy-D-glucal is reduced

SCHEME II



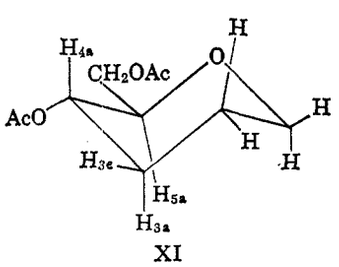
III, R = OAc
IX, R = H

with platinum in acetic acid, minor amounts (<6%) of products which probably arise from rearrangements to compounds having unsaturation between C-2 and C-3[9,10] are observed. In addition, when the reduction is performed with a high ratio of III to catalyst, a small proportion of 1,5-anhydro-D-mannitol is produced.

The palladium-catalyzed hydrogenation of tetra-*O*-acetyl-2-hydroxy-D-glucal has also been examined. The major product is, as reported by Zervas,[8] tetra-*O*-acetyl-1,5-anhydro-D-mannitol (IV) which was obtained in yields varying from 70 to 89% depending on the solvent used (Table II). Hydrogenolysis occurs to only a minor extent and, in most cases, tetra-*O*-acetyl-1,5-anhydro-D-glucitol (II) is the major contaminant as has previously been reported by Richtmyer, Carr, and Hudson.[11]

To verify that the structure assigned to di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (V) by Bergmann and Breuers[5] was correct, the nmr spectrum of the acetate, benzylidene, and 6-*O*-trityl-4-*O*-acetyl derivatives were examined.

The acetyl derivative (V) in deuteriochloroform gave methyl proton frequencies at τ 7.97 and 7.93 ppm characteristic of equatorial acetoxyl groups.[12] A sextet centered at τ 5.35 having an area equivalent to one proton was assigned to H_{4a} (XI). This proton is split



XI

equally by H_{3a} and H_{5a} to give a triplet[13] which is further split to a sextet by H_{3e}. The coupling constants are in reasonable agreement with the values in similar systems[13] and are $J_{3a-4a} = J_{4a-5a} = 9.7$ cps; $J_{3e-4a} = 4.7$ cps.

The spectrum of the benzylidene derivative was also consistent with the proposed structure. Integration of the spectrum gave five protons in the region τ 2.35–2.94, one proton at 4.48, six protons in the region 5.55–7.00, and four protons in the region 7.72–8.55. These groups were assigned to the phenyl protons, methinyl proton, C-1, C-4, C-5, and C-6 protons, and the C-2 and C-3 protons, respectively.

The tritylacetyl derivative of the dideoxy compound gave an nmr spectrum which indicated the presence of one trityl group (τ 2.77 ppm) and one acetoxyl group (8.33 ppm). The chemical shift of the methyl protons of the acetoxyl group is higher than expected for an equatorial acetoxyl function (approximately τ 8.0 ppm) and considerably higher than expected for an axial acetoxyl which usually absorbs at lower field. The shift to higher field appears to be due to the presence of a trityl group at the 6 position since the effect is observed in the tritylacetyl derivatives of 1,5-anhydro-2-deoxy-D-*arabino*-hexitol and 1,5-anhydro-D-glucitol, both of which have absorptions at τ 8.33 ppm equivalent to a single acetoxyl group. The trityl group in these compounds would be expected to occupy a position normal to the "plane" of the pyranose ring and, owing to the ring currents of the phenyl groups, would shield acetyl groups at C-4. The observed change in chemical shift (+0.3 ppm = 18 cps) is in reasonable agreement with the values calculated by Johnson and Bovey[14] for protons in this kind of environment.

The nmr spectrum of the acetyl derivative VI confirms the structural assignment. There are three acetoxyl groups, two at τ 7.95 ppm and one at 7.91 ppm, indicating all are equatorial.[12] Integration of the nmr spectrum of the tritylacetyl derivative prepared from the alditol obtained by deacetylation of VI indicated the presence of one trityl group (centered at τ 2.75 ppm) and two acetoxyl groups, one at 8.08 ppm as expected for an equatorial acetoxyl and one at 8.33.

Experimental Section

Removal of solvents was accomplished with a rotary evaporator at water aspirator pressure. Nuclear magnetic resonance spectra were obtained on a Varian A-60 analytical nmr spectrometer. Tetramethylsilane (TMS) was used as an internal standard in deuteriochloroform solutions. Gas chromatographic analyses were performed on an Aerograph Hy-Fi, Model 600-D, having a flame ionization detector operated with a hydrogen flow rate of 30 ml/min. A 4 ft $\times$ 1/8 in. column packed with neopentyl glycol sebacate and 10% on 80–100 mesh Gas Chrom Q (Applied Science Laboratories, Inc.) was used with helium as the carrier gas at 30 ml/min. The temperature of the column was 150° when silyl derivatives were used and 170° when acetyl derivatives were used.

Silyl derivatives were prepared by dissolving approximately 10 mg of the mixed alditols in 0.5 ml of pyridine and adding 0.2 ml of hexamethyldisilazane and 0.1 ml of trimethylchlorosilane. After 5 min, 2λ of the reaction mixture was injected. Acetyl derivatives were prepared using pyridine and acetic anhydride and warming the sample for 30 min. In those cases where the acetyl derivatives were used in the reaction, a sample of the reaction mixture was injected directly.

1,5-Anhydroalditols.—The free sugar (0.1 *M*) was acetylated in pyridine (300 ml) at 0° using an excess (200 ml) of acetic anhydride. After 18 hr the excess reagent was destroyed with water (20 ml) and excess pyridine was removed at 50°. The product was isolated by partitioning the syrup so obtained between methylene chloride and successive washes of 2 *N* sulfuric acid, saturated sodium bicarbonate, and water, drying the methylene chloride layer over sodium sulfate, and removing the solvent. The syrupy acetate was dissolved in an equivalent weight of 30% hydrobromic acid in glacial acetic acid and allowed to

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remain at room temperature for 2 hr, after which time the excess reagent was removed at 50°. The crude syrup so obtained was dissolved in methylene chloride and partitioned successively between saturated sodium bicarbonate and water. The methylene chloride layer was dried over sodium sulfate and concentrated at 40°. The resulting syrup was dissolved in 200 ml of ethyl acetate (previously dried over drierite) and transferred to a Parr reaction bottle containing 1.0 g of platinum catalyst (Adam's catalyst) which had been prepared from platinum oxide and washed several times by decantation using dry ethyl acetate. Diethylamine (25 ml) was added and hydrogenation was conducted starting with a hydrogen pressure of 50 psi. When the consumption of hydrogen was complete, the catalyst was removed by filtration and the filtrate concentrated at 50°. The product so obtained was dissolved in methylene chloride and extracted three times with water. The methylene chloride layer was dried and concentrated to yield the acetylated 1,5-anhydroalditol as a syrup which was dissolved in methanol (200 ml) and treated with approximately 0.5 g of sodium. After 4 hr at room temperature, Dowex 50W-X8 (H^+) (50 ml) was added and the mixture stirred for 30 min. Removal of the resin by filtration and evaporation of the solvent afforded the free 1,5-anhydroalditol.

If appreciable reducing sugar was present (Benedict's test), the product was dissolved in 100 ml of 0.5 *N* aqueous sodium hydroxide and aerated overnight, after which time the solution was treated batchwise with 150 ml of Dowex 50W-X8 (H^+) to remove sodium ions and then with Rexyn 203 to remove organic acids. Removal of the solvent at 60° afforded the 1,5-anhydroalditol which in most cases was essentially pure and crystallized spontaneously. The yields given in Table I were estimated on the basis of the weight of the material obtained at this stage and the amount of impurity present in it as evaluated by gas chromatography carried out on the silyl and acetyl derivatives. In all cases ethanol proved to be a satisfactory solvent for recrystallization.

1,5-Anhydroribitol.—D-Ribose (5.00 g) was converted to 2,3,4-tri-*O*-benzoyl-β-D-ribopyranosyl bromide[4] which was hydrogenated as described for the acetylglycosyl halides. The product was isolated and debenzoylated using similar procedures and gave a crystalline mass which was shown by gas chromatographic analysis of the silyl derivatives to be at least 95% 1,5-anhydroribitol. Pure material was obtained by recrystallization from ethanol.

Platinum- and Palladium-Catalyzed Reductions of III and IX.—Experiments involving the reduction of III and IX by platinum were performed by prereducing platinum oxide in the solvent for the hydrogenation, then adding the compound in crystalline form. Unless otherwise stated, the ratio of compound to catalyst is 1.5–2.0:1.0 mole/mole. When the reduction was performed in the presence of a modifier, the modifier was added with the substrate after the reduction of the catalyst.

Palladium catalyst was prepared from 10% palladium chloride on charcoal by reduction in the appropriate solvent followed by filtration and washing with the solvent to remove hydrogen chloride. When the consumption of hydrogen was complete, the catalyst (platinum or palladium on charcoal) was removed by filtration and gas chromatographic analysis was conducted on the filtrate (acetyl derivatives) or on the silyl derivatives after isolation and deacetylation of the products.

1,5-Anhydro-2,3-dideoxy-4,6-*O*-benzylidene-D-*erythro*-hexitol was prepared by the procedure given by Bergmann and Breuers[5] from 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol obtained by deacetylation of the product of the platinum–diethylamine reduction of tetra-*O*-acetyl-2-hydroxy-D-glucal (III) and tri-*O*-acetyl-D-glucal (IX). The product was recrystallized from acetone–water (1:1) and had mp 137.5–138.5° and $[\alpha]_D$ −4.1 ±0.2° (*c* 8.87, tetrachloroethylene) (lit. mp 137–137.5°, $[\alpha]^{26}_D$ 0° using a 2% solution in a 0.5-dm tube).[5]

1,5-Anhydro-2-deoxy-D-*arabino*-hexitol was prepared by catalytic deacetylation of tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hexitol (VI). The product, after several recrystallizations from ethanol–hexane, had mp 76–77° and $[\alpha]^{29}_D$ +16.4° (*c* 7.39, water). Fischer[15] reported mp 86–87° and $[\alpha]^{19}_D$ +16.37°. A sample prepared according to Fischer also had mp 76–77° alone and mixed with the isolated material.

Registry No.—II, 13137-69-4; III, 3366-47-0; IV, 13121-61-4; V, 13391-23-6; VI, 13035-12-6; IX, 2873-29-2.

(15) E. Fischer, *Ber.*, **47**, 196 (1914).

Inside Yohimbanes. The Dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine System

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The condensation of tryptamine with 2-formylcyclohexaneacetic acid produced the two *trans* epimers of 1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizin-6-one. Reduction of the lactams afforded *trans,anti-* and *trans,syn*-1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahydrobenz[*a*]indolo[3,2-*h*]quinolines (**4** and **6**). By an oxidation and subsequent reduction, the *cis,syn* and *cis,anti* isomers (**9** and **11**) were obtained. The stereochemistry of the four isomers was assigned on the basis of chemical, nuclear magnetic resonance, and infrared data.

During our work on the total synthesis of yohimbane[1] we became interested in the possibility of obtaining the inside yohimbanes[2] (**4**, **6**, **9**, and **11**). This system should be available from the condensation of tryptamine (**1**) with 2-formylcyclohexaneacetic acid (**2**) and subsequent reduction of the lactam function. The acid aldehyde **2**, whose preparation has been described in our earlier work,[1] is a mixture of isomers in which the *trans* is predominant.

When the condensation of **1** and **2** was carried out in glacial acetic acid a good yield of crude lactam was obtained. Fractional crystallization afforded a 60% yield of one isomer (**3**). Reduction of lactam **3** with lithium aluminum hydride gave the first isomer (**4**) of the inside yohimbane system. The second and third crops from the crystallization of the crude lactam contained at least one more lactam, as evidenced by thin layer chromatography. Reduction of these crops, followed by column chromatography, afforded a second base (**6**) which was isomeric with compound **4** (see Scheme I).

Since it did not seem feasible to obtain the other stereoisomers from the condensation, we turned to an indirect oxidation–reduction scheme. The *t*-butyl hypochlorite oxidation[3] of **4** gave the dehydro compound **8**. Since this reaction proceeds through the base of the dehydro compound (**8b**), in which there is no stereo-

(1) G. C. Morrison, W. A. Cetenko, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 2695 (1966).

(2) An aromatic ring E version of this system has been described by S. Sygasawa and Y. Deguchi, *Chem. Pharm. Bull.*, **8**, 879 (1960).

(3) W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).