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Note

Intermediates in the synthesis of Laetrile™: the crystal and molecular structures of methyl (2,3,4-tri-*O*-acetyl-α-D-glucosyl bromide)uronate and methyl (ethyl 2,3,4-tri-*O*-acetyl-β-D-glucosid)uronate*

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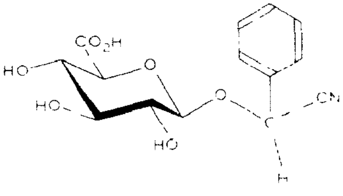
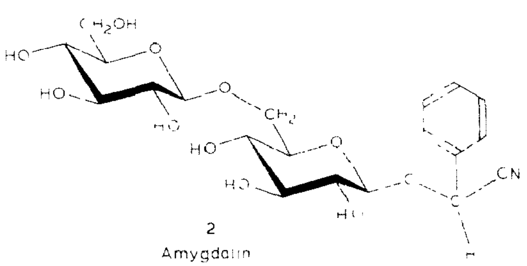
In 1961, Krebs and Krebs[1] obtained a patent on a compound named Laetrile™, which they claimed to have identified as having structure **1**. Amygdalin (**2**), a compound occurring naturally in apricot stones, is[2,3] closely related to **1**. Syntheses of **2** [*O*-β-gentiobiosyl-D-(−)mandelonitrile] have been reported[4,5], but a total synthesis of **1** by non-enzymic methods does not appear to have been achieved. A route to **1** appeared to be feasible through the Koenigs–Knorr reaction[2,6], but, although preparation of a benzyl D-glucosiduronic acid was successful, further efforts were abandoned when **1** was synthesized by an enzymic method[2].



1
Laetrile



2
Amygdalin

Methyl (2,3,4-tri-*O*-acetyl-α-D-glucosyl bromide)uronate (**3**; $C_{13}H_{17}BrO_9$) was prepared, as an intermediate in the synthesis of Laetrile™, by treatment of the corresponding tetraacetate with hydrogen bromide in acetic acid. Compound **3** forms monoclinic crystals from ethanol. The space group is $P2_1$, with unit-cell dimensions: $a = 919.2(9)$, $b = 1689.3(2)$, $c = 553.6(2)$ pm, $\beta = 93.64(1)°$. The calculated density is 1.536 g/cm^3 for two molecules per unit cell.

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*This work has been adapted from a dissertation submitted by R.M.D. to the University of Maryland in partial fulfilment of the requirements for the Ph.D. degree. A preliminary report was given at the Winter, 1978, meeting of the American Crystallographic Association, Norman, OK, Paper No. PB17.
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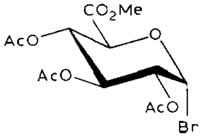
An anomalous density led to identification of a solvolysis product, namely, methyl (ethyl 2,3,4-tri-*O*-acetyl-β-D-glucosid)uronate (**4**; $C_{15}H_{22}O_{10}$), which forms orthorhombic crystals, space group $P2_12_12_1$, with unit-cell dimensions: a = 1755.8(2), b = 1426.5(2), c = 745.8(2) pm. The observed density is 1.28 g/cm^3, compared to a density of 1.288 g/cm^3 calculated for four molecules per unit cell. The crystal structure of each compound was solved and refined. The solvolysis product differs from bromide **3** in the configuration of C-1.



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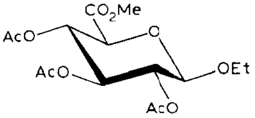

4

EXPERIMENTAL

Chemistry. — Optically pure α-D-glucofuranurono-6,3-lactone ("D-glucurone", Aldrich Chemical Co., Inc.) was converted into methyl tetra-*O*-acetyl-D-glucuronate by classical procedures[7–9]. Fractional recrystallization of its mixed tetraacetates yielded the α and β anomers, both of which reacted with hydrobromic acid in acetic acid to give the identical bromide **3** (m.p. 101–102°). Single crystals of **3** that appeared to be suitable for X-ray diffraction studies were obtained by recrystallization from ethanol. However, at room temperature, and on exposure to air, **3** decomposed to a black gum. Crystals of **3** could be kept for long periods only when recrystallization from this solvent was conducted at low temperatures, and the crystals were then stored in a freezer.

Determination of structure. — A colorless platelet of **3** was found to be monoclinic, but it decomposed before integrated intensity data had been collected.

Another crystal, from a crop that had been allowed to remain in contact with the ethanolic mother-liquor, was found to be orthorhombic. The measured density was unexpectedly low, compared to that calculated for the original monoclinic crystal. A density calculated for the ethyl glycoside (**4**), which could have resulted from a solvolytic displacement of the bromine, was more reasonable. Intensity data for **4** were then collected (Picker FACS-I automated diffractometer, MoKα X-rays, λ = 71.07 pm; additional details are given in Table I). The structure was solved and refined by conventional methods[10,11], with hydrogen atoms being located from geometric considerations.

Following the solution of structure **4**, a freshly prepared sample of **3** was obtained. A suitable crystal was selected, mounted on a glass fiber, and then coated with clear lacquer in order to retard decomposition. The data collection and structure determination for **3** were similar to those for **4**.

TABLE I

CRYSTAL DATA FOR AND STRUCTURE ANALYSIS[a] OF **4** AND **3**

	Physical properties	
	4	**3**
Empirical formula	$C_{15}H_{22}O_{10}$	$C_{13}H_{17}BrO_9$
Molecular weight	362.316	397.166
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1$
a (pm)	1755.8(2)	919.9(2)
b	1426.5(2)	1689.3(2)
c	745.8(2)	553.6(2)
β(degrees)		93.64(1)
V (cm^3)	1.8680×10^{-21}	8.5855×10^{-22}
Z	4	2
Density (measured, g/cm^3)	1.28	
Density (calculated, g/cm^3)	1.288	1.536
	Data collection and refinement	
Reflections measured	2071	1695
Reflections observed (3σ)	893	918
Final R values		
unit weights	0.062	0.058
weighted ($1/\sigma$)	0.082	0.073

[a] The estimated standard deviation of the last significant digit is given in parentheses.

RESULTS AND DISCUSSION

The final atomic positional coordinates and thermal parameters for **4** and **3** are given in Table II*. The bond lengths and angles are normal for both molecules, and are not tabulated. The results of the refinement for **3** are substantially less precise than those for **4**, but are sufficient to establish its stereochemistry. Torsion angles are shown on the projections of **4** and **3** in Figs. 1 and 2, respectively.

The molecule of **4** was found to have a β-ethoxyl group on C-1, instead of the bromine atom expected. The hypothesized formation of an ethyl glycoside by solvolysis was thus confirmed. Both **3** and **4** have the $^4C_1$(D) conformation. The major difference between **3** and **4** is in the orientation of the acetyl substituent on O-2. The acyloxy carbon atom C-21 is approximately (+)-anticlinal to C-1 in **4**, but (+)-synclinal in **3**. A similar effect reported for 1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4,6-

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*The hydrogen atom and thermal parameters have been omitted from Table II. The complete Table, as well as Tables III and IV, listing the observed and calculated structure factors for **4** and **3**, respectively, can be obtained on request from Elsevier Scientific Publishing Company, BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/245/*Carbohydr. Res.*, 116 (1983) 150–155.

TABLE II

ATOMIC POSITIONAL PARAMETERS[a] FOR METHYL (ETHYL 2,3,4-TRI-*O*-ACETYL-β-D-GLUCOSID)URONATE ($C_{15}H_{22}O_{10}$) (**4**) AND METHYL (2,3,4-TRI-*O*-ACETYL-α-D-GLUCOSYL BROMIDE)URONATE ($C_{13}H_{17}BrO_9$) (**3**)

	4			**3**		
Atom	x/a	y/b	z/c	x/a	y/b	z/c
Br	—	—	—	2311(2)	10000	2350(4)
C-1	1976(4)	2338(5)	3104(9)	301(2)	945(1)	522(3)
C-11	2457(5)	0940(5)	4251(11)	—	—	—
C-12	2606(7)	−0027(7)	3722(13)	—	—	—
C-2	1839(3)	2889(4)	1436(8)	405(2)	871(1)	472(3)
C-21	2613(4)	2791(5)	−1232(9)	620(2)	945(1)	417(4)
C-22	3409(4)	2936(7)	−1906(12)	733(2)	966(1)	214(3)
C-3	1495(3)	3838(4)	1902(9)	326(2)	806(1)	332(2)
C-31	1654(3)	5046(4)	−0382(10)	465(2)	713(1)	113(4)
C-32	1265(4)	5450(5)	−2017(10)	556(2)	640(1)	156(4)
C-4	0790(3)	3714(4)	2996(9)	199(2)	777(1)	481(3)
C-41	−0199(4)	4814(5)	3510(12)	077(2)	651(1)	426(4)
C-42	−0362(5)	5813(5)	4062(14)	018(2)	596(1)	240(4)
C-5	0969(4)	3107(4)	4632(10)	095(2)	852(1)	513(3)
C-6	0279(4)	2901(6)	5778(12)	−022(2)	828(1)	703(5)
C-61	−0550(5)	3425(9)	8034(14)	−239(2)	760(2)	735(5)
O-1	2231(3)	1463(3)	2692(6)	—	—	—
O-2	2560(2)	3025(3)	0534(6)	515(1)	901(1)	306(2)
O-21	2073(3)	2526(5)	−2075(7)	630(1)	967(1)	611(2)
O-3	1250(2)	4299(3)	0233(6)	425(1)	738(1)	336(2)
O-31	2232(3)	5313(3)	0319(8)	436(1)	747(1)	−070(2)
O-4	0547(2)	4639(3)	3540(6)	120(1)	721(1)	326(2)
O-41	−0664(3)	4228(4)	3153(11)	095(2)	644(1)	647(3)
O-5	1261(3)	2244(3)	3972(6)	183(1)	909(1)	647(2)
O-6	−0088(4)	2196(5)	5580(11)	−009(1)	842(1)	910(3)
O-61	0130(3)	3564(4)	6886(7)	−129(2)	794(1)	569(3)

[a] All values for **4**, and the Br parameters for **3**, have been multiplied by 10^4; others are multiplied by 10^3. The estimated standard deviation of the last significant digit is given in parentheses.

tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranose suggests that this difference is most probably due [12] to steric factors associated with a β-substituent on C-1.

The isolation of crystals of a reaction product (**4**) formed during recrystallization of bromide **3** is an interesting illustration of a hazard intrinsic to the assignment of stereochemistry by crystal-structure determination by unsuspecting crystallographers. In retrospect, it is clear that consideration must always be given to the possibility that solvolysis may occur whenever recrystallization involves the dissolution of a reactive compound in an active solvent.

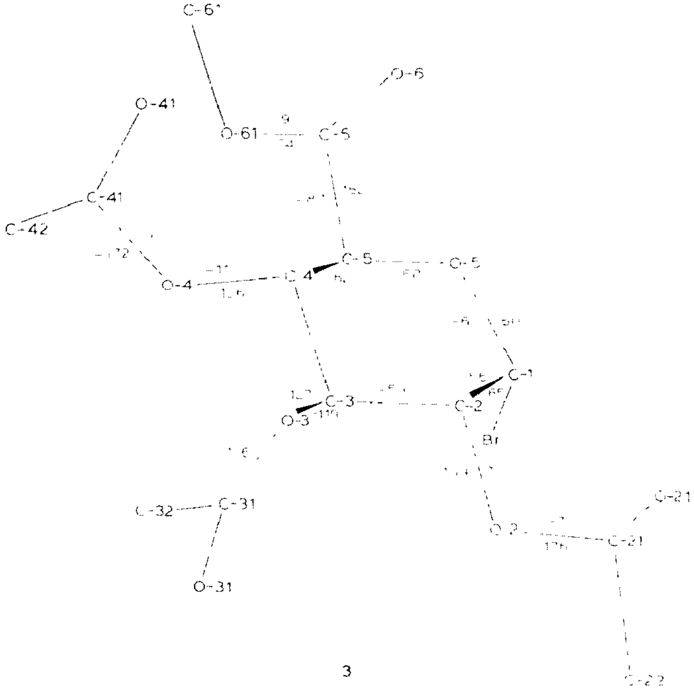

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Fig. 1. A projection view of **4**, showing torsion angles in degrees. The estimated standard deviations are not shown, but they are generally less than 2°

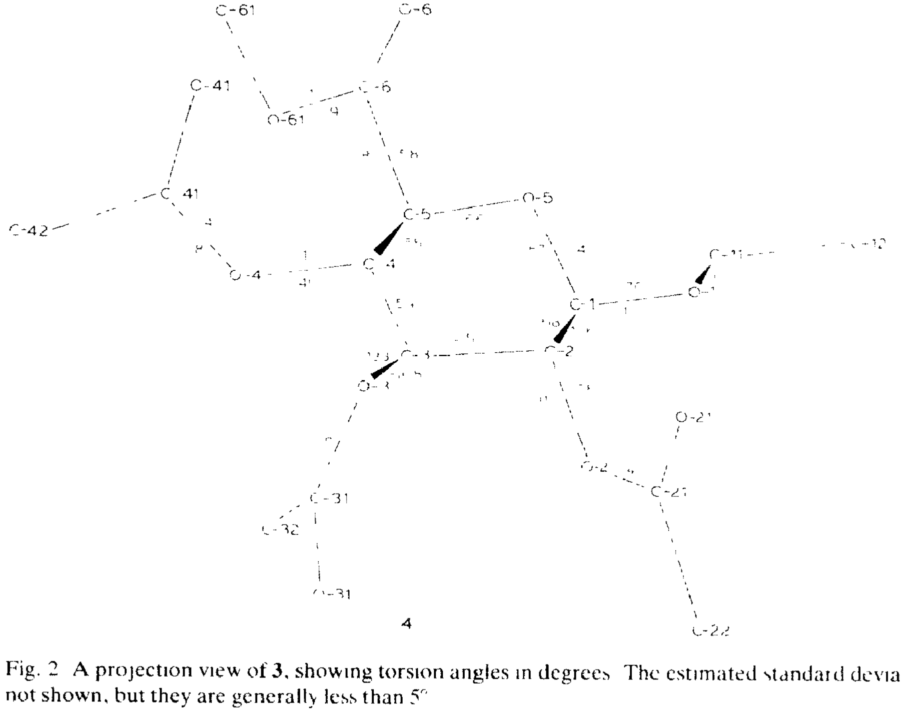

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Fig. 2 A projection view of **3**, showing torsion angles in degrees The estimated standard deviations are not shown, but they are generally less than 5°

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