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CATALPA GLYCOSIDES - II[1]

THE STRUCTURE OF CATALPOSIDE

J.M. Bobbitt, D.W. Spiggle and S. Mahboob

Department of Chemistry, University of Connecticut, Storrs, Conn.

and

W. von Philipsborn and H. Schmid

Organisch-chemisches Institut der Universität, Zürich, Switzerland

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STRUCTURE Ia has recently[2] been proposed for catalposide, the major glucoside of the genus Catalpa. The assignment was based upon the following evidence. Reduction with lithium in liquid ammonia yielded bisdesoxyaucubin, XV (isolated as the tetraacetate) which was obtained in a similar[3] manner from aucubin. Catalposide and its saponification product, des-p-hydroxybenzoylcatalposide, III (catalpol[2]) give crystalline acetates which were considered to be heptaacetates. On the basis of chemical and NMR evidence, I, rather than Ia, is a preferred structure for catalposide. The chemical evidence will be presented first.

Catalposide has been shown[1] to form a dihydroderivative, V, a methyl ether, IV, and a dihydromethyl ether, VII. Both catalposide and dihydrocatalposide yield hexamesylates (hexamethansulfonates) and the corresponding methyl ethers yield pentamesylates. Thus, catalposide contains six hydroxyl groups rather than seven.[2] In addition, catalposide takes up five moles of

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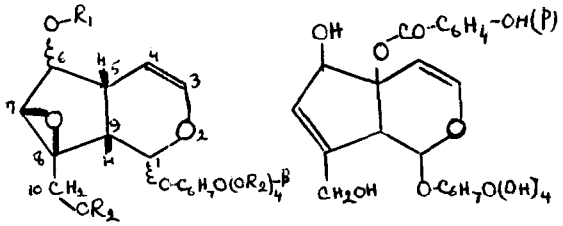
[1] J.M. Bobbitt, H. Schmid and T.B. Africa, J. Org. Chem. 26, 3090 (1961).

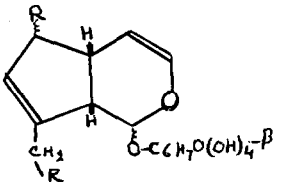
[2] W.H. Lunn, D.W. Edward and J.T. Edward, Chem. & Ind. 1488 (1961).

[3] J. Grimshaw and H.R. Juneja, Chem. & Ind. 656 (1960).

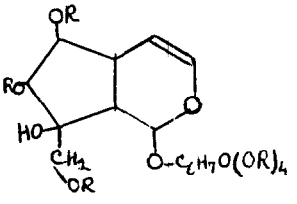


Ia

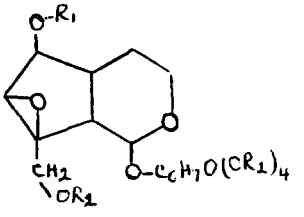
I = R_1=Co-C_6H_4-OH(P); R_2=H
II = R_1=Co-C_6H_4-OCOCH$_3$(P); R_2=CCCH$_3$
III = R_1=R_2=H
IV = R_1=COC$_6$H$_4$-OCH$_3$(P); R_2=H



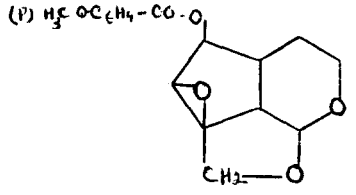
XIV = R=CH
XV = R=H



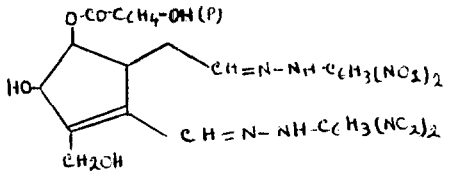
IX = R=H
X = R=CCCH$_3$



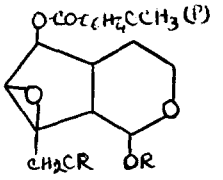
V = R_1=CCC$_6$H$_4$-OH(P); R_2=H
VI = R_1=COC$_6$H$_4$-CCCCH$_3$(P); R_2=OCOCH$_3$
VII = R_1=COC$_6$H$_4$-OCH$_3$(P); R_2=H
VIII = R_1=R_2=H



XIII



XVI



XI = R=H
XII = R=CCCH$_3$

hydrogen with platinum oxide and acetic acid.[1] Under identical conditions, ethyl p-hydroxybenzoate takes up four. Therefore, catalposide has one double bond rather than two.[2] It should be noted that aucubin, XIV, always takes up at least two moles of hydrogen.[4] The presence of D-glucose and the p-hydroxybenzoate in I have been established.[1] The lability of I to emulsin[2] indicates a β-glucoside linkage.

Hydrolysis of I in the presence of Amberlite IRA-400-OH yields two products which can be separated by chromatography over silica gel. A qualitative kinetic study showed that des-p-hydroxybenzoylcatalposide, III, $C_{15}H_{22}O_{10}$ (m.p. 201-203° $[\alpha]_D^{25.5}$ -103.9° in methanol; infrared band at 6.04 μ (KBr) for enol ether, m.p. of acetate 141-142°) was formed first. Compound III then reacted with water to yield IX, $C_{15}H_{24}O_{11}$ (m.p. 120-122°; $[\alpha]_D^{25.5}$ -125.5° in methanol; infrared band at 6.06 in KBr for enol ether). A similar hydrolysis of the dihydro-derivatives V and VII yielded a dihydrodes-p-hydroxybenzoylcatalposide, VIII, $C_{15}H_{24}O_{10}$ (m.p. 219-221°; $[\alpha]_D^{24}$ -72° in methanol; no infrared band in 6 μ region; m.p. of acetate 62-66° and 150.5-151.5°).

Compound IX is of special interest because it contains, in the aglucone, four contiguous hydroxyl groups, one of which is tertiary and resists acetylation (heptaacetate, X, $C_{29}H_{38}O_{18}$, m.p. 131-133°, infrared bands in Nujol at 2.88 μ for hydroxyl and at 6.04 μ for enolic double bond). The structure of IX is uniquely described by its reaction with five moles of periodate[5] to yield one mole of formaldehyde (C 10), two moles of formic acid (C 7 and C 3) and one mole of nonvolatile acid (carboxyl at C 8). Under identical conditions, III and α-methyl-D-glucoside react with two moles of periodate to yield one of formic acid.

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[4] P. Karrer and H. Schmid, Helv. Chem. Acta 29, 525 (1946).

[5] J.M. Bobbitt, Advanc. Carbohydrate Chem. 11, 1 (1956) and references cited therein.

In des-p-hydroxybenzoylcatalposide, III, two of the four hydroxyl groups of IX lie in an ether grouping for which there are six possibilities (ether bridge in brackets): A (6,7); B (6,8); C (6,10); D (7,8=III); E (7,10) and F (8,10). The fact that the ether in III opens on base treatment strongly indicates that it is an epoxide or a trimethylene oxide. The presence of an epoxide is confirmed by a positive test given by catalposide methyl ether, its dihydroderivative and compound VIII with the specific epoxide reagent, sodium thiosulfate.[6] In fact the oxirane oxygen of VIII can be titrated to the extent of 80 per cent. Under identical conditions trimethylene oxide and α-methyl-D-glucoside give negative tests, as does IX. Thus C and E and probably B also are ruled out because they are not epoxides. The observation that the aglycone part of III does not react with periodate is in favor of the absence of two contiguous hydroxyl groups in III, leaving D as representing the ether linkage in III. There are two weak points in this argument which will be removed by the NMR data presented below. The strained trimethylene oxide in B might conceivably react with sodium thiosulfate and, the two contiguous hydroxyl groups on C 6 and C 7 of F may be locked in such an extreme trans position that they do not react with periodate.

The position of the hydroxybenzoyloxy group at C 6 is established and the general structure is supported by the acid degradations of dihydrocatalposide methyl ether, VII. Hydrolysis with 0.5 N sulfuric acid (in a benzene-water mixture at 65°) yields a mixture of two compounds which is separable on silica gel; the major product, dihydrocatalpogenin methyl ether (XI) (m.p. 95-96.5°, $[\alpha]_D^{25}$ -108° (in methanol), XI and the minor product, anhydrodihydrocatalpogenin methyl ether, m.p. 119-120.5°, XIII.

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6 W.C.J. Ross, J. Chem. Soc. 2257 (1950); see also J.M. Ross, D.S. Tarbell, W.E. Lovett and A.D. Cross, J. Amer. Chem. Soc. 78, 4675 (1956).

Compound XI gives a positive Tollens' test where starting material and XIII do not, and, furthermore, it forms a diacetate, XII, m.p. 114.5-116°, while XIII has no hydroxyl in the infrared and forms no acetate. This type of ring closure has been noted in the aucubin series.[7] The oxirane oxygen in XI can be titrated to the extent of 20 per cent before decomposition occurs.[6] The ring closure from XI to XIII requires a free hydroxyl at C 10 in catalposide.

Nuclear Magnetic Resonance Evidence

Nuclear magnetic resonance spectral studies of catalposide and all of the above mentioned compounds again disprove structure I for the glucoside. In particular, the troublesome argument about the number of acetyl groups in the various acetates is resolved and structures with ether bridges from C 6 to C 8 (B) and C 8 to C 10 (F) are ruled out.

The 60 Mc NMR spectrum[8] of I (D_2O) shows the expected quartet (two identical AB systems) of the four aromatic protons of the p-hydroxybenzoic ester moiety. The doublet of the vinyl proton at C 3 is centered at 383 c.p.s. and shows an allylic fine-splitting. Aucubin, XIV, shows among others, the following signals: 384 c.p.s. (proton on C 3); a quartet at 312 c.p.s. (proton on C 4) and a multiplet at 356 c.p.s. (vinyl proton at C 7). The latter peak is missing in the spectrum of I. In the NMR spectrum of dihydrocatalposide (D_2O), V,[1] the signal at 383 c.p.s. is lacking and three protons are found in the 285-330 c.p.s. region. The 285-330 c.p.s. region of the spectrum of I shows four protons, one of which

[7] M.W. Wendt, W. Haegele, E. Simonitsch and H. Schmid, Helv. Chim. Acta 43, 1440 (1960).

[8] The NMR spectra were measured on a Varian A-60 instrument. Chemical shifts for the spectra in $CDCl_3$ are relative to tetramethylsilane as internal standard. For the spectra in D_2O a dilute solution of tetramethylsilane was used as an external standard; HDO-Signal=286 c.p.s. For integration the water signals were shifted thermally. The substances dissolved in D_2O were evaporated to dryness several times (with D_2O) before measuring the spectra.

must then arise from C 4 and correspond to the C 4 proton of aucubin (312 c.p.s.). Careful integrations of the acetyl region of the NMR spectrum ($CDCl_3$) of acetylated catalposide, II, and dihydrocatalposide, V, show a ratio of aromatic acetyl to aliphatic acetyl protons of 1:5.0 ± 0.2. The ratio of the vinyl proton on C 3 (doublet at 380 c.p.s.) to the total acetyl protons of II is 1:18 ± 1. The acetyl region in the spectrum of II taken in pyridine is clearly resolved and shows six peaks with correct integrals for the six different acetyl groups. The vinyl proton on C 7 of Ia is not present in catalposide, and the acetate problem is resolved in favor of a hexaacetate for catalposide.

The vinyl proton at C 3 of compound III appears in the NMR spectrum (D_2O) as a quartet centered at 391 c.p.s. with coupling constants J_1 = 6 c.p.s. and J_2 = 1.5 c.p.s. Therefore, the proton is coupled with the allylic proton at C 5 as well as the neighboring proton at C 4. The 285-325 c.p.s. region contains signals from three protons while that of I contains four. Thus, the p-hydroxybenzoyl group is attached to a secondary[9] hydroxyl group in the aglucone. The acetyl derivative of III is a hexaacetate (two acetyl signals of about equal intensity with a total area corresponding to 18 ± 1 H based upon the vinyl proton on C 3 at 378 c.p.s.; $CDCl_3$). The NMR spectrum (D_2O) of the dihydroderivative VIII lacks the vinyl proton signals but does show two protons in the 280-320 c.p.s. region which appear in two doublets, one at 292 c.p.s. (J = 6.5 c.p.s.) and one at 296 c.p.s. (J = 8.5 c.p.s.). These are the acetal protons on C 1' and C 1[10] which, accordingly, each have one proton on neighboring carbons. The high coupling constants make a β-configuration probable for the glucoside

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[9] L.M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry p. 55. Pergamon Press, London (1955).

[10] The corresponding protons in the spectrum of aucubin, XIV, produce doublets at 292 c.p.s. (J = 7 c.p.s.) for C 1 and at 320 c.p.s. (J = 5 c.p.s.) for C 1.

linkage.[11] Thus C 1, C 3, C 4, C 5 and C 9 are defined and confirmed as they appear in I.

The NMR spectrum of X ($CDCl_3$) shows the expected signal for a hydroxyl and a signal at 378 c.p.s. for the vinyl proton at C 3. An unsymmetrical double signal (intensity 3:4) arising from the seven acetyl groups (21-22 protons) appears.

In the region from 180 c.p.s. towards higher field, the NMR spectra of I and III (D_2O) show signals of only two protons (proton on C 9, epoxide proton[12] or perhaps the proton on C 5[13]). In structure F one would expect three to four protons in this region. Structure F also appears less possible because the total number of protons (7.3 ± 0.2) in the 270-325 c.p.s. region of the spectrum of II corresponds to a total of the proton on C 4, the four protons on carbons containing secondary, acetylated hydroxyl groups and the two acetal protons on C 1 and C 1'. Thus, there is no ether between C 8 and C 10 (F).

In the NMR spectrum of XI ($CDCl_3$) one can find, besides the expected aromatic and methoxyl protons, a multiplet localized at 325 c.p.s. corresponding to the one proton at C 6 and a multiplet at 280 c.p.s. corresponding to the single proton at C 1 (on addition of acid this multiplet becomes a doublet, J = 8 c.p.s.). In the spectrum of diacetyl XI, XII ($CDCl_3$), these two signals merge to a single absorption multiplet at about 333 c.p.s. correspondong to two protons. The position of the multiplet-doublet at 280 c.p.s. and its shift after acetylation relate this signal to the proton on C 1 and show the existence of a hemiacetal in XI. Finally, the spectrum of XII contains a four line AB absorption (τ_A = 269 c.p.s.,

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[11] Ref. 9, p. 84.

[12] See G.V. Tiers, C.Y. Hopkins and H.J. Bernstein, Canad. J. Chem. 37, 775 (1959).

[13] In the NMR spectrum of aucubin, this absorption is at 160 c.p.s.

ν_B = 241 c.p.s., J = 12 c.p.s.) which corresponds to the two protons on C 10, deriving their non-equivalence from an adjacent asymmetric center. The observed multiplicity requires the absence of a proton at C 8. The two acetyl residues give single peaks at 126 and at 127 c.p.s. each corresponding to three protons. The NMR spectrum ($CDCl_3$) of XIII (the anhydrocompound from the dihydrocatalpogenin), shows the expected aromatic and methoxyl signals, a broad singlet at 245 c.p.s. (two protons on C 10) and a well defined multiplet at 313 c.p.s. corresponding to the proton on the ester bearing carbon and the one on C 1. On the basis of its integration, this multiplet must consist of one doublet and some other signal which is more than a doublet. Since the doublet corresponds to the proton on C 1, the proton at the ester bearing carbon must be coupled with more than one neighboring hydrogen. Therefore, structure B is impossible and XI, XII and XIII are confirmed.

The degradation[2] of I to XV can be rationalized in two ways. The epoxide can activate the oxygens at C 6 and at C 10 to hydrogenolysis and then itself be reduced to a tertiary alcohol at C 9 and dehydrated. Alternately, the epoxide reduction and dehydration can preceed the loss of oxygen at C 6 and C 10. Structure XVI can be written for the bis-dinitrophenylhydrazone from amorphous catalpogenin[2] and can be considered to arise from an epoxide-allyl alcohol rearrangement.

Structures XV and XIII determine the relative stereochemistry of the centers at C 5, C 7, C 8 and C 9 in catalposide.[1]

All new compounds mentioned in this communication gave correct analyses.

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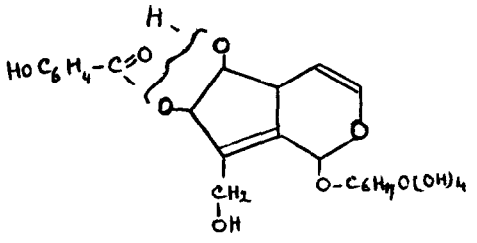
support.

After this manuscript was completed, a paper by W.H. Lunn, D.W. Edward and J.D. Edward, Canad. J. Chem. 40, 104 (1962); appeared in which a revised structure Ib is proposed for catalposide. The evidence given in our paper clearly disproves also structure Ib for the glucoside.



Ib