Ⅶ and 2.25 g. (35%) of skatole. Further elution of the column by CH_2Cl_2–AcOEt (1:1) provided 433 mg. (5.9%) of Ⅷ.

When pyridine was added to a brominated solution, small amount of I was obtained besides Ⅶ.

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Tadahiro Iwashige and Hiromichi Saeki*1 : Benzylation of Carbohydrate Derivatives in Dimethyl Sulfoxide.*2

(*Central Research Laboratories, Sankyo Co., Ltd.*[*1])

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Alkylation which is an essential procedure in the carbohydrate chemistry mainly consisting of methylation and benzylation; the former is worth structural determination and the latter is useful as an important synthetic procedure.

Various reaction conditions of benzylation have been described in the literature.[1,2] Some attempts were carried out under milder conditions recently, where silver oxide[3] or sodium hydride[4] in dimethylformamide, sodium hydride in the absence of solvent[5,6] have been employed. Further, the elegant benzylation[7] of acetyl carbohydrate derivatives has been reported. As inferred from these results obtained so far, relatively excessive basic reagents and benzyl halogenides are employed, and longer reaction periods, sometimes higher temperature, are required, and satisfactory yields are not obtained constantly depending greatly on the carbohydrate derivatives and the reaction conditions. Therefore, it is desirable for benzylation to be done with less basic reagent and benzyl halogenide, at mild temperature for a short reaction period to get good yields.

Now, it is known that the dimethyl sulfoxide promotes the rate of substitution reaction. Although several reports[8] on the more effective and competitive methylation of some monosaccharides and polysaccharides in aprotic solvents such as dimethylformamide or dimethyl sulfoxide with some basic reagents, comparing with the classical methods of Haworth[9] and Purdie,[10] have been already published, studies on the benzylation of carbohydrate derivative in dimethyl sulfoxide have not been made.

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*1 1-2-58, Hiromachi, Shinagawa-ku, Tokyo (岩重忠博, 佐伯博道).

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However, there seems to be some difficulties to do benzylation in dimethyl sulfoxide, since benzyl halogenide itself would undergo some reaction in the presence of strong basic reagents in dimethyl sulfoxide.[11]

From this point of view, the benzylation with an appropriate basic reagent in dimethyl sulfoxide was investigated in a series of carbohydrate derivatives with the increase of hydroxyl group to be benzylated and some varieties of stereochemical environment.

The derivatives described are 1,2,5,6-di-O-isopropylidene-α-D-glucofuranose (I), methyl 5-O-trityl-α-L-arabinofuranoside (II) and its β-anomer (III), methyl 6-O-trityl-α-D-glucopyranoside (IV), methyl α-D-glucopyranoside (V), methyl β-D-galactofuranoside (VI), sucrose (VII), and sodium hydride, sodium amide, sodium (potassium) hydroxide, potassium *tert*-butoxide, sodium carbonate, and silver oxide were used as basic reagents.

Benzylation was carried out under several reaction conditions, mostly general conditions, employing about 1.5 and 1.5 to 3 times calculated amount of basic reagents and benzyl chloride respectively in about 10 to 20 volume parts of dimethyl sulfoxide to the carbohydrate derivative, and all experiments were carried out at room temperature.

As summarized in Table I, almost satisfactory results were obtained in case of sodium hydride, sodium (potassium) hydroxide, and sodium amide. Incidentally, the decrease of yields was observed with increase of basic reagents and benzyl chloride in case of sodium hydride and sodium amide, as under usual reaction conditions applied so far. This decrease of the yields seems to be caused by the stilben formation through the carbene intermediate from benzyl chloride.[11] The marked decrease of yield was also observed in the benzylation of sucrose with sodium amide, probably due to the formation of unidentified side products. In case of potassium *tert*-butoxide, I was benzylated with the fairly good yields, but the yield seems to decrease with the increase of hydroxyl group to be benzylated, and so no further study was made. In addition, sodium carbonate and silver oxide were not effective for benzylation of I even in prolonged reaction periods. Consequently, the satisfactory results were obtained with sodium hydride, sodium (potassium) hydroxide, and sodium amide, especially with these first two.

Table I. Yield[a] of Benzylation in Dimethyl Sulfoxide

Compound	NaH	NaOH (KOH)	$NaNH_2$	*t*-BuOK	Na_2CO_3	Ag_2O	Product
1,2;5,6-di-O-isopropylidene-α-D-glucofuranose (I)	93[b] (1)[c]	95(KOH) (1)	96.5 (1.5)	81.5 (3)	0 (4)	0 (4)	3-O-benzyl-1,2;5,6-di-O-isopropylidene-α-D-glucofuranose (VIII)
Methyl 5-O-trityl-α-L-arabinofuranoside (II)	98 (2)	92.5 (2)	88 (2)	58 (3)			Methyl 2,3-di-O-benzyl-5-O-trityl-α-L-arabinofuranoside (IX)
Methyl 5-O-trityl-β-L-arabinofuranoside (III)	85 (3)						Methyl 2,3-di-O-benzyl-5-O-trityl-β-L-arabinofuranoside (X)
Methyl 6-O-trityl-α-D-glucopyranoside (IV)	92						Methyl 2,3,4-tri-O-benzyl-6-O-trityl-α-D-glucopyranoside (XI)
Methyl α-D-glucopyranoside (V)	95.5 (2)	95 (2)	96.5 (2)				Methyl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside (XII)
Methyl β-D-galactofuranoside (VI)	91 (2.5)						Methyl 2,3,5,6-tetra-O-benzyl-β-D-galactofuranoside (XIII)
Sucrose (VII)	98 (2.5)	85 (2.5)	60 (2)				Octa-O-benzylsucrose (XIV)

a) Yield obtained after the purification by chromatography or recrystallization.
b) Yield in %.
c) Reaction time in hour, required after the addition of benzyl chloride.

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Experimental

General Procedures——Initially, about 1.5 times calculated amount of basic reagent was added into dimethyl sulfoxide in nitrogen atmosphere and the dimethyl sulfoxide solution of carbohydrate derevative was added dropwise and further stirred at room temperature over a period of 30 minutes to an hour to complete the salt formation of derivative. Then, about 1.5 to 3 times calculated amount of benzyl chloride was added dropwise and further stirred for 1 to 3 hr. Totally, 10 to 20 volume parts of dimethyl sulfoxide to the starting carbohydrate derivative was employed. Sometimes, occasional cooling is necessary when the moderate heat evolution occurs. Finally, the reaction mixture was poured into 2 to 3 volume parts of ice water and extracted with ether. The etheral solution was dried, evaporated and a purified product was obtained from the residue by chromatographic procedure or recrystallization. The typical examples of experiment are described below.

3-O-Benzyl-1,2,5,6-di-O-isopropylidene-α-D-glucofuranose (VIII)——The sodium hydride (2.75 g.) was added into dimethyl sulfoxide (40 ml.), stirring under nitrogen atmosphere and 1,2,5,6-di-O-isopropylidene-α-D-glucofuranose (I) (15 g.) in dimethyl sulfoxide (40 ml.) was added dropwise and further stirred at room temperature for 30 min. Then, benzyl chloride (18.3 g.) was added dropwise and stirred at room temperature for an hour. The reaction mixture was poured into ice water (200 ml.) and extracted with ether. The etheral solution was dried with anhydrous magnesium sulfate and evaporated off. The residue was chromatographed on silica gel (450 g.), eluting with benzene to get the syrupy compound (VIII) (18.8 g.), $[\alpha]_D^{20}$ −27.7°(c=3.32, EtOH) : lit. $[\alpha]_D^{24}$ −25.5°(c=0.5, EtOH)[3] : $[\alpha]_D^{28}$ −28.3°(c=1.3, EtOH).[12] *Anal.* Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found : C, 65.16; H, 7.65.

Methyl 2,3-Di-O-benzyl-5-O-trityl-α-L-arabinofuranoside (IX)——The powdered sodium hydroxide (0.94 g.) was added into dimethyl sulfoxide (10 ml.), stirring under nitrogen atmosphere and methyl 5-O-trityl-α-L-arabinofuranoside[13] (II) (3.0 g.) in dimethyl sulfoxide (20 ml.) was added dropwise and further stirred at room temperature for an hour. Then, benzyl chloride (6.0 g.) in dimethyl sulfoxide (15 ml.) was added dropwise and further stirred at room temperature for 2 hr. and the reaction mixture was poured into ice water (100 ml.), extracted with ether. The etheral solution was dried, evaporated off. The syrupy residue was chromatographed on silica gel (100 g.), eluting with benzene to get the syrupy benzylated product after the removal of excessive benzyl chloride. The syrupy product was triturated with methanol containing a small amount of ethyl acetate to get methyl 2,3-di-O-benzyl-5-O-trityl-α-L-arabinofuranoside (IX) (4.0 g.), m.p. 80~81°, $[\alpha]_D^{27}$ −41.2°(c=3.3, $CHCl_3$).[13] *Anal.* Calcd. for $C_{39}H_{38}O_5$: C, 79.84; H, 6.53. Found : C, 79.69; H, 6.48.

Methyl 2,3-Di-O-benzyl-5-O-trityl-β-L-arabinofuranoside (X)——According to the preparation of VIII, the syrupy compound (X), $[\alpha]_D^{27.5}$ +31.3°(c=2.94, $CHCl_3$)[13] was obtained in yield of 85%. *Anal.* Calcd. for $C_{39}H_{38}O_5$: C, 79.84; H, 6.53. Found : C, 80.07; H, 6.33.

Methyl 2,3,4-Tri-O-benzyl-6-O-trityl-α-D-glucopyranoside (XI)——According to the preparation of VIII, the syrupy compound (XI), $[\alpha]_D^{20}$ +17.9°(c=2.96, $CHCl_3$) was obtained in yield of 92%. *Anal.* Calcd. for $C_{47}H_{46}O_6$: C, 79.86; H, 6.56. Found : C, 79.87; H, 6.67.

Methyl 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranoside (XII)——The sodium amide (2.58 g.) was added into dimethyl sulfoxide (15 ml.), stirring under nitrogen atmosphere, and methyl α-D-glucopyranoside (V) (2.0 g.) in dimethyl sulfoxide (25 ml.) was added dropwise and further stirred at room temperature for an hour, then benzyl chloride (16.7 g.) was added dropwise, stirred at room temperature for 2 hr. The reaction mixture was poured into ice water (100 ml.), extracted with ether. The etheral solution was dried and evaporated off. The residue was chromatographed on silica gel (200 g.), eluting with benzene to remove mainly excessive benzyl chloride, then with ethyl acetate-benzene (3:97) to obtain the syrupy methyl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside (XII) (5.25 g.), $[\alpha]_D^{20}$ +23.8°(c=3.42, $CHCl_3$) : lit. $[\alpha]_D^{25}$ +32.2°(c=5, $CHCl_3$)[14] : $[\alpha]_D^{25}$ +18.7° (c=1.5, $CHCl_3$).[5] *Anal.* Calcd. for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found : C, 76.09; H, 6.91.

Methyl 2,3,5,6-Tetra-O-benzyl-β-D-galactofuranoside (XIII)——According to the preparation of VIII, the syrupy compound (XIII), $[\alpha]_D^{20}$ −49.2°(c=2.97, $CHCl_3$) was obtained in yield of 91%. *Anal.* Calcd. for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found : C, 75.81; H, 7.05.

1,3,4,6-Tetra-O-benzyl-β-D-fructosyl-2,3,4,6-tetra-O-benzyl-α-D-glucoside (Octa-O-benzyl-sucrose) (XIV)——The sodium hydride (1.68 g.) was added into dimethyl sulfoxide (15 ml.), stirring under nitrogen atmosphere and the sucrose (2.0 g.) in dimethyl sulfoxide (25 ml.) was added dropwise and further stirred at room temperature for 40 min. The benzyl chloride (16 g.) was added dropwise and further stirred at room temperature for 2.5 hr. The reaction mixture was poured into ice water (100 ml.), extracted with ether. The etheral solution was dried, evaporated off. The residue was chromatographed on silica gel (200 g.), eluting with benzene initially to remove mainly excessive benzyl chloride, then with ethyl acetate-benzene

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(3:97) to get the octa-O-benzyl-sucrose (XIV) (6.05 g.), $[\alpha]_D^{20}$ +38.6° (c=1.62, $CHCl_3$): lit. $[\alpha]_D^{26}$ +31.6° (c=1.65, $CHCl_3$).[5] *Anal.* Calcd. for $C_{68}H_{70}O_{11}$: C, 76.81; H, 6.63. Found: C, 77.11; H, 6.79.

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Jun-ichi Matsumoto and Shinsaku Minami*1 : Studies on Nitrofuran Derivatives. Ⅷ.*2 Synthesis of 3-(5-Nitro-2-furyl)isoxazoles.

(*Research Laboratory, Dainippon Pharmaceutical Co., Ltd.*[1])

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In our previous paper,*2 the synthesis of 3-(5-nitro-2-furyl)-Δ^2-isoxazolines and -isoxazoles which involved the 1,3-dipolar cycloaddition reactions of 5-nitro-2-furonitrile oxide (Ⅴ) with various enamines was reported. The excellent antibacterial activities of these nitrofuran derivatives prompted us further study on the synthesis of this class of the compounds. The present paper deals with the synthesis from 5-nitro-2-furhydroxamoyl chloride[1] (Ⅰ) and compounds containing active methylene groups.

As one of the methods for the preparation of isoxazoles, Quilico[2] has studied a reaction of hydroxamoyl chlorides with active methylene compounds. Application of this reaction to the hydroxamoyl chloride (Ⅰ) using β-keto esters, β-diketones and β-keto nitriles led to the formation of a series of 4,5-di-substituted 3-(5-nitro-2-furyl)isoxazoles (Ⅳ). The reaction was carried out effectively by mixing equimolar amounts of the hydroxamoyl chloride (Ⅰ) and the sodium salt (Ⅱ or Ⅲ) of the active methylene compound at low temperature.

The hydroxamoyl chloride (Ⅰ) reacted readily with sodioacetoacetates and sodiobenzoylacetate to give 5-methyl-3-(5-nitro-2-furyl)-4-isoxazolecarboxylates (Ⅳa and Ⅳb) and ethyl

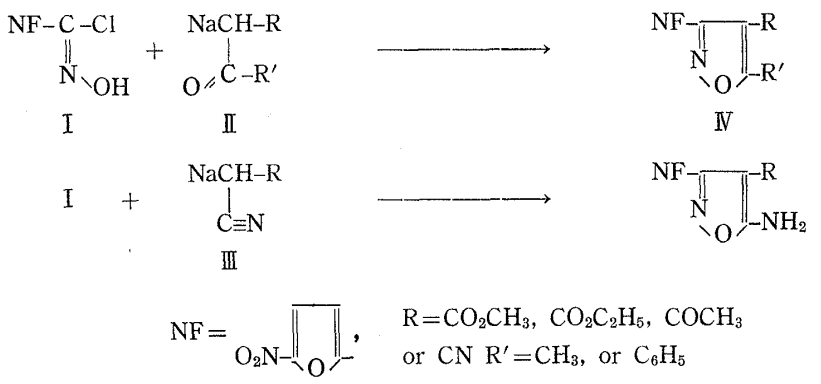

Chart 1.

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*1 Ebie, Fukushima-ku, Osaka (松本純一, 南 新作).

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2) A. Quilico: "The Chemistry of Heterocyclic Compounds" A. Weissberger Ed., 19 (1962), John Wiley & Sons, Inc., New York, and references cited therein.