Branched-chain Sugars. IV. Synthesis of 5,6-Dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene-6-*C*-nitro-3-*O*-substituted-α-D-glucose Derivatives[1]

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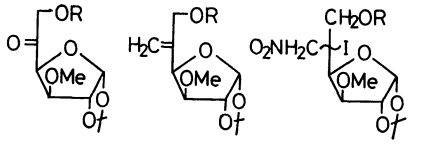
(Received June 22, 1973)

Addition of nitryl iodide to 5-deoxy-1,2,*O*-isopropylidene-3-*O*-methyl-5-*C*-methylene-6-*O*-substituted-α-D-*xylo*-hexofuranoses (**3** and **4**), and subsequent hydrogenation with sodium borohydride gave a mixture of the corresponding 5,6-dideoxy-5-*C*-hydroxymethyl-6-*C*-nitro derivatives of D-*gluco* and L-*ido* forms. The configuration of both isomers were determined by intramolecular cyclization into the corresponding nitrocyclohexanetetrols. The ratios of D-*gluco* to L-*ido* product were 1:2 in the case of 6-*O*-trityl derivative (**3**) and 4:5 in the case of 6-*O*-benzyl derivative (**4**), respectively.

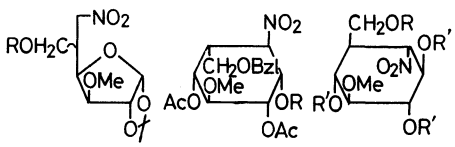
In the previous paper,[1] addition of vinylmagnesium bromide to 5,6-dideoxy-1,2-*O*-isopropylidene-6-*C*-nitro-3-*O*-substituted-α-D-*xylo*-hex-5-enofuranoses gave exclusively the corresponding L-*ido*-type product. In order to synthesize a 5,6-dideoxy-6-*C*-nitro-5-*C*-hydroxymethyl derivative of D-*gluco* configuration, another pathway including addition of nitryl iodide[2] to 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-*C*-methylene-6-*O*-substituted-α-D-*xylo*-hexofuranoses (**3** and **4**) and hydrogenation with sodium borohydride was examined, and the configuration of the product was determined to be a mixture of D-*gluco* and L-*ido* forms by intramolecular cyclization into the corresponding nitrocyclitol.

Results and Discussion

As the starting materials, 6-*O*-trityl (**1**) and 6-*O*-benzyl derivatives (**2**) of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hexofuranos-5-ulose were synthesized by dimethyl sulfoxide oxidation of the corresponding 5-hydroxy derivatives,[3,4] respectively. Treatment of **1** and **2** with triphenylphosphonium methylide gave the corresponding 5-*C*-methylene derivatives (**3** and **4**) in 50 and 85% yield, respectively. Addition of nitryl iodide, prepared from silver nitrite and iodine, to **3** and **4** in ether in the dark place gave the corresponding addition product as crystals (**5**) and a sirup (**6**) in good yields, respectively. The homogeneity of **5** was deduced from the presence of the single methoxy signal in the NMR spectrum, however, the configuration at C_5-position could not be determined because of its instability. **6** was deduced to be a mixture of C_5-epimers and a small amount of unchanged **4**, and was used without further purification. Attempted elimination of **5** and **6** into the corresponding nitro olefin by use of potassium carbonate or 1,5-diazabicyclo-[5.4.0]undec-5-ene were unsuccessful. Hydrogenation of **5** and **6** in ethanol–tetrahydrofuran with sodium borohydride at 0 °C gave the corresponding 5,6-dideoxy-5-*C*-hydroxymethyl-6-*C*-nitro derivatives (**7** and **8**) in 55 and 79% yield, respectively. Both the compounds showed two kinds of methoxy proton signals in NMR spectra, indicating they are a mixture of C_5-epimers in the ratios of 1 to 2 and of 2 to 3, respectively. For resolution and assignment of both the epimers, **7** and **8** were de-*O*-isopropylidenated by treatment with 70% acetic acid at 90 °C for 10 hr under monitering with tlc, and cyclized intramolecularly without further purification. In the case of **8**, cyclization in ethanol at pH 9 for 40 hr at 30 °C, neutralization with Amberlite IR-120, and purification of the product on silica-gel column with benzene–ethyl acetate (2: 3) gave the corresponding nitrocyclitols in 30% yield, which on acetylation gave 1-*O*-ethyl-3-*O*-methyl-(3,6/1,2,4,5)-5-benzyloxymethyl-6-nitrocyclohexanetetrol (**9**)[5] as crystals. When the cyclization was accomplished in 50% aqueous methanol in the presence of sodium bicarbonate at 30 °C for 3 days and the reaction mixture was then treated as above, two kinds of sirupy nitrocyclohexanetetrol were obtained in 31 and 21% yield, which upon acetylation gave 1,2,4-tri-*O*-acetyl-3-*O*-methyl-(3,6/1,2,4,5)-5-benzyloxymethyl-6-nitrocyclohexanetetrol (**10**)[5] and its (1,3,5/2,4,6)-diastereoisomer (**11**) as crystals. The ratio of the both



(**1**) R=Trityl (**3**) R=Trityl (**5**) R=Trityl
(**2**) R=Benzyl (**4**) R=Benzyl (**6**) R=Benzyl



(**7**) R=Trityl (**9**) R=Et (**11**) R=Benzyl, R′=Ac
(**8**) R=Benzyl (**10**) R=Ac (**12**) R=R′=H
(**13**) R=R′=Ac

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2) W. A. Szareck, J. S. Jewell, J. Szazerek, and J. K. N. Jones, *Can. J. Chem.*, **47**, 4473 (1969).

3) G. W. Huffman, B. A. Lewis, F. Smith, and D. R. Spriestersbach, *J. Amer. Chem. Soc.*, **77**, 4346 (1955).

4) J. Kenner and G. N. Richards, *J. Chem. Soc.*, **1954**, 3277.

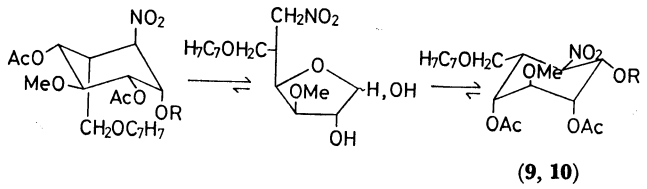
5) For easier understanding, the numbering and figures of nitrocyclitols for nomenclature were cited from that of original compounds. Other points were followed by "Tentative Rules for Cyclitol Nomenclature" of IUPAC (1967 rule).

Table 1. NMR parameters of *O*-acetylated nitrocyclitols

Compound	H_1	H_2	H_3	H_4	H_5	H_6	Other protons
9	4.C8(dd) $J_{1,2}$=3.7	5.47(td) $J_{2,3}$=3.7	3.8—3.2 $J_{3,4}$=3.0	5.28(td) $J_{4,5}$=2.5	2.85(m) $J_{5,6}$=12.0	4.80(t) $J_{1,6}$=10.0	7.29 (Ph), 4.48 and 4.27 ($PhCH_2O$; ABq, J=12.0), 3.48 (OMe), 3.8—3.2 (C–CH_2O, OCH_2Me), 1.05 (C–Me; t, J=7.0), 2.01 and 1.88 (OAc)
10	5.59(dd) $J_{1,2}$=3.5	5.50 $J_{2,3}$=3.5	3.7—3.3 $J_{3,4}$=3.0	5.27(m) $J_{4,5}$=3.0	2.92(m) $J_{5,6}$=11.5	4.45(t) $J_{1,6}$=11.5	7.27 (Ph), 4.47 and 4.27 ($PhCH_2O$; ABq, J=12.0), 3.48 (OMe), 3.7—3.3 (C–CH_2O; m), 2.02, 1.93 and 1.88 (OAc)
11	5.54(dd) $J_{1,2}$=10.0	5.05(dd) $J_{2,3}$=9.5	3.55 $J_{3,4}$=9.0	5.19(dd) $J_{4,5}$=11.0	2.39(tm) $J_{5,6}$=10.5	4.89(t) $J_{1,6}$=10.5	7.28 (Ph), 4.38 ($PhCH_2O$; s), 3.40 (OMe), 3.55—3.07 (C–CH_2O; m), 2.02 and 1.95 (OAc)
13	5.55(t) $J_{1,2}$=10.0	5.06(dd) $J_{2,3}$=9.0	3.46(t) $J_{3,4}$=9.0	5.09(t) $J_{4,5}$=9.0	2.55(tm) $J_{5,6}$=11.5	4.28(dd) $J_{1,6}$=10.0	4.22 and 3.72 (C–CH_2O; each q, $J_{5'a,5'b}$=12.5, $J_{5'a,5}$=3.5, $J_{5'b,5}$=2.5), 3.43(OMe), 2.10, 2.05 and 1.98(OAc)

epimers in the original crude nitrocyclitol was again estimated to be 4: 5 from the intensities of H_5 proton signals (δ 2.92 and 2.39) of the corresponding acetate. The main product **11** indicates that the L-*ido* form was predominant in **8**. In the case of **7**, a similar cyclization gave 3-*O*-methyl-(1,3,5/2,4,6)-5-hydroxymethyl-6-nitrocyclohexanetetrol (**12**)[5] as crystals in 37% yield, which on acetylation gave the corresponding tetra-*O*-acetate (**13**). The ratio of the expectable isomers in the crude nitrocyclitol estimated by the similar way as above (δ 2.92 and 2.55) was 1: 2, indicating again L-*ido* form was predominant in **7**, but the minor isomer could not be isolated in a pure state.

Configurations of **9**, **10**, **11**, and **13** predicted above were determined from the NMR parameters shown in Table 1, which were analyzed by double resonance technique. The proton signals at the branched point were distinguished by its multi-splittings and higher resonating magnetic field than others. Other ring protons appeared in a lower field in the order of alkoxy, nitro and acetoxy positions. The large *trans*-diaxial coupling constants in **11** and **13** indicate that the all substituents are in equatorial conformation, while small *gauche* coupling in H_2–H_4 of **9** and **10** indicate that substituents at these position are in axial conformation. As shown in Fig. 1, this conformation would be caused by the preferential adoption of the nitro group[6] and benzyloxymethyl group into an equatorial orientation.



(**9**, **10**)

Fig. 1. Conformation of (3,6/1,2,4,5)-type isomers

Experimental

All melting points are uncorrected. The solutions were evaporated under diminished pressure at a bath temperature not exceeding 45 °C. Specific rotations were measured in a 0.5-dm tube, with a Carl Zeiss photoelectric polarimeter. The IR spectra were recorded with a Hitachi Model EPI-GS spectrophotometer. The NMR spectra were taken in deuteriochloroform with a JMN-4H-100 MHz Spectrometer using tetramethylsilane as an internal standard. Chemical shifts and coupling constants were recorded in δ and Hz units, and frequencies in cm^{-1}.

*1,2-O-Isopropylidene-3-O-methyl-6-O-trityl-α-*D*-xylo-hexofuranos-5-ulose (1).* A solution of 1,2-*O*-isopropylidene-3-*O*-methyl-6-*O*-trityl-α-D-glucofuranose (41.5 g) in dimethyl sulfoxide (200 ml) and acetic anhydride (70 ml) was stood at room temperature for 21 hr, poured into ice-water (5 l) with stirring. The gummy precipitate was separated from the water layer by decantation, and dissolved in benzene. The benzene solution was washed with saturated sodium bicarbonate solution and water, and evaporated to give crystals which were recrystallized from ligroin. Yield, 17.5 g (45%), mp 146—147 °C, $[\alpha]_D^{23}$ −41° (*c* 0.5, $CHCl_3$). IR: 1740 (C=O), NMR: 7.5—7.1 (Ph_3C–; m), 5.87 (H_1; d, $J_{1,2}$= 3.5), 4.85 (H_4; d, $J_{3,4}$=3.5), 4.47 (H_2; d), 4.09 (H_3; d), 4.01 (H_6; s), 3.18 (OCH_3), 1.46 and 1.28 (2×C–CH_3).

Found: C, 73.00; H, 6.22%. Calcd for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37%.

*6-O-Benzyl-1,2-O-isopropylidene-3-O-methyl-α-*D*-xylo-hexofuranos-5-ulose (2).* A solution of 6-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (3.0 g, 9.35 mmol) in dimethyl sulfoxide (50 ml) and acetic anhydride (10 ml) was kept at room temperature for 1 day, poured into ice-water (500 ml), and extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution and water, evaporated, and the sirup obtained was fractionated on a silicagel (Wakogel C-200) column with benzene–methanol (50: 1) to give a pure sirup (1.5 g, 50%). $[\alpha]_D^{23}$ −73° (*c* 0.5, $CHCl_3$). IR: 1728 (C=O); NMR: 7.32 (Ph; m), 5.96 (H_1; d, $J_{1,2}$=3.0), 4.71 (H_4; d, $J_{3,4}$=3.5), 4.55 (H_6; s), 4.51 (H_2; d), 4.35 (–CH_2–; s), 4.06 (H_3; d), 3.28 (OCH_3), 1.42 and 1.28 (2×C–CH_3).

Found: C, 62.53; H, 6.72%. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88%.

*5-Deoxy-1,2-O-isopropylidene-3-O-methyl-5-C-methylene-6-O-trityl-α-*D*-xylo-hexofuranose (3).* To a suspended solution of triphenylmethylphosphonium bromide (28.2 g, 77.6 mmol) in tetrahydrofuran (400 ml) was added dropwise *n*-butyllithium in *n*-hexane (41.4 ml of 15% solution, 97 mmol) with stirring at 0 °C, and after 10 min was further added a solution of **1** (18.4 g, 38.8 mmol) in tetrahydrofuran (60 ml). The resulted solution was stirred for 1 hr, filtered, and evaporated. The resulted sirup was extracted with *n*-hexane, and

6) F. W. Lichtenthaler, "Fortschritte der Chemischen Forschung; Topics in Current Chemistry," Vol. 14, No. 4, p. 556 (1970).

the extract was washed with water, dried, and evaporated to give a sirup which was crystallized and recrystallized from ethanol–*n*-hexane. Yield, 9 g (50%), mp 97—98.5 °C, $[\alpha]_D^{23}$ −44° (*c* 0.5, $CHCl_3$). IR: 1650 (C=C); NMR: 7.58—7.17 (Ph_3C), 5.92 (H_1; d, $J_{1,2}=3.5$), 5.37 ($H_{5'}$; m, $J_{4,5'}\simeq J_{5',6a}\simeq J_{5',6b}\simeq 2$), 4.82 ($H_4$; m), 4.49 ($H_2$; d), 3.75 and 3.50 ($H_{6a}$ and H_{6b}; ABq, $J_{a,b}=12.0$), 3.49 (H_3; d, $J_{3,4}=3.0$), 3.07 (OCH_3), 1.50 and 1.30 ($2\times C\text{–}CH_3$).

Found: C, 76.16; H, 7.04%. Calcd for $C_{30}H_{32}O_5$: C, 76.24; H, 6.83%.

*6-O-Benzyl-5-deoxy-1,2-O-isopropylidene-3-O-methyl-5-C-methylene-α-*D-xylo-*hexofuranose (4).* Compound **3** (3.45 g, 10.7 mmol) was treated with triphenylmethylphosphonium bromide (7.6 g, 21.4 mmol) and *n*-butyllithium (26.7 mmol) as above to give a sirupy product in 85% (3 g) yield. $[\alpha]_D^{23}$ −57° (*c* 0.5, $CHCl_3$). IR: 1640 (C=C).

Found: C, 67.05; H, 7.95%. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55%.

*5,6-Dideoxy-5-iodo-1,2-O-isopropylidene-3-O-methyl-6-C-nitro-5-C-trityloxymethyl-α-*D-xylo-*hexofuranose (5).* To a suspended solution of iodine (5.30 g, 21.0 mmol) and silver nitrite (2.66 g, 17.2 mmol) in ether (500 ml) under stirring at 0 °C in the dark state, was added a solution of **3** (0.7 g, 14.8 mmol) in ether, and after stirring 1 day at room temperature the reaction mixture was filtered and evaporated. The resulted sirup was extracted with chloroform, and the extract was washed with sodium thiosulfate solution and water, dried, and evaporated to give a sirup (6.7 g, 70%) which was crystallized from benzene–*n*-hexane. Mp 171—172 °C, $[\alpha]_D^{23}$ −8° (*c* 0.5, $CHCl_3$). IR: 1540 and 1370 (NO_2); NMR: 7.63—7.20 (Ph_3C), 5.83 (H_1; d, $J_{1,2}=3.5$), 4.95 and 4.81 (H_{6a} and H_{6b}; ABq, $J_{a,b}=13.0$), 4.88 (H_4; d, $J_{3,4}=3.0$), 4.37 (H_2; d), 3.97 and 3.27 ($H_{5'a}$ and $H_{5'b}$; ABq, $J_{a,b}=10.0$), 3.47 (H_3; d), 2.81 (OCH_3), 1.55 and 1.30 ($2\times C\text{–}CH_3$).

Found: C, 55.90; H, 5.02; N, 2.26%. Calcd for $C_{30}H_{32}NO_7I$: C, 55.82; H, 5.00; N, 2.17%.

*5,6-Dideoxy-1,2-O-isopropylidene-3-O-methyl-6-C-nitro-5-C-trityloxymethyl-α-*D-gluco- *and β-*L-ido-*furanose (7).* To a solution of **5** (6.0 g, 9.1 mmol) in tetrahydrofuran (90 ml) and ethanol (800 ml) was added portionwise sodium borohydride (2.46 g) at 0 °C, and after stirring for 1 day a small amount of water was added to decompose the hydride. The reaction mixture was then evaporated, the resulted residue was extracted with chloroform, and the extract was washed with water, dried, and evaporated to give a sirup which was crystallized from benzene–ethanol. Yield, 2.4 g (55%), mp 152—153 °C, $[\alpha]_D^{23}$ −46° (*c* 0.5, $CHCl_3$). IR: 1540 and 1365 (NO_2).

Found: C, 69.53; H, 6.46; N, 2.76%. Calcd for $C_{30}H_{33}NO_7$: C, 69.35; H, 6.39; N, 2.70%.

NMR spectrum of this crystal showed still two methyl proton signals (δ 3.17 and 2.99) in the intensity ratio 1:2.

*5-C-Benzyloxymethyl-5,6-dideoxy-1,2-O-isopropylidene-3-O-methyl-6-C-nitro-α-*D-gluco- *and β-*L-ido-*furanose (8).* Compound **4** (2.67 g, 0.34 mmol) was treated with nitryl iodide prepared from iodine (2.93 g, 11.5 mmol) and silver nitrite (1.49 g, 9.6 mmol) by a similar manner as in the case of **5**. NMR spectrum of the sirupy product (3.36 g, 85%) showed three kinds of methoxy proton signals (δ 3.14, 3.23, and 3.43), indicating the presence of C_5-epimers and a small amount of **4**. This sirup (3.3 g, 6.8 mmol) was hydrogenated with sodium borohydride (7 equimolar amount) to give a sirupy product which was purified with silica-gel column. Yield, 2.0 g, (79%), $[\alpha]_D^{23}$ −50° (*c* 0.5, $CHCl_3$). IR: 1540 and 1370 (NO_2).

Found: C, 59.86; H, 7.27; N, 3.50%. Calcd for $C_{18}H_{25}NO_7$: C, 58.84; H, 6.86; N, 3.81%.

NMR spectrum of this product showed two kinds of methoxy proton signals (δ 3.25 and 3.28) in the intensity ratio of 2:3, indicating the presence of C_5-epimers.

2,4-Di-O-acetyl-1-O-ethyl-3-O-methyl-(3,6/1,2,4,5)-5-benzyloxymethyl-6-nitrocyclohexanetetrol (9). A solution of **8** (300 mg, 0.82 mmol) in acetic acid (70%, 20 ml) was heated at 90 °C for 10 hr, and evaporated to give the de-*O*-isopropylidenated product as a sirup (260 mg). The pH of a solution of this sirup in ethanol (20 ml) was adjusted to 8.5—9 with 2M potassium hydroxide, stood for 40 hr at 30 °C, neutralized with Amberlite IR-120, evaporated to give a sirup which was fractionated on a silica-gel column (Wakogel C-200), using benzene–ethyl acetate as effluent. The purified sirupy nitrocyclitol (90 mg, 35%) was acetylated with acetic anhydride in the presence of *p*-toluenesulfonic acid as a catalyst to give **9** (70 mg, 70%). Mp 123—124 °C, $[\alpha]_D^{23}$ +45° (*c* 0.5, $CHCl_3$). IR: 1740 and 1720 (ester), 1540 and 1370 (NO_2).

Found: C, 57.67; H, 6.82; N, 3.15%. Calcd for $C_{21}H_{29}NO_9$: C, 57.39; H, 6.65; N, 3.19%.

1,2,4-Tri-O-acetyl-3-O-methyl-(3,6/1,2,4,5)-5-benzyloxymethyl-6-nitrocyclohexanetetrol (10) and Its (1,3,5/2,4,6)-Diastereomer (11). A solution of de-isopropylidenated **8** (520 mg), prepared from **8** (613 mg, 1.67 mmol) as above, and sodium bicarbonate (135 mg, 1.6 mmol) in aqueous methanol (50%, 40 ml) was stood at 30 °C for 3 days with stirring, neutralized with Amberlite IR-120, and evaporated to give a sirup which was fractionated into two nitrocyclitols [the first fraction, 160 mg (31%) and the second one, 110 mg (21%)], on a silica-gel column (Wakogel C-200) with benzene–ethyl acetate (1:1) as the effluent. Acid-catalyzed acetylation of the both nitrocyclitols gave the corresponding tri-*O*-acetate **10** (60 mg) and **11** (70 mg), respectively. **10**; mp 123—124 °C, $[\alpha]_D^{23}$ +44° (*c* 0.5, $CHCl_3$). IR: 1750 and 1730 (ester), 1545 and 1360 (NO_2).

Found: C, 55.71; H, 6.12; N, 3.05%. Calcd for $C_{21}H_{27}NO_{10}$: C, 55.62; H, 6.00; N, 3.09%.

11; mp 155—156 °C, $[\alpha]_D^{23}$ +29° (*c* 0.5, $CHCl_3$). IR: 1730 (ester), 1550 and 1360 (NO_2).

Found: C, 55.82; H, 5.98; N, 3.19%. Calcd for $C_{21}H_{27}NO_{10}$: C, 55.62; H, 6.00; N, 3.09%.

3-O-Methyl-(1,3,5/2,4,6)-5-hydroxymethyl-6-nitrocyclohexanetriol (12) and Its Tetra-O-acetate (13). A solution of *7* (1.0 g, 1.92 mmol) in 70% acetic acid (40 ml) was heated at 90 °C for 10 hr, evaporated, and the sirup obtained was redissolved in water and extracted three times with benzene. Evaporation of the water layer gave the hydrolyzed product (450 mg) as a sirup. A solution of this sirup (300 mg, 1.27 mmol) and sodium bicarbonate (106 mg, 1.26 mmol) in aqueous methanol (50%, 12 ml) was kept at 30 °C for 3 days, neutralized with Amberlite IR-120, and evaporated to give a sirup. Fractionation of this sirup on a silica-gel column with benzene–ethyl acetate gave crystalline **12**, which was recrystallized from ethanol. Yield, 110 mg (37%), mp 119—120 °C, $[\alpha]_D^{23}$ −17° (*c* 0.2, water). IR: 3540 and 3350 (OH), 1530 and 1365 (NO_2).

Found: C, 38.35; H, 6.42; N, 5.57%. Calcd for $C_8H_{15}NO_7\cdot 1/2\ H_2O$: C, 39.02; H, 6.55; N, 5.69%.

Acid-catalyzed acetylation of **12** gave the corresponding tetra-*O*-acetate in 40% yield. Mp 166—167 °C, $[\alpha]_D^{23}$ −4° (*c* 0.5, $CHCl_3$). IR: 1730 (ester), 1544 and 1360 (NO_2).

Found: C, 47.54; H, 5.84; N, 3.36%. Calcd for $C_{16}H_{23}NO_{11}$: C, 47.41; H, 5.72; N, 3.46%.

The authors arei ndebted to Mr. H. Matsumoto for NMR measurements, and members of Laboratory of Organic Analysis for microanalyses.