Catalpa Glycosides. IV.[1] The Stereochemistry of Catalposide

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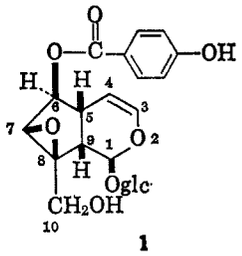
Received October 31, 1966

The stereochemistry at C-1 and C-6 has been established for catalposide through a study of the nmr spectra of several derivatives. This, coupled with previous data, allows the proposal of the complete structure and stereochemistry for the glucoside.

In the previous paper of this series,[1a] the stereochemistry of catalposide (**1**) was proposed for the asymmetric centers at C-5, C-7, C-8, and C-9. This was based partially on our own work and partially on that of Lunn, Edward, and Edward.[3] Recently, the absolute stereochemistry of the ring junction in aucubin (**2**) has been proven to be as shown.[4] Since catalposide has been degraded to a derivative of aucubin[3] in which



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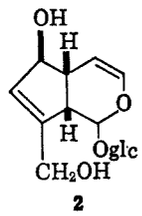

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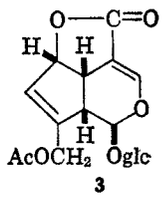

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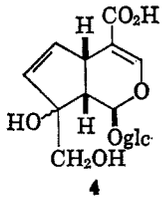

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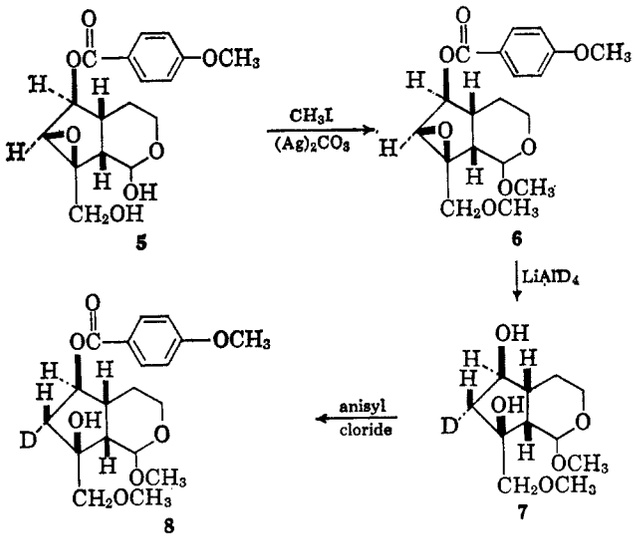
C-5 and C-9 are intact, its absolute stereochemistry is as shown in **1**. This leaves two centers for further study, C-1 and C-6.

The stereochemistry at C-6 is a matter of difficult, but routine chemistry. It has been shown to be β in aucubin (**2**)[4] and α in asperuloside (**3**).[5] The stereochemistry at C-1, however, is another matter. It is an acetal carbon attached by another acetal linkage to glucose. Any reactions carried out on C-1 will destroy its asymmetry. The stereochemistry at C-1 has been proposed as shown for asperuloside (**3**)[5] and monotropein (**4**),[6] but the only evidence presented is that the bulky glucose residue will be less hindered in this position. This latter situation is quite true, but does not rule out a situation where nature favors a more hindered molecule. The configuration at C-1′ in glucose is also open to some doubt. This stereochemistry is proposed in catalposide as a β-glucoside linkage based upon

SCHEME I



enzymic reactions.[3,7] It is conceivable that the double acetal linkage may be anomalous in its behavior toward enzymes.

In this paper we will establish the coupling constants of the protons on C-5, C-6, and C-7 by nmr spectroscopy. We will use these constants to approximate the dihedral angles between the protons and thus establish the stereochemistry at C-6. In a similar fashion, we will establish the coupling constants between the protons on C-1 and C-9 and between C-1′ and C-2′ (in the glucose). This will allow a proposal of the stereochemistry at C-1 and C-1′.

For the study of C-6, three new compounds were prepared. Dihydrocatalpogenin methyl ether (**5**)[1a] was methylated with methyl iodide–silver carbonate to give dihydrocatalpogenin trimethyl ether (**6**). Ether **6** was reduced with lithium aluminum deuteride to give **7** which was reanisylated to give **8** (see Scheme I). In this sequence of reactions, the proton on C-7 which was α in **5** is β in **8**, assuming that the deuteride reduction took place by a backside displacement.[8] In the nmr spectrum of **6** (Figure 1) the proton on C-6 appears as a quartet at 325 cps with coupling constants of 9 cps and 1.2 cps (owing to the protons at C-5 and C-7). The effective inversion of C-7 (**6** → **8**) should change one of the coupling constants and allow the assignment of coupling constants to the C-5–C-6 protons and to the C-6–C-7 protons. In the spectrum of **8** (Figure 1), the proton at C-6 appears at 310 cps as a quartet with coupling constants of about 2.5 and 3.5 cps. The 9-cps coupling constant appears to have changed. Thus, in **6** the C-5–C-6 protons have a coupling constant of 1.2

(1) (a) Paper III: J. M. Bobbitt, D. W. Spiggle, S. Mahboob, H. Schmid, and W. von Philipsborn, *J. Org. Chem.*, **31**, 500 (1966). (b) This work was sponsored in part by Grant CA-5267 from the National Institutes of Health, Public Health Service.

(2) Abstracted in part from the Ph.D. theses of D. E. K., University of Connecticut, 1965, and the M.S. thesis of A. Y.-w. L., University of Connecticut, 1966.

(3) W. H. Lunn, D. W. Edward, and J. T. Edward, *Can. J. Chem.*, **40**, 104 (1962).

(4) H. Uda, M. Maruyama, K. Kabuki, and S. Fujise, *Nippon Kagaku Zasshi*, **85**, 279 (1964); *Chem. Abstr.*, **61**, 14767 (1964).

(5) L. H. Briggs, B. F. Cain, P. W. Le Quesne, and J. N. Shoolery, *J. Chem. Soc.*, 2595 (1965).

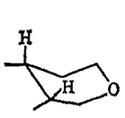
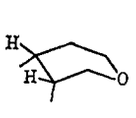
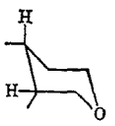
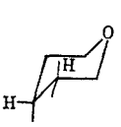
(6) H. Inouye, T. Arai, and Y. Miyoshi, *Chem. Pharm. Bull.* (Tokyo), **12**, 888 (1964).

(7) For a historical summary of the chemistry of catalposide, see J. M. Bobbitt, H. Schmid, and T. B. Africa, *J. Org. Chem.*, **26**, 3090 (1961).

(8) P. J. Leroux and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 41 (1951).

TABLE I

CALCULATED COUPLING CONSTANTS[a]

Compd	Conformations	J					Obsd J values
6	C-6 proton (α)	5,6	*1.0*	*1.7*	*1.0*	6.0	$J_{5,6}$ = 1.2
		6,7	*6.5*	*5.2*	*6.0*	3.5	
	C-6 proton (β)	5,6	7.5	7.2	6.7	7.5	$J_{6,7}$ = 9.0
		6,7	0.0	0.0	0.1	0.5	
8	C-6 proton (α)	5,6	*2.3*	*3.6*	0.0	7.0	$J_{5,6}$ = 2.5
		6,7	*2.3*	*2.3*	1.0	1.0	
	C-6 proton (β)	5,6	8.0	8.1	5.3	7.0	$J_{6,7}$ = 3.5
		6,7	8.0	8.2	7.2	8.1	
9	C-1 proton (α)	1,9	*9.0*	1.7	0.0	9.0	$J_{1,9}$ = 8.8
	C-1 proton (β)	1,9	1.7	1.7	4.5	1.7	

[a] These constants were calculated from Dreiding models using the Karplus relationship. See ref 9.

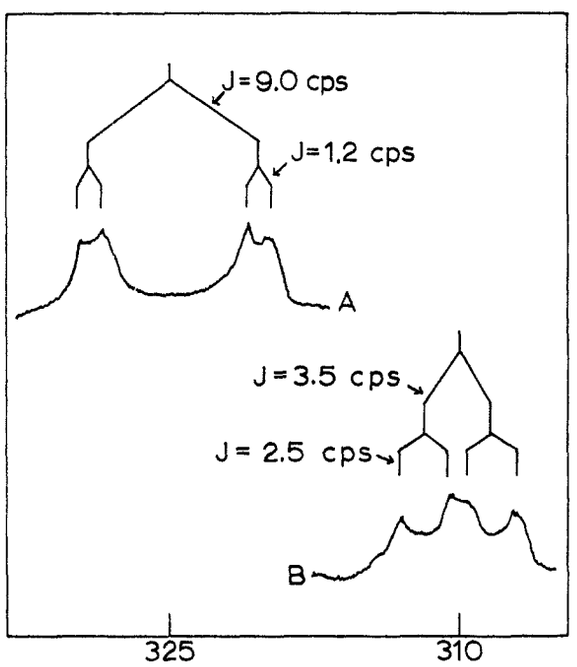
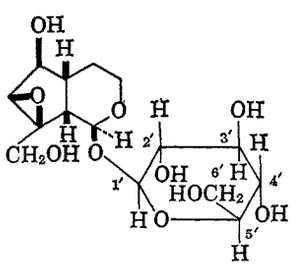


Figure 1.—Nmr spectra (60 Mc) of 6 (A) and 8 (B) in deuteriochloroform.

cps and the C-6–C-7 protons have a coupling constant of 9 cps. In **8**, it is impossible to assign specific coupling constants to specific structures but both are small.

In Table I, the coupling constants calculated[9] from the dihedral angles arising from all of the possible conformations of the pyran ring are recorded, with the C-6 proton in both the α and the β positions. For **6**, the coupling constants (1.2 cps for C-5–C-6 and 9 cps for C-6–C-7) fit three of the four conformations when the C-6 proton is α (*italics* in Table I) and none of the conformations when the proton is β. This assignment is confirmed by the spectrum of **8** in which the coupling constants of 2.5 and 3.5 fit two of the conformations when the C-6 proton is α (*italics* in Table I) and again none of the conformations when the proton is β. The coupling constants do not fit the calculated values exactly, which is to be expected,[9] but the relative values are quite similar. Thus, the proton at C-6 is clearly α and the oxygen is β as shown in **1**.

The stereochemistry at C-1 and C-1′ can be derived using a similar argument. The nmr spectrum of dihydrodeshydroxybenzoylcatalposide (**9**), as recorded



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previously[1a] shows a pair of doublets at 296 cps corresponding to two protons at C-1 (coupled with the C-9 proton) and C-1′ (coupled with the C-2′ proton). The coupling constants are 6.5 and 8.8 cps. In all likelihood, the 6.5-cps doublet corresponds to the C-1′ proton because it has been demonstrated that the C-1 proton in methyl β-D-glucopyranoside has a coupling constant of 7.0 cps.[10] This is not certain, however, since **9** is a fairly complex molecule and the constants cannot be predicted precisely. The question of which coupling constant belongs to which proton was resolved beyond question by two experiments. In the first experiment, compound **9** was oxidized with periodate[11] and the nmr spectrum of the product was measured. The two doublets seen in the spectrum of **9** changed to two doublets with coupling constants of 8.8 and 8.8 cps. Since the aglucone portion of **9** has been shown[1a] not to react with periodate, only the glucose moiety should be affected and only the doublet associated with the C-1′ proton should be altered. Thus, the doublet with the coupling constant of 6.5 in **9** which is changed to 8.8 by oxidation can be assigned to the C-1′ proton. The coupling constant of the C-1 proton must then be 8.8. This was further confirmed by proton-decoupling experiments using a 100-Mc nmr instrument. When the sample (**9**) was irradiated at 237 cps (corresponding to the C-9 proton) the

(9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963). It is well known that no quantitative significance should be attached to the Karplus equation. What we shall be doing is to use the Karplus equation in conjunction with reasonable molecular geometries to distinguish between "large" (>7 cps) and "small" (<3.5 cps) observed coupling constants.

(10) S. Furberg and B. Pedersen, *Acta Chem. Scand.*, **17**, 1160 (1963).

(11) J. M. Bobbitt, *Advan. Carbohydrate Chem.*, **11**, 1 (1956), and references cited therein.

8.8-cps doublet collapsed. When the samples was irradiated at 335 cps (corresponding to the proton at C-2′), the 6.5-cps doublet collapsed (Figure 2).

Table I shows the coupling constants calculated from the C-1–C-9 dihedral angles for all of the conformations of the pyran ring, with the C-1 proton in both the α and the β positions. For **9**, the coupling constant of 8.8 cps fits two of the conformations with the C-1 proton α (*italics* in Table I) and none of those with the C-1 proton β. Thus, the stereochemistry of C-1 is as shown in **1**.

It should be noted that the coupling constant assigned to C-1 of monotropein (**4**) was 3–4 cps[6] compared with 8.8 cps for **9**. This is almost surely due to the strained ring system in **9** as compared to **4**. This can easily be confirmed from the spectra of **6** and **8**. The C-1 proton in **6** is a doublet at 253 cps with a coupling constant of 8 cps (strained system) and the C-1 proton in **8** is a doublet with a coupling constant of 3.5 cps (strain free system).

Experimental Section[12]

Dihydrocatalpogenin Trimethyl Ether (6).—Dihydrocatalpogenin methyl ether[15a] (0.617 g) was dried under vacuum at 59° over phosphorus pentoxide and dissolved in 50 ml of methyl iodide. Silver carbonate (3 g) was added and the mixture was heated to reflux for 12 hr. During the reflux, fresh samples (1 g) of silver carbonate were added at 3-hr intervals. The mixture was filtered and the precipitate was washed twice with chloroform. The combined filtrate and washings were evaporated to dryness and dried overnight. Thin layer chromatography (benzene–ether, 1:4) showed an incomplete reaction. The methylation process was then repeated *twice* more until a single major product was seen on tlc. This crude product weighed 0.637 g (95%). An analytical sample was prepared by preparative tlc and finally distilled in an air bath at 210° (10^{-4} mm).

Anal. Calcd for $C_{16}H_{15}O_4(OCH_3)_3$: C, 62.69; H, 6.64; OCH_3, 25.55. Found: C, 62.84; H, 6.63; OCH_3, 25.12.

Lithium Aluminum Deuteride Reduction of 6 to Yield 7.—Dihydrocatalpogenin trimethyl ether (0.311 g) was dissolved in 24 ml of ether and added with stirring to 0.753 g of lithium aluminum deuteride in 15 ml of ether. An additional 15 ml of ether was added and the mixtue was allowed to reflux for 4 hr. The mixture was cooled and the following reagents were added successively according to the general method of Amundsen and Nelson:[13] 40 ml of ether, 0.8 ml of water, 0.7 ml of 20% sodium hydroxide, and 2.7 ml of water. The mixture was filtered and the precipitate was washed with two portions of ether. The combined filtrate and ether washings were evaporated to yield a mixture of two products (**7** and anisyl alcohol). These were separated on four preparative tlc (methanol–ether, 1:9) layers (20 cm × 20 cm × 1 mm) to yield 0.168 g (84%) of **7**. The analytical sample was distilled in an air bath at 110° (10^{-4} mm).

(12) All melting points were taken on a Kofler micro hot stage apparatus and are corrected. The nmr spectra were taken on Varian Associates A-60 and HA-100 (compound **9**) instruments. The shifts were measured against tetramethylsilane as an external standard. The microanalyses were performed by H. Fröhofer of the Organic Chemistry Institute of the University of Zürich, Switzerland. Thin layer chromatography was done on silica gel G (qualitative) and silica gel PF_{254} (preparative) layers prepared with the Stahl–Desaga apparatus (Brinkmann, Westbury, N. Y.). Preparative layers were 1 mm in thickness. Solvent ratios are volume/volume. The visualization of the tlc chromatograms of catalposide and its derivatives was carried out by spraying them with 3 *N* hydrochloric acid and heating them at 110° for a few minutes. Black spots resulted. Preparative chromatograms of compounds **6** and **8** were visualized by observing the chromatograms prepared with silica gel PF_{254} under an ultraviolet light at 254 mμ. Compound **7** was visualized by the edge-spray method: J. M. Bobbitt, "Thin-Layer Chromatography," Reinhold Publishing Corp., New York, N. Y., 1963, p 113.

(13) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

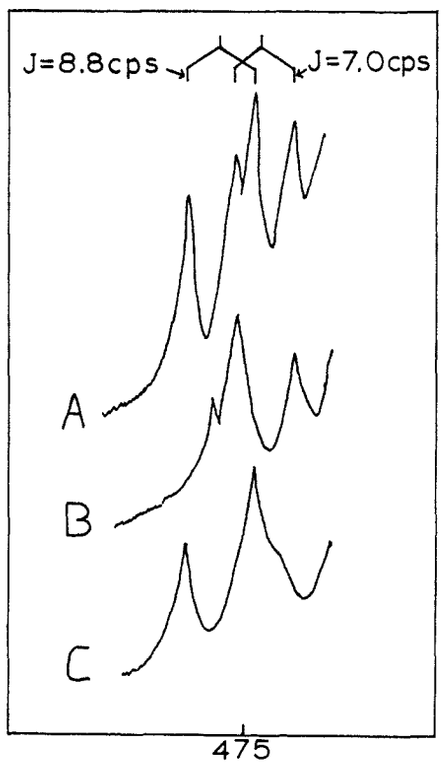

Figure 2.—Nmr spectrum (100 Mc) of **9** (A) in deuterium oxide, (B) irradiated at 234 cps, and (C) at 338 cps. The pair of doublets which occurs at 296 cps on the 60-Mc instrument[15a] appears at 475 cps using a 100-Mc instrument. The points of irradiation appear at 142 and 201 cps on the 60-Mc spectrum.[15a]

Anal. Calcd for $C_{11}H_{19}DO_5$: C, 56.64; H, 8.21. Found: C, 56.53; H, 8.28.

Anisylation of 7 to Yield 8.—Compound **7** (0.26 g) was dissolved in 2 g of dry pyridine and treated with 0.5 ml of freshly distilled anisoyl chloride. The mixture was allowed to stand overnight at 30° and was slowly added to 20 ml of stirred 5% aqueous sodium bicarbonate. After 30 min the mixture was filtered and the residue (mostly anisic anhydride) was well washed with water. The filtrate and washings were evaporated to dryness and the residue was extracted several times with absolute ethanol. The ethanol washings showed one major spot on tlc (benzene–ethyl acetate, 3:2) and were evaporated to dryness. The product was isolated by preparative tlc (three layers 20 cm × 20 cm × 1 mm) to yield 0.151 g of **8** (37%). The analytical sample was distilled in an air bath at 220° (10^{-4} mm).[14]

Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 61.46; H, 6.77.

Periodate Oxidation of 9.—Compound **9** (0.075 g) was treated with 0.20 g of sodium metaperiodate in 1 ml of deuterium oxide. After 20 min the mixture was centrifuged and the supernatant liquid was placed in the nmr tube.

Registry No.—**1**, 6736-85-2; **6**, 10050-99-4; **7**, 10051-02-2; **8**, 10051-00-0; **9**, 6736-86-3.

Acknowledgment.—In addition to the financial support previously noted, the authors are grateful to Mr. W. C. Jankowski of Varian Associates, for the HA-100 nmr spectra and to Professor A. B. Foster of the Royal Cancer Hospital, for helpful suggestions.

(14) The analysis does not check very closely owing to a slight decomposition during distillation. The compound itself is extremely unstable to traces of acid. However, the nmr spectrum agreed in all respects with the proposed structure.