Alternative syntheses of methylated sugars. XIII.* Unambiguous synthesis of methyl 2,4-di-*O*-methyl-α-D-galactopyranoside and methyl (methyl 2,4-di-*O*-methyl-α-D-galactopyranosid)uronate

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Treatment of methyl 3,4-*O*-isopropylidene-2-*O*-methyl-α-D-galactopyranoside with benzaldehyde in the presence of boron trifluoride etherate gave a high yield of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-galactopyranoside *I*. Benzylation of *I*, debenzylidenation, tritylation, acetylation and methylation afforded new derivatives of methyl α-D-galactopyranoside *II*—*VI* the latter of which was the key intermediate in the synthesis of the title glycosides. One-step debenzylation and detritylation of *VI* gave the 2,4-di-*O*-methyl derivative of methyl α-D-galactopyranoside *VIII* and the title galacturonic acid derivative *X* was obtained from *VI* by detritylation, oxidation of the fully substituted, except HO-6, derivative *VII*, esterification of the formed acid followed by hydrogenolysis of the ester *IX*.

Воздействием бензальдегида на метил-3,4-*O*-изопропилиден-2-*O*-метил-α-D-галактопиранозид в присутствии BF_3-эфирата с высоким выходом был получен метил-4,6-*O*-бензилиден-2-*O*-метил-α-D-галактопиранозид *I*. Его бензилированием, дебензилиденированием, тритилированием, ацетилированием и метилированием были получены до сих пор не описанные производные метил-α-D-галактопиранозида *II*—*VI*, причем последний из них был основным промежуточным соединением при синтезе гликозидов. Производные метил-α-D-галактопиранозид *VIII* и метил(метил-α-D-галактопиранозид)уронат *X* были получены из *VI* одноступенчатым дебензилированием и детритилированием или же детритилированием, окислением полностью замещенного, кроме HO-6, производного *VII*, этерификацией полученного производного уроновой кислоты и гидрогенолизом эфира *IX*.

In connection with other works in this laboratory the need arose for methyl (methyl 2,4-di-*O*-methyl-α-D-galactopyranosid)uronate. Since because of the difficulties involved in the synthesis of suitable intermediates the derivatives of methyl α-D-galactopyranoside methylated at HO-2 and HO-4 have not yet been obtained by a regulated synthesis we have undertaken to prepare two compounds of this class in a way outlined in Scheme 1. Of the title glycosides only methyl 2,4-di-*O*-

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-methyl-α-D-galactopyranoside has been previously described in the literature, as obtained by *Smith* [1] from the products of methylation analysis of a polysaccharide.

The starting point in the presented synthesis of *VIII* and *X* was methyl 4,6-*O*--benzylidene-2-*O*-methyl-α-D-galactopyranoside (*I*), first prepared by *Bell et al.* [2]. In the last stages of the procedure the authors removed the 3,4-*O*-isopropylidene group from methyl 3,4-*O*-isopropylidene-2-*O*-methyl-α-D-galactopyranoside by mild acid hydrolysis and benzylidenated the resulting methyl 2-*O*-methyl-α-D-galactopyranoside with benzaldehyde and fused zinc chloride. *Hall et al.* [3] treated methyl 2,3-di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranoside with benzaldehyde and fused zinc chloride and obtained the corresponding 4,6-*O*-benzylidene derivative showing that by means of a Lewis acid-catalyzed acetal exchange reaction some cyclic acetals of sugars can be prepared which otherwise would be obtainable only with difficulty. Since it is known that aromatic aldehydes tend to form cyclic products with 6-membered dioxan ring rather than with 5-membered dioxolane ring [4] we have made an attempt to convert the above-described 3,4-*O*-isopropylidene derivative to *I* in a one-step procedure.

As showed below, when methyl 3,4-*O*-isopropylidene-2-*O*-methyl-α-D-galactopyranoside is treated with benzaldehyde in the presence of boron trifluoride etherate the acetal-exchange occurs within a few minutes and the wanted derivative *I* can be isolated in a high yield. Methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-galactopyranoside obtained by the described procedure was in all respects identical with the previously described [2] substance.

Benzylation of *I* afforded a new crystalline substance *II* which was debenzylidenated and tritylated to give the trityl ether *V* Compound *V*, which crystallizes only with difficulty and tends to form gels with common organic solvents was most conveniently isolated by means of its 4-*O*-acetate *IV*, and it is recommended that for synthetic purposes the compound be used in the form of the chromatographically pure syrup obtainable from the crystalline *IV* by a simple deacetylation.

Methylation of *V* produced the fully substituted derivative *VI*, the key intermediate in the synthesis of the glycosides *VIII* and *X*. High yield of *VIII* was obtained by a one-step debenzylation and detritylation of *VI* with sodium in liquid ammonia [5]. In the p.m.r. spectrum of methyl 2,4-di-*O*-methyl-α-D-galactopyranoside described herein one doublet for H-1 was present ($J_{1,2}$ 3.5 Hz) showing that only the α-anomer was present. Its physical constants (m.p. 109—110°C, and $[\alpha]_D$ +191°) also indicate a high anomeric purity. The compound isolated from a natural source [1] (m.p. 105°C, and $[\alpha]_D$ +142°) by fractional crystallization from a mixture of α- and β-anomers, the latter of which is the less soluble one, was probably anomerically unpure.

The hitherto unknown methyl (methyl 2,4-di-*O*-methyl-α-D-galactopyranosid)-uronate (*X*) was obtained from *VI* by detritylation and oxidation of the obtained *VII*, having only HO-6 unsubstituted, with chromium trioxide and dilute sulfuric acid in acetone under the optimum conditions [6], esterification of the produced uronic acid derivative, and hydrogenolysis of the ester *IX*. The title ester *X* as well as its syrupy precursor *IX* were characterized by means of their crystalline uronoamides.

Experimental

Melting points were determined on a Kofler hot-stage. Optical rotations were measured with a Perkin—Elmer automatic polarimeter Model 141. The p.m.r. spectra were measured at 80 MHz in chloroform-*d* (internal standard tetramethylsilane) using a Tesla BS 487 B spectrometer. Mass spectra were obtained with an MCh-1306 instrument under the previously described conditions [7]. Thin-layer chromatography (t.l.c.) on Silica gel G coated glass slides and preparative chromatography on columns of dry-packed silica gel (0.1—0.15 mm) [8] using 40% of the mobile phase for equilibration instead of the recommended 10% [8] was performed with: *A*. benzene—acetone 10 : 1, *B*. chloroform—acetone 4 : 1, *C*. benzene—acetone 15 : 1, *D*. benzene—*n*-heptane 2 1, *E*. benzene—acetone 4 : 1, and *F*. chloroform—methanol 10 : 1. The solvent ratios are based on volumes. Detection was carried out by charring with 5% sulfuric acid in ethanol. 1,2-Dimethoxyethane was dried as described [9] and stored over sodium hydride. Boron trifluoride etherate was freshly distilled from calcium hydride. Other chemicals were commercial products, reagent grade, used as supplied.

Uronoamides were prepared by amonolysis [10] of the corresponding methyl esters. Solutions were concentrated under diminished pressure (10—15 torr) at <40°C.

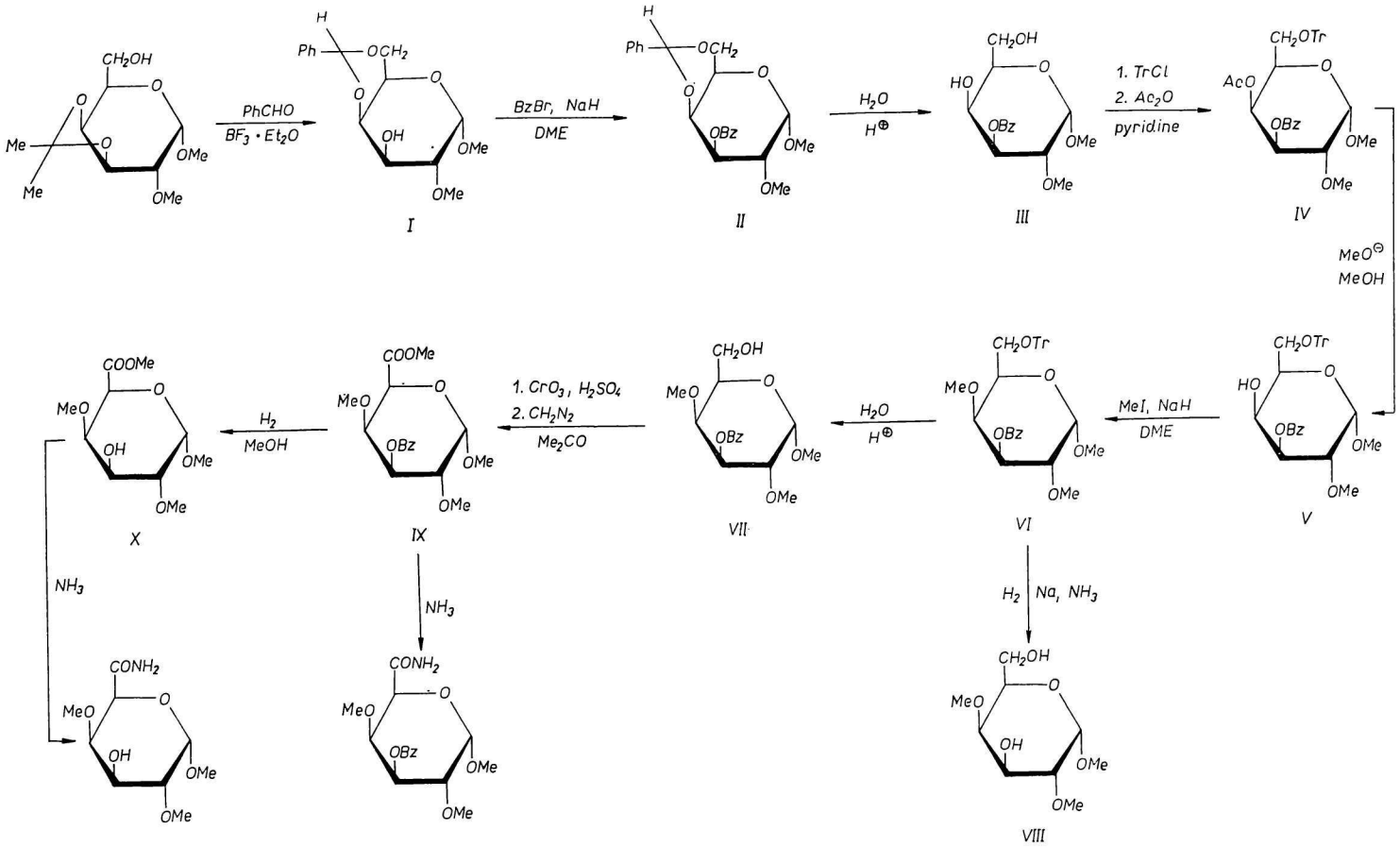
Methyl 4,6-O-benzylidene-2-O-methyl-α-D-galactopyranoside (I)

Boron trifluoride etherate (300 μl) was added under stirring at 20°C to a solution of methyl 3,4-*O*-isopropylidene-2-*O*-methyl-α-D-galactopyranoside [2] (8 g) in benzaldehyde (32 ml). External tap-water cooling was removed after 5 min at which time the product started to crystallize. The reaction mixture was transferred with the aid of chloroform (100 ml) into a solution of potassium pyrosulfite (130 g) in water (320 ml) and the mixture was stirred until the content of the vessel thickenned as a result of the formation of the benzaldehyde—sulfite addition product. Chloroform (100 ml) and water (900 ml) were added and the stirring was continued for 1 hr. The chloroform phase was separated and the water layer was extracted with chloroform (3 × 30 ml). The combined extracts were washed with a saturated solution of sodium bicarbonate and water, dried with anhydrous sodium sulfate and concentrated. The solid residue was crystallized from ethanol to give 6.8 g of *I* melting at 151—152°C and having $[\alpha]_D^{21}$ +128° (*c* 1.05, chloroform). The second crop of *I* (1.6 g, total yield 88.3%) obtained from the concentrated mother liquor melted at 143—150°C and showed $[\alpha]_D^{21}$ +130° (*c* 1.03, chloroform). Ref. [2] gives m.p. 152°C and $[\alpha]_D^{20}$ +131.6° (*c* 2.3, chloroform).

Both products gave identical p.m.r. spectra containing one sharp singlet for the benzylic proton at δ 5.49 showing that the whole amount of the isolated *I* was a single diastereoisomer. Other definite signals in the p.m.r. spectrum were at δ 7.19—7.68 (5-proton multiplet, aromatic protons), δ 4.95 (1-proton doublet, H-1, $J_{1,2}$ 3.5 Hz), δ 2.74 (1-proton singlet, OH), δ 3.39 and 3.45 (two 3-proton singlets, 2 × CH_3).

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-galactopyranoside (II)

To a solution of *I* (12.6 g) in 1,2-dimethoxyethane (300 ml) sodium hydride (3.1 g) was added followed by the addition of benzyl bromide (10 ml) and the mixture was stirred under a gentle reflux with the exclusion of atmospheric moisture and carbon dioxide for ~1 hr after which time t.l.c. in solvent *A* showed that the conversion of the starting material (R_F 0.2) to a single product (R_F 0.5) was completed. The reaction



Ac — acetyl, Bz — benzyl, DME — 1,2-dimethoxyethane, Et — ethyl, Me — methyl, Ph — phenyl, Tr — trityl.

Scheme 1

mixture was cooled and the excess of the benzylation agents was destroyed by an addition of methanol and, after dilution of the solution with water, the organic solvents were removed. More water was added (total volume ~ 1 liter) and the separated crystalline product was filtered and washed with water and *n*-heptane to remove benzyl methyl ether. The crude product was partitioned between chloroform and water, dried with anhydrous sodium sulfate and concentrated. The solid residue was crystallized from ethanol to give 15.1 g (91.9%) of chromatographically pure *II* melting at 130—132.5°C. A portion, after recrystallization from the same solvent, melted at 130—131°C and showed $[\alpha]_D^{22}$ +158° (*c* 1, chloroform).

For $C_{22}H_{26}O_6$ (386.43) calculated: 68.37% C, 6.78% H, 16.06% CH_3O; found: 68.35% C, 6,84% H, 15.93% CH_3O.

Methyl 3-O-benzyl-2-O-methyl-α-D-galactopyranoside (III)

A solution of *II* (15 g) in a mixture of ethanol (30 ml) and 6 N acetic acid (90 ml) was heated at 80°C for 2 hrs after which time t.l.c. (solvent *A*) showed a complete disappearance of the starting material. The solution was concentrated and evaporated several times with water and ethanol to remove acetic acid. Then the t.l.c. showed that two products were present (R_F 0.4 and 0.6, solvent *B*). The faster moving 6-*O*-acetate [10, 11] was converted to the main component of the reaction mixture by addition of some methanolic sodium methoxide to the solution of the crude product in methanol and after usual work-up 11.5 g (~100%) of chromatographically pure *III* was obtained. The syrup, which could not be induced to crystallize, showed $[\alpha]_D^{22}$ +105° (*c* 1.12, chloroform).

For $C_{15}H_{22}O_6$ (298.33) calculated: 60.39% C, 7.43% H, 20.81% CH_3O; found: 60.56% C, 7.26% H, 21.01% CH_3O.

Methyl 3-O-benzyl-2-O-methyl-6-O-trityl-α-D-galactopyranoside (V)

Trityl chloride (10 g) was dissolved at room temperature in a solution of *III* (10 g) in dry pyridine (50 ml) and after ~3 hrs at 90—100°C t.l.c. (solvent *B*) showed that only traces of the starting material were present. The solution was cooled and, after addition of acetic anhydride (10 ml), left for 16 hrs at ambient temperature after which time one main component (R_F 0.7) was present in the reaction mixture, as showed by t.l.c. in system *C*. Isolation in the usual manner gave the 4-*O*-acetate *IV* (16.7 g, 85.5%), m.p. 149—150°C (from chloroform—ether, twice), $[\alpha]_D^{22}$ +64° (*c* 1, chloroform).

For $C_{36}H_{38}O_7$ (582.66) calculated: 74.20% C, 6.57% H, 10.65% CH_3O; found: 74.17% C, 6.30% H, 10.35% CH_3O.

Methanolic sodium methoxide (1 N, 5 ml) was added to a suspension of *IV* (4.3 g) in dry methanol (20 ml) and the mixture was heated under stirring and exclusion of atmospheric moisture at 50°C. Approximately 1 hr after the dissolution of the starting material t.l.c. (solvent *C*) showed that *IV* (R_F 0.7) disappeared completely from the reaction mixture and that a single product was formed. The solution was concentrated and the jelly-like mass was broken-up by co-evaporation with toluene to give 4 g (~100%) of crude *V* suitable as such for the next step.

A portion of the obtained material was partitioned between ether and water and the ether phase was concentrated. Crystallization from chloroform—methanol or chloroform—*n*-heptane gave an analytical sample of *V* melting at 104—106°C and showing $[\alpha]_D^{22}$ +54° (*c* 1, chloroform).

For $C_{34}H_{36}O_6$ (540.63) calculated: 75.53% C, 6.71% H, 11.48% CH_3O; found: 75.68% C, 6.47% H, 11.21% CH_3O.

Methyl 3-O-benzyl-2,4-di-O-methyl-6-O-trityl-α-D-galactopyranoside (VI)

Compound *IV* (8.6 g) was deacetylated as described above and sodium hydride (1.5 g) was added to the solution of the crude product of deacetylation in 1,2-dimethoxyethane (100 ml), followed by the addition of methyl iodide (4.2 ml). The mixture was stirred at room temperature with the exclusion of atmospheric moisture and carbon dioxide until the reaction was completed (t.l.c. in solvent *C*). The reaction mixture was worked up as described in the above-described etherification procedure and the product *VI* (7.1 g, 87% based on the amount of the starting *IV*, R_F 0.75) was crystallized from ethanol. After recrystallization from the same solvent compound *VI* melted at 105—107°C and showed $[\alpha]_D^{22}$ +50.5° (*c* 1.05, chloroform).

For $C_{35}H_{38}O_6$ (554.65) calculated: 75.80% C, 6.91% H, 16.79% CH_3O; found: 75.58% C, 6.70% H, 16.49% CH_3O.

Methyl 3-O-benzyl-2,4-di-O-methyl-α-D-galactopyranoside (VII)

To a solution of *VI* (11 g) in glacial acetic acid (45 ml) water was added at 90°C until faint turbidity followed by addition of a small amount of ethanol until clear solution was formed. The solution was heated at ~100°C for 4 hrs and then left overnight at room temperature. The separated triphenylcarbinol was filtered, washed with a small amount of cool ethanol and acetic acid was removed by concentration of the filtrate with several additions of ethanol and water. The t.l.c. of the syrupy residue in the system *E* showed that, in addition to large amount of *VII* (R_F 0.3), the 6-*O*-acetate [10, 11], formed spontaneously during concentration of the solution of the product in dilute acetic acid, was also present. After deacetylation as described above the crude product was rid of the residual triphenylcarbinol by elution from a silica gel column with systems *D*, benzene, and *E*. Pure compound *VII* (6 g, 97%) was obtained as a syrup showing $[\alpha]_D^{21}$ +92.5° (*c* 1.03, chloroform). All attempts to crystallize the substance failed.

For $C_{16}H_{24}O_6$ (312.35) calculated: 61.52% C, 7.35% H, 29.81% CH_3O; found: 61.70% C, 7.53% H, 29.70% CH_3O.

Methyl 2,4-di-O-methyl-α-D-galactopyranoside (VIII)

A solution of *VI* (5.4 g) in 1,2-dimethoxyethane (50 ml) was added dropwise under stirring to a mixture of liquid ammonia and 1,2-dimethoxyethane (10 : 1, ~ 250 ml) while the temperature of the mixture was kept close to the boiling point. Under continued stirring sodium (~1 g) cut to small pieces was added until permanent dark blue colour developed, indicating that the reaction was completed. The excess of sodium was destroyed with ammonium chloride (4.2 g) and ammonia was allowed to evaporate. The solids were filtered and the solution containing one charring component, as showed by t.l.c. (R_F 0.4, solvent *F*) was evaporated. The semi-solid residue was partitioned between ether and water and the water solution, still containing non-carbohydrate reaction by-products, was concentrated, and the residue chromatographed on a silica gel column. After repeated crystallization from acetone—ether compound *VIII* melted at 109—110°C and showed $[\alpha]_D^{22}$ +191° (*c* 1.04, water). Ref. [1] gives m.p. 105°C and $[\alpha]_D^{18}$ +142° (*c* 1.1, water).

Mass spectrum of *VIII* was qualitatively identical with that of the corresponding

derivative of D-glucose [12] and the definite signals in its p.m.r. spectrum were at δ 4.95 (1-proton doublet, H-1, $J_{1,2}$ 3.5 Hz), δ 3.60, 3.51, and 3.43 (three 3-proton singlets, 3 × CH_3), δ 2.86 (2-proton singlet, 2×OH).

Methyl (methyl 2,4-di-O-methyl-α-D-galactopyranosid)uronate (X)

A solution of chromium trioxide (6.2 g) in 3.5 M sulfuric acid (26.4 ml) was added under stirring to a solution of *VII* (7 g) in acetone (112 ml) at 0°C. Cooling was terminated after 10 min and the mixture was stirred for an additional 60 min and then filtered through a sintered-glass-funnel of medium porosity on to crushed ice. The solids were washed with acetone, and the combined filtrate and washings were concentrated to remove the organic solvent. The aqueous phase was washed with chloroform which was then backwashed with water. The chloroform solution was dried with anhydrous sodium sulfate, evaporated to dryness and the solution of the residue (8.7 g) in a small amount of methanol was added to the top of a column of freshly prepared, freshly distilled water- and methanol-washed Amberlite IRA 402 (OH^-) resin (2.5 × 30 cm). Elution with methanol removed some unreacted starting material and oxidation by-products, and methyl 3-*O*-benzyl-2,4-di-*O*-methyl-α-D-galactopyranuronic acid was eluted with methanol—acetic acid—water 45 : 45 : 10 mixture. This eluate was concentrated by co-distillation with water to remove acetic acid, the residue (6.6 g) was dissolved in methanol and an excess of diazomethane in ether was added. Evaporation gave a syrup containing, as showed by t.l.c. (solvent *A*), one major product (R_F 0.5). After purification by column chromatography on silica gel pure syrupy methyl (methyl-3-*O*-benzyl-2,4-di-*O*-methyl-α-D-galactopyranosid)uronate *IX* was obtained showing $[\alpha]_D^{21}$ +106° (*c* 1.04, chloroform).

For $C_{17}H_{24}O_7$ (340.36) calculated: 59.98% C, 7.11% H, 36.47% CH_3O; found: 59.80% C, 7.04% H, 36.60% CH_3O.

Methyl 3-*O*-benzyl-2,4-di-*O*-methyl-α-D-galactopyranosiduronamide, when crystallized from ether—hexane (twice), melted at 114.5—116.5°C and showed $[\alpha]_D^{21}$ +90° (*c* 1.05, chloroform).

For $C_{16}H_{23}O_6N$ (325.35) calculated: 59.06% C, 7.12% H, 4.30% N; found: 59.06% C, 6.84% H, 4.25% N.

Catalytic hydrogenolysis of *IX* in methanol at room temperature and atmospheric pressure over 5% palladium-on-charcoal catalyst (10%, w/w) gave the final uronate *X* in a theoretical yield. The substance crystallized immediately upon removal of the solvents and after repeated crystallization from methyl acetate—ether melted at 118.5—119°C. The optical rotation observed for the substance was $[\alpha]_D^{22}$ +131° (*c* 0.99, chloroform). Its mass spectrum contained all the features characteristic of the fragmentation of methyl (methyl 2,4-di-*O*-methyl-hexopyranosid)uronates [7].

For $C_{10}H_{18}O_7$ (250.24) calculated: 48.0% C, 7.25% H, 49.61% CH_3O; found: 48.12% C, 7.19% H, 49.92% CH_3O.

The corresponding amide melted at 186—187°C (from methanol—ether, twice) and showed $[\alpha]_D^{21}$ +101° (*c* 1.05, chloroform).

For $C_9H_{17}O_6N$ (235.24) calculated: 45.95% C, 7.29% H, 5.96% N; found: 45.93% C, 7.43% H, 5.91% N.

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