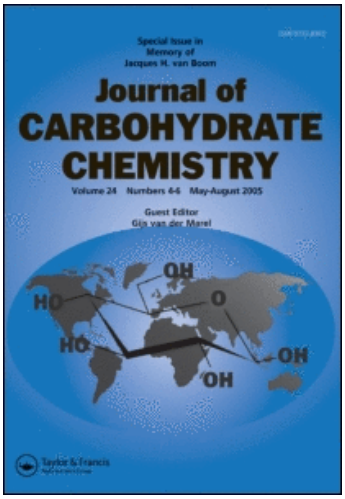

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Ashry, El Sayed H. El , Kilany, Yeldez El and Mousaad, Ahmed(1987) 'D-Glucosyl Kojic Acid Derivatives, Potential Precursors for the Cyclic Carboxylate Equivalents of Gaba Mimetic Agents', Journal of Carbohydrate Chemistry, 6: 4, 609 — 618
To link to this Article: DOI: 10.1080/07328308708058890
URL: http://dx.doi.org/10.1080/07328308708058890

J. CARBOHYDRATE CHEMISTRY, 6(4), 609-618 (1987)

D-GLUCOSYL KOJIC ACID DERIVATIVES, POTENTIAL PRECURSORS FOR THE CYCLIC CARBOXYLATE EQUIVALENTS OF GABA MIMETIC AGENTS.[1,2]

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Received August 4, 1986 - Final Form August 5, 1987

ABSTRACT

Precursors for the cyclic carboxyl equivalents of γ-aminobutyric acid (GABA) were synthesized. 5-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-2-[4-phenyl-1,2,3-triazol-1-yl)methyl]-4H-pyran-4-one could be prepared by the glucosidation of 2-chloromethyl-5-hydroxy-4H-pyran-4-one. Nucleophilic displacement of the chlorine with azide ion gave the corresponding azidodeoxy derivative that upon 1,3-dipolar cycloaddition with phenylacetylene yielded the triazolyl derivative.

INTRODUCTION

There is considerable interest in the development of systematically active γ-aminobutyric acid-mimetic agents.[3-6] Muscimol (**3**) is one of the active naturally occurring GABA-like agents,[7-11] which suggested the use of 2-(aminomethyl)-5-hydroxy-4H-pyran-4-one (kojic amine) (**2**), as an analog incorporating another type of cyclic carboxyl equivalent.[3] This latter novel analog may also possess many of the properties, both in vivo and in vitro, expected for GABA-like compounds. Kojic amine was found to be orally active as a muscle relaxant in the cat flexor spasm procedure and showed a potent and specific inhibition of sodium independent [^{3}H] GABA binding to rat brain membranes.[3] The therapeutic value of GABA with an imino link[12-16] encourages exploration for

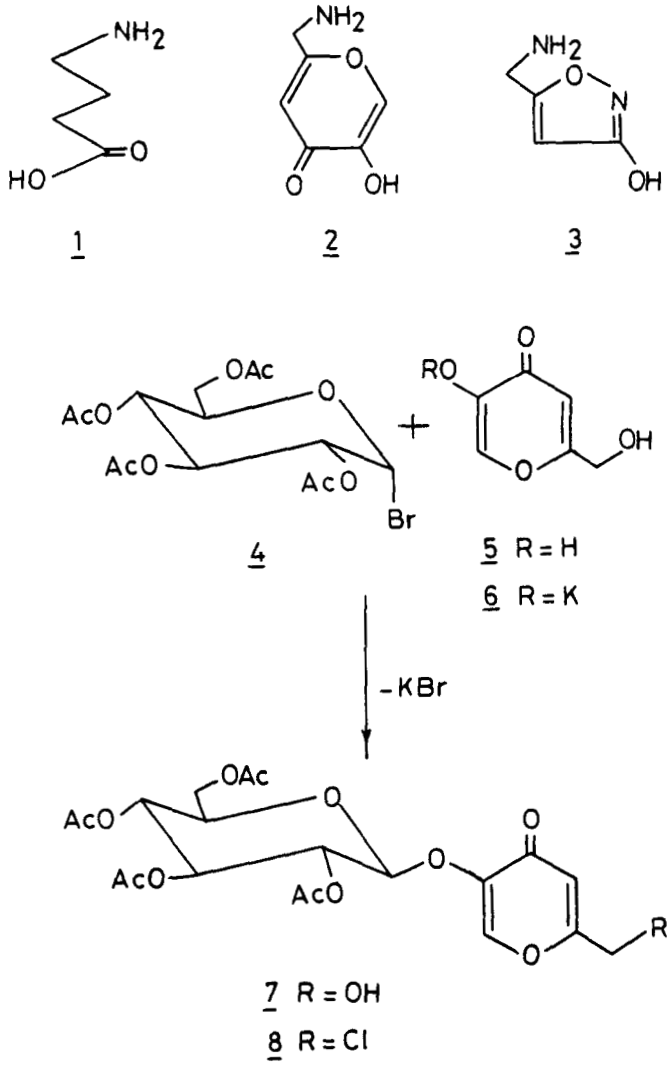
nontoxic GABA mimetic agents. The attachment of a sugar moiety to a kojic acid residue may change its solubility properties and consequently its therapeutic significance. Our interest in chemical synthesis with carbohydrate molecules[17-19] drew our attention to construction of a glycosylated GABA like system as found in kojic amine.

RESULTS AND DISCUSSION

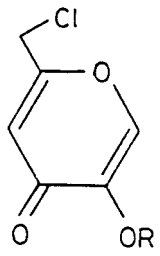
To achieve the synthesis of the target compounds, two building blocks were considered, a glucosyl donor and an acceptor of the hydroxypyrone type. Two synthetic approaches were considered for the target molecules. The glucosyl donor may react with 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one (**5**) regioselectively at the 5-hydroxyl function keeping the hydroxymethyl group available for subsequent transformation towards the desired target. Alternatively, the target aglycon may be constructed in a suitable manner to be a glycosyl acceptor, and then glycosylated.

Although our preliminary attempts at the first approach were unsuccessful, they nevertheless did serve as a model for the exploration of the glucosylation reaction. The glucosylating agent, 2,3,4,6-tetra-*O*-acetyl-α-**D**-glucopyranosyl bromide (**4**), selectively glucosylated the hydroxyl group on position 5 of kojic acid via its potassium salt **6**, to give **7** by a procedure similar to that reported by Hann.[20] Compound **7** did not give characteristic coloration with ferric chloride, indicating the absence of the enolic hydroxyl group of kojic acid. ^{1}H NMR, ^{13}C NMR and IR spectral data agreed with the assigned structure.

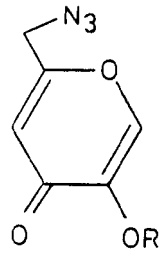
The proton decoupled ^{13}C spectrum of the glucoside **7** is composed of 18 signals, twelve from the glucosyl component and six from the aglycon. The ^{13}C NMR chemical shift assignments for the glucosyl part were deduced by comparison with spectra of some derivatives of aryl and alkyl **D**-glucopyranoside.[21] The lines corresponding to C-1 and C-6 were readily recognized by their characteristic chemical shifts. The downfield position of C-1 (98.93 ppm) of **7** was attributed to the presence of the kojic acid residue, and is close (98.8 ppm) to that of phenyl β-**D**-glucopyranoside.[21] The C-2 (70.91 ppm) and C-3 (72.32 ppm) resonances appeared at comparable chemical shifts to those of the β-series. The C-4 is far remote from the structural changes on



C-1 as its absorption appeared close to that of the corresponding carbon in both the α- and β-series. The C-5 resonance appeared at 71.95 ppm indicating the β-orientation in **7**, since C-5 appeared at ca. 71.4-72.5 ppm for the β-series and at ca. 66.8-68.1 ppm for the α-series. Although the methyl groups of the four acetates appeared as two singlets, their presence was confirmed by the presence of four different carbonyl carbons in the spectrum.



NaN_3

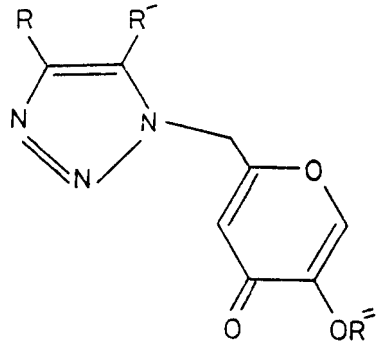


9 R = H
10 R = K

11 R = H
12 R = K
13 R = y

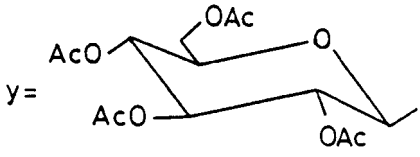
+4
-KBr

8



14a R = H, R' = Ph, R'' = H
14b R = Ph, R' = H, R'' = H
15a R = H, R' = H, R'' = y
15b R = Ph, R' = H, R'' = y

y =



The ^{13}C chemical shifts of the aglycon part were based on the reported chemical shifts of some model compounds.[22] The C-2' appeared at 167.06 ppm, which was in a downfield position from that of C-3' (113.40 ppm). This pronounced deshielding was due to a composite of the resonance effects of both the ring oxygen and the C-4' carbonyl which induces a higher density of positive charge on C-2' and a reverse effect on C-3'. The C-4' resonance appeared at 174.30 ppm, and it was slightly deshielded relative to the C-4 signal (173.6 ppm) in kojic acid. The shielded nature of its resonance could be a result of the rather low positive charge density on it due to extensive delocalization.[22] The C-5' of **7** was deshielded due to the effect of glucosylation of its hydroxyl group. A similar deshielding effect (147.7 ppm) was found in the 5-*O*-methyl derivative of kojic acid.[22] The C-6' of **5** (139.0 ppm) was found to be highly deshielded upon glucosylation of the C-5'-hydroxyl group and appeared at 143.86 ppm. However, the presence of a methyl group on the C-5 hydroxyl group, instead of the glucosyl residue, did not effect the resonance of C-6 (138.2 ppm) whereas the presence of an acetyl group on that position caused a high deshielding effect on C-6 (147.6 ppm). Consequently, the pronounced deshielding of C-6' resonance of **7** was due to the anisotropic effect of the acetyl carbonyl groups of the glucosyl residue.

The next step in the synthetic sequence was the conversion of **7** into 5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-**D**-glucopyranosyl)-2-(chloromethyl)-4H-pyran-4-one (**8**). When **7** was treated with thionyl chloride, the anticipated product **8** could not be isolated, since decomposition took place. The glucosidic linkage was labile to the hydrogen chloride generated in the reaction. However, **8** could be prepared by the glucosidation of the preformed chlorokojic acid **10** upon treatment with 2,3,4,6-tetra-*O*-acetyl-α-**D**-glucopyranosyl bromide. Its IR and ^{1}H NMR spectra agreed with the structure.

Nucleophilic displacement of the chlorine with azide ion was carried out on 2-(chloromethyl)-5-hydroxy-4H-pyran-4-one (**9**) to give 2-(azidomethyl)-5-hydroxy-4H-pyran-4-one (**11**). Similarly, **8** survived the condition of nucleophilic displacement to afford the corresponding azido derivative (**13**). Alternatively, the same compound was obtained by the reaction of **4** with **12**. The IR spectra of **11** and **13** showed the N_3 group at 2145 and 2100 cm^{-1}, respectively, in addition to the characteristic bands of the pyrone ring.

A model study of the 1,3-dipolar cycloaddition of phenylacetylene to 2-(azidomethyl)-5-hydroxy-4H-pyran-4-one was carried out. The ^{1}H NMR spectrum of the isolated product showed the presence of the aromatic protons as well as a singlet at δ 8.67 due to triazole ring-proton. The structure 5-hydroxy-2-[(4(5)-phenyl-1,2,3-triazol-1-yl)-methyl]-4H-pyran-4-one (**14b**) or the alternative structure **14a** could be deduced for the product. The position of the phenyl substituent on the triazole ring was not ascertained, although reported[23] data for the cylcoaddition of phenylacetylene with azido sugars suggests **14a** may be rejected based on steric factors.

The dipolar cycloaddition was carried out on the glucoside **13** by reaction with phenylacetylene to give 5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-[(4(5)-phenyl-1,2,3-triazol-1-yl)methyl]-4H-pyran-4-one (**15b** or **a**. The structure of the product was deduced from its IR and ^{1}H NMR spectra. As with **14**, it was not possible to clearly assign the location of the phenyl substituent on the triazole ring.

EXPERIMENTAL

General Methods. Melting points were determined with a Kofler-block apparatus and are uncorrected. Infrared spectra were recorded with a Unicam SP 200 spectrometer, ^{1}H NMR spectra were measured with an EM-390 NMR spectrometer for solutions in DMSO-d_6 or $CDCl_3$ using tetramethylsilane as an external or internal standard. Chemical shifts are given on the δ scale. TLC was performed on "Bakerflex" silica gel 1B-F (2.7-7.5 cm^{-1}) plates. Microanalyses were performed in the Faculty of Science, Cairo University, Cairo, Egypt.

5-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-2-(hydroxymethyl)-4H-pyran-4-one (**7**). A solution of kojic acid (1.10 g, 7.7 mmol) and potassium hydroxide (0.43 g, 7.7 mmol) in 8 mL of ethanol was added to a solution of **4** (3.16 g, 7.7 mmol) in chloroform (10 mL). Ethanol was added and the reaction mixture was heated under reflux for 1/2 h, then cooled, and water (100 mL) added. The mixture was extracted with chloroform (5 x 20 mL) and the combined organic layers washed with an ice cold solution of 3% sodium hydrogencarbonate (30 mL), ice water (30 mL) and dried over anhydrous calcium chloride. The chloroform was evaporated to give a crystalline residue that was washed with ether. The product was recrystallized from ethanol to give colourless needles

(0.8 g, 22% yield): R_f 0.67 (9:1 chloroform-methanol); R_f 0.52 (2:3 ethyl acetate-n-hexane); mp 200-202 °C (lit.[20] mp 200-201 °C); IR (KBr) 3400 (OH), 1750 (OAc), 1655 (CO), 1625 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.87 (s, 1H, H-6'), 6.49 (d, 1H, J ca. 0.8 Hz, H-3'), 5.22 (m, 4H, H-1, -2, -3, -4), 4.49 (s, 2H, CH_2), 4.19 (m, 2H, CH_2OAc), 3.70 (m, 1H, H-5), 2.13, 2.07, 2.03, 2.02 (4s, 12H, 4OAc). Irradiation at δ 3.70 collapsed the signal at δ 4.19 into an AB quartet and a broad singlet at δ 3.2 ppm disappeared upon addition of a drop of D_2O. ^{13}C NMR ($CDCl_3$), the glucopyranose part: δ 170.45, 169.93, 169.82 and 169.33 (4CO), 20.64 and 20.46 (4Me), 61.40 (C-6), 71.95 (C-5), 68.10 (C-4), 72.32 (C-3), 70.91 (C-2) and 98.93 (C-1); kojic part δ 60.62 (C-7), 143.86 (C-6'), 147.93 (C-5'), 174.30 (C-4'), 113.40 (C-3'), 167.6 (C-2').

2-(Chloromethyl)-5-hydroxy-4H-pyran-4-one (9). This compound was prepared from kojic acid as previously described in the literature: mp 166 °C (lit.[24] mp 166 °C); IR (KBr) 3270 (OH), 1660 (CO), 1630 cm^{-1} (C=C).

5-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-2-(chloromethyl)-4H-pyran-4-one (8). Compound **9** (1.24 g, 7.7 mmol) was dissolved in a solution of potassium hydroxide (0.43 g, 7.7 mmol) in ethanol (8 mL) and the mixture was then added to a solution of **4** (3.16 g, 7.7 mmol) in chloroform (10 mL). Ethanol was added to the reaction mixture to give a solution that was processed according to the prepartion of **7**. The product was recrystallized from ethanol to give colourless needles (0.5 g, 13% yield): R_f 0.5 (2:3 ethyl acetate-n-hexane); mp 158-159 °C; IR (KBr) 1765 and 1750 (OAc), 1680 (CO), 1635 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.87 (s, 1H, H-6'), 6.50 (s, 1H, H-3'), 5.2 (m, 4H, H-1, -2, -3, -4), 4.30 (s, 2H, CH_2), 4.2 (m, 2H, CH_2OAc), 3.75 (m, 1H, H-5), and 2.1, 2.03 and 2.00 (3s, 12H, 4OAc).

Anal. Calcd for $C_{20}H_{23}ClO_{12}$: C, 48.9; H, 4.7. Found: C, 48.6; H, 4.7.

2-(Azidomethyl)-5-hydroxyl-4H-pyran-4-one (11). Compound **11** was prepared from **9** by reaction with sodium azide as reported in the literature: mp 129-130 °C (lit.[25] mp 131-132 °C); IR (Nujol) 3240 (OH), 2145 (N_3), 1665 (CO) and 1630 cm^{-1} (C=C).

5-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-2-(azidomethyl)-4H-pyran-4-one (13). A solution of compound **11** (1.29 g, 7.7 mmol), in ethanolic solution (8 mL) of potassium hydroxide (0.43 g, 7.7 mmol) was

added to a solution of **4** (3.16 g, 7.7 mmol) in chloroform (10 mL). The mixture was processed according to the preparation of **7**. The product was recrystallized from ethanol to give colourless needles (0.6 g, 16% yield): R_f 0.3 (1:4 ethyl acetate-n-hexane); mp 160-161 °C; IR (KBr) 2100 (N_3), 1755 and 1740 (OAc), 1655 (CO) and 1630 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.77 (s, 1H, H-6'), 6.32 (s, 1H, H-3'), 5.15 (m, 4H, H-1, -2, -3, -4), 4.15 (m, 2H, CH_2OAc), 4.12 (s, 2H, CH_2), 3.65 (m, 1H, H-5), 2.08 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.00 (s, 6H, 2OAc).

Anal. Calcd for $C_{20}H_{23}N_3O_{12}$: C, 48.3; H, 4.7; N, 8.5. Found: C, 48.4; H, 4.7; N, 8.1.

5-Hydroxy-2-[(4(5)-phenyl-1,2,3-triazol-1-yl)methyl]-4H-pyran-4-one (**14**). A solution of compound **11** (0.8 g, 4.8 mmol) in *N*,*N*-dimethylformamide (8 mL) was treated with phenylacetylene (0.6 g, 5.9 mmol) and the reaction mixture was heated under reflux on a water-bath for 4 h. The solvent was removed under reduced pressure to give a crystalline product (0.6 g, 47% yield). The product was recrystallized from ethanol as colourless needles; mp 161-162 °C; IR (KBr): 3260 (OH), 1642 (CO) and 1623 cm^{-1} (C=C); NMR (DMSO-d_6) δ 9.27 (s, 1H, OH), 8.67 (s, 1H, triazole H-5), 8.06 (s, 1H, H-6), 7.85 (m, 2H, o-aromatic protons), 7.4 (m, 3H, m- and p-aromatic protons), 6.47 (s, 1H, H-3) and 5.67 (s, 2H, CH_2), the OH singlet at δ 9.27 exchanged in the presence of D_2O.

Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.4; H, 4.1; N, 15.6. Found: C, 62.8; H, 4.1; N, 15.4.

5-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-2-[(4(5)-phenyl-1,2,3- triazol-1-yl)methyl]-4H-pyran-4-one (**15**). A solution of compound **13** (1.2 g, 2.4 mmol) in *N*,*N*-dimethylformamide (8 mL) was treated with phenylacetylene (0.3 g, 2.9 mmol) and the reaction mixture was heated under reflux on a water-bath for 4 h. The solvent was removed under reduced pressure to give a syrupy product which was purified using column chromatography (eluted by ethyl acetate-n-hexane 2:3); IR (KBr) 1760 (OAc), 1665 (C=O) and 1640 cm^{-1} (C=C); NMR (DMSO-d_6) δ 8.67 (s, 1H, Ph-C=C-H), 7.96 (s, 1H, H-6'), 7.9 and 7.4 (2m, 5H, aromatic protons), 6.37 (s, 1H, H-3'), 5.26 (m, 4H, H-1, -2, -3, -4), 4.5 (m, 2H, CH_2OAc), 4.2 (s, 2H, CH_2), 3.7 (m, 1H, H-5), 2.03 and 2.00 (2s, 12H, 4OAc).

Anal. Calcd. for $C_{28}H_{29}N_3O_{12}$: C, 56.1; H, 4.9; N, 7.0. Found: C, 56.4; H, 5.1; N, 7.2.

ACKNOWLEDGMENT

The authors are grateful to Dr. T. Huckerby for measuring the ^{13}C NMR spectrum.

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