The Formic Acid–Formaldehyde Methylation of Amines[1]

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The formic acid–formaldehyde methylation of benzylamines has been investigated relative to reaction parameters and competing reactions. The formation of tertiary amine is favored over secondary amine, even when less than stoichiometric amounts of formaldehyde are used. Excess formaldehyde gives only a small increase in the tertiary amine yield. Formation of benzaldehyde is markedly reduced by the addition of sodium formate, presumably through enhancement of the reduction step of the methylation sequence. The absence of acid or specific base catalysis of the aldehyde formation along with a substituent effect trend suggests that the carbonyl side product results from hydrolysis of a benzylideneamine formed in an oxidation–reduction sequence of primary amine and Schiff base.

Although the formic acid–formaldehyde (Eschweiler–Clarke[2,3]) methylation of amines is a method of extensive synthetic utility,[4] it has received only limited critical investigation.[4a,5] In contrast to the mixtures which are often obtained through the methylation of primary amines with methyl iodide, the formic acid–formaldehyde method generally leads to good yields of the *N,N*-dimethyl tertiary amines. In some cases the formation of a carbonyl product derived from the amine can markedly reduce the useful yield.[6]

In the following, we have used benzylamines as our model and have approached the reaction from three aspects: (1) in what way do the reaction parameters affect the synthetic utility of the reaction, (2) what is the origin of the carbonyl side product, and (3) can the reaction mechanism be more clearly defined through the use of proposed intermediates and the detection of minor side products?

Results and Discussion

The formation of *N,N*-dimethylbenzylamine (**5**) from benzylamine (**1**) using formic acid–formaldehyde is expected to follow the sequence given in Scheme I. Work

SCHEME I

$$\underset{\mathbf{1}}{C_6H_5CH_2NH_2} + H_2C{=}O \rightleftharpoons C_6H_5CH_2NHCH_2OH \rightleftharpoons$$

$$\underset{\mathbf{2}}{C_6H_5CH_2N{=}CH_2} + H_2O$$

$$\mathbf{2} + HCO_2H \longrightarrow \underset{\mathbf{3}}{C_6H_5CH_2NHCH_3} + CO_2$$

$$\mathbf{3} + H_2C{=}O \rightleftharpoons C_6H_5CH_2\overset{CH_3}{\overset{|}{N}}CH_2OH \overset{H^+}{\rightleftharpoons}$$

$$\underset{\mathbf{4}}{C_6H_5CH_2\overset{CH_3}{\overset{|}{{}^+N}}{=}CH_2} + H_2O$$

$$\mathbf{4} + HCO_2H \longrightarrow \underset{\mathbf{5}}{C_6H_5CH_2N(CH_3)_2} + CO_2 + H^+$$

using ^{14}C-labeled formaldehyde or formic acid has confirmed that under the usual reaction conditions the methylation can be attributed to the formaldehyde and the reduction to the formic acid.[7]

When benzylamine (**1**) in 3 molar equiv of formic acid (88%) is allowed to react with 0.5–4.0 molar equiv of formaldehyde at 80°, the major basic product is *N,N*-dimethylbenzylamine (**5**) accompanied by small amounts of unreacted starting material **1** and *N*-methylbenzylamine (**3**). In addition, benzaldehyde (**6**), *N*-benzylformamide (**7**), *N*-benzyl-*N*-methylformamide (**8**), and *N*-methyldibenzylamine (**9**) are found. Selected reactions run at 50° provide comparable results with a considerably decreased rate of reaction.

As is illustrated in Figure 1, the yield of tertiary amine **5** increases in a nearly linear manner with increasing formaldehyde up to 1.5 molar equiv and then appears to level off somewhat below the maximum theoretical yield. Consistent with this is the corresponding decrease in primary and secondary amines, **1** and **3**, respectively, found principally as the formamides in the reaction mixture. These results demonstrate that formation of the tertiary amine **5** is the preferred reaction pathway, even when less than a stoichiometric amount of formaldehyde is utilized. The secondary to tertiary amine methylation is clearly faster than the primary to secondary amine reaction.

Formamide formation slows the methylation sequence by making the amine less available. A similar result has been observed in the related Wallach reaction.[8] When *N*-benzylformamide (**7**) is used as the starting material in an excess of formaldehyde, only about 50% of the amide is hydrolyzed and converted to further products. In this case the major reaction product is the Schiff base **2**, since insufficient formic acid is produced by the hydrolysis of **7** for complete reduction. Tertiary amine **5** and a trace of secondary amide **8** account for the formic acid released.

In order to demonstrate the importance of the Schiff base **2** in the proposed reaction scheme, a run using preformed **2** was carried out under the usual reaction conditions. As shown in Table I, the results are very similar to a run starting with benzylamine (**1**).

The formation of a carbonyl product, in this case benzaldehyde (**6**), generally is observed in the formic acid–formaldehyde methylation reaction and can reduce the synthetic utility.[6] The formation of such a carbonyl product has generally been attributed to hydrol-

(1) Acknowledgment is made to the National Science Foundation, to the donors of the Petroleum Research Fund administered by the American Chemical Society, and to the California State College, Los Angeles Foundation, for partial support of this work.

(2) W. Eschweiler, *Chem. Ber.*, **38**, 880 (1905).

(3) H. T. Clarke, H. B. Gillespie, and S. Z. Weishaus, *J. Amer. Chem. Soc.*, **55**, 4571 (1933).

(4) (a) M. L. Moore, *Org. React*, **5**, 301 (1949); (b) L. Spialter and J. A. Pappalardo, "The Acyclic Aliphatic Tertiary Amines," Memillan, New York, N. Y., 1965, p 45.

(5) A. F. Meiners, C. Bolze, A. L. Scherer, and F. V. Morriss, *J. Org. Chem.*, **23**, 1122 (1958).

(6) W. E. Parham, W. T. Hunter, R. Hanson, and T. Lahr, *J. Amer. Chem. Soc.*, **74**, 5646 (1952).

(7) W. Tarpey, H. Hauptmann, B. M. Tolbert, and H. Rapoport, *ibid.*, **72**, 5126 (1950).

(8) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).

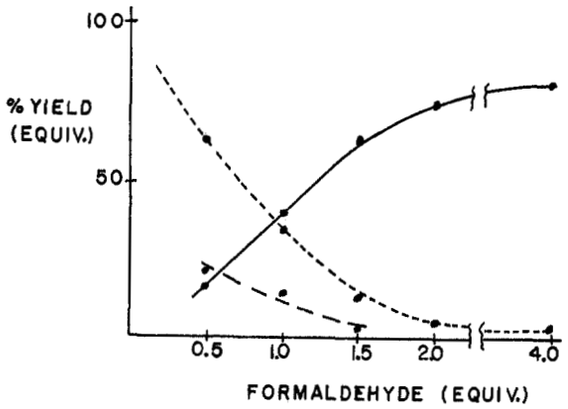


Figure 1.—Yield of primary amine + amide (------), secondary amine + amide (— —), the tertiary amine (——) as formaldehyde proportion changes.

TABLE I

COMPARISON OF PRODUCT YIELDS USING BENZYLAMINE (1) OR SCHIFF BASE 2 AS STARTING MATERIAL

Products	% yield[a] Benzylamine (1)[b]	Schiff base 2[c]
Primary amine 1	0	0
Primary amide 7	5.2	4.5
Secondary amine 3	0.1	0
Secondary amide 8	0.3	0
Tertiary amine 5	75	68
Benzaldehyde (6)	22	22
Schiff base 2		Trace

[a] Reported as equivalent per cent. [b] Reaction run for 24 hr at 80° using 1.0 equiv of 1, 2.0 equiv of formaldehyde, and 3.0 equiv of formic acid. [c] Reaction run for 24 hr at 80° using 1.0 equiv of 2, 1.8 equiv of formaldehyde, and 3.6 equiv of formic acid.

ysis of the isomerized Schiff base **10** as illustrated for our system.[3,9] Cope, *et al.*,[9] considered the stereochem-

$$\underset{\mathbf{2}}{C_6H_5CH_2N{=}CH_2} \rightleftharpoons \underset{\mathbf{10}}{C_4H_5CH{=}NCH_3} \xrightarrow{H_2O} C_6H_5CHO + CH_3NH_2$$
$$\mathbf{6}$$

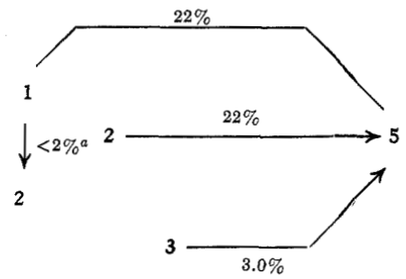
ical consequences of the isomerization by investigating the formic acid–formaldehyde methylation of optically active amines in which the asymmetric carbon atom is adjacent to the nitrogen atom. They found that the tertiary amine product showed essentially complete retention of configuration even when the appropriate carbonyl product was also formed. This suggests that the isomerized Schiff base **10** must be hydrolyzed considerably faster than it isomerizes to Schiff base **2** and that **10** is not the source of secondary amine **3**.

In order to better understand the equilibrium between Schiff base **2** and isomerized Schiff base **10** and its relationship to the carbonyl product benzaldehyde, both of these compounds were prepared and subjected to various aspects of the methylation reaction. As discussed earlier (Table I) the reaction of Schiff base **2** with formic acid–formaldehyde leads to products similar to the benzylamine reaction. On the other hand, the reaction of the isomerized Schiff base **10** with formic acid–formaldehyde leads to over 97% of benzaldehyde with less than 3% of amines observed. This indicates that the extent of isomerization of **10** to **2** must be small, consistent with the stereochemical results.[9]

In this study the benzaldehyde appears to be produced after formation of the Schiff base **2**, since very little benzaldehyde is found during the methylation of *N*-methylbenzylamine (**3**) or by the initial formation of the Schiff base.[10] The relevant data is shown in Scheme II.

SCHEME II

EQUIVALENT PER CENT OF BENZALDEHYDE FORMED IN VARIOUS STAGES OF THE METHYLATION REACTION



[a] See ref 10.

An alternate route to benzaldehyde formation might involve hydrolysis of the benzylideneamine (**11**) formed through an oxidation–reduction interaction between Schiff base **2** and primary amine **1**. This appears to be

$$\underset{\mathbf{2}}{C_6H_5CH_2N{=}CH_2} + \underset{\mathbf{1}}{C_6H_5CH_2NH_2}$$
$$\Uparrow\Downarrow$$
$$\underset{\mathbf{3}}{C_6H_5CH_2NHCH_3} + \underset{\mathbf{11}}{C_6N_5CH{=}NH}$$
$$\downarrow$$
$$C_6H_5CHO + NH_3$$
$$\mathbf{6}$$

the mechanism for aldehyde formation in the Sommelet reaction.[11]

Actually one does not expect the isomerization, **2** → **10**, to occur readily under the reaction conditions,[12] although such an isomerization can be favored with suitable compounds.[13] In order to determine if acid or specific base catalysis might be involved in such an isomerization, the methylation reaction was run with the addition of hydrochloric acid (to provide a pH below 1). No significant difference in the tertiary amine **5** to benzaldehyde (**6**) yields was observed. In contrast, the addition of 3 equiv of sodium formate to a typical methylation (to test the possibility of a specific base-catalyzed isomerization) resulted in a marked decrease in benzaldehyde (from the usual 22 to 4%). Addition of sodium acetate shows a similar but smaller reduction of aldehyde formation, presumably through the subsequent

(9) A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, *J. Amer. Chem. Soc.*, **82**, 4651 (1960).

(10) The independent formation of Schiff base **2** from **1** and formaldehyde is carried out in the absence of formic acid, thus does not exactly duplicate reaction conditions. However, benzaldehyde formation in this step is unexpected.

(11) (a) S. J. Angyal, D. R. Penman, and G. P. Warwick, *J. Chem. Soc.*, 1742 (1953); (b) S. J. Angyal, *Org. React.*, **8**, 197 (1954); (c) V. Franzen, *Justus Liebigs Ann. Chem.*, **600**, 109 (1956); (d) H. R. Snyder and J. R. Demuth, *J. Amer. Chem. Soc.*, **78**, 1981 (1959).

(12) (a) J. R. Demuth, *Diss. Abstr.*, **16**, 235 (1956); (b) F. G. Baddar and Z. Iskander, *J. Chem. Soc.*, 203 (1954).

(13) E. J. Corey and K. Achiwa, *J. Amer. Chem. Soc.*, **91**, 1429 (1969).

increase in formate. It appears that formate, acting as the reducing agent, increases the relative rate of secondary (and subsequently tertiary) amine formation at the expense of the pathway to the carbonyl product. This may be a useful technique for increasing the synthetic utility of the reaction.

We have also carried out the methylation reaction with a series of substituted benzylamines. One would predict that election-withdrawing groups would favor the isomerization route to the aldehyde (**2** → **10** → **6**),[12b] while they would inhibit the transfer of hydride required for the oxidation–reduction pathway (**1** → **11** → **6**). Our results (Table II) indicate a small effect. The

TABLE II

INFLUENCE OF SUBSTITUENT ON TERTIARY AMINE *vs.* ALDEHYDE FORMATION WITH SUBSTITUTED BENZYLAMINES

Substituent[a]	% tertiary amine	% aldehyde	Ratio
p-OCH_3	75	23	3.2
p-CH_3	74	14	5.3
m-CH_3	79	19	4.2
H	76	22	3.5
m-OCH_3	85	15	5.7
p-Cl	86	9	9.5
m-Cl	85	7	12.1

[a] Arranged in increasing electron-withdrawing influence: C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 2, 323 (1964), and ref 14.

trend is, in general,[14] consistent with electron-withdrawing groups decreasing the relative amount of aldehyde formation as expected for the oxidation–reduction isomerization pathway.[15]

In the methylation reactions of benzylamine (**1**), a small amount of *N*-methyldibenzylamine **9** (<2%) is observed. This product presumably arises from a typical Wallach reaction[8] of the benzaldehyde (**6**) and *N*-methylbenzylamine (**3**) formed during the reaction.

$$\underset{\mathbf{6}}{C_6H_5CHO} + \underset{\mathbf{3}}{C_6H_5CH_2NHCH_3} \xrightarrow{H^+}$$

$$C_6H_5CH{=}\overset{+}{N}(CH_3)CH_2C_6H_5 \xrightarrow{HCO_2H} \underset{\mathbf{9}}{(C_6H_5CH_2)_2NCH_3} + CO_2 + H^+$$

Interestingly, the reaction of the isomerized Schiff base **10** with formic acid in the presence of water[16] yields a significant amount of **9** (see Table III). In this case the

TABLE III

REACTION OF ISOMERIZED SCHIFF BASE **10** WITH FORMIC ACID

Product	Equivalent %
6	34
9	17
3	2
10 (recovered)	23

(14) The results are based on final product analysis, thus are not expected to follow substituent values closely. It is, however, surprising that the methyl substituents are somewhat out of the expected order.

(15) Snyder and Demuth[11d] propose hydride loss from the nitrogen atom rather than the carbon atom in the Sommelet reaction. This is a surprising conclusion since one would expect a positive center at carbon to be favored. We believe that their results are not sufficiently internally consistent to strongly support this suggestion. Work with deuterium labeled benzylamines also supports hydride loss from the benzyl position.[11c]

(16) To account for the water normally present from the 36% formaldehyde.

large amount of benzaldehyde formed readily combines with the secondary amine **3** formed by reduction.

Conclusions

It appears that the use of excess formaldehyde in the methylation reaction is synthetically wasteful since the tertiary amine yield is not significantly improved. The use of pre-formed Schiff base does not improve the desired reaction although amide formation may be reduced. The addition of sodium formate is a simple technique for favoring the methylation at the expense of the carbonyl side product. The pathway to the aldehyde side product is best explained as due to the hydrolysis of the benzylideneamine formed through an oxidation–reduction sequence of Schiff base **2** and tertiary amine **1**.

Experimental Section

Benzylamine and 36% formaldehyde were obtained from Matheson Coleman and Bell, and 88% formic acid from Mallinckrodt. The substituted benzylamines were obtained commercially with the exception of the *m*-methoxyl compound which was obtained through sodium–ethanol reduction of the corresponding oxime. Analyses were carried out using an F & M Model 720 gas chromatograph. An 11-ft 15% Carbowax 20M on Anachrome U column was used for analysis of the amines and an 8-ft 10% Ucon 50 on Chromosorb WAW column was used for the amides, benzaldehyde, and *N*-methyldibenzylamine. Peak areas were determined by a Disc integrator and independently determined, correction factors were applied to obtain the final analysis. Where appropriate, independent synthesis was used for product identification. Infrared spectra were obtained as solutions in CCl_4 or $CHCl_3$ using a Perkin-Elmer Infracord. Nucler magnetic resonance spectra were obtained using a Varian A-60 spectrometer in CCl_4 or $CDCl_3$ and are reported as downfield from internal TMS.

Typical Methylation.—To a 25-ml round-bottom flask is added 5.0 g (0.05 mol) of benzylamine. The flask is cooled in an ice bath and 7.2 g (0.15 *M*) of 88% formic acid is slowly added followed by 10.2 g (0.13 mol) of 36% formaldehyde. The flask is equipped with a magnetic stirrer and a condenser and placed in an 80° constant temperature bath for 24 hr. Bubbling begins very soon and continues to a noticeable extent for about 3 hr. The mixture is cooled and 15 ml of 6 *N* HCl is added. The mixture is extracted three times with 15 ml of ethyl ether, and the combined ether extracts are washed with 5 ml of water and then dried over magnesium sulfate. Evaporation gives 0.36 g of nonbasic material. The aqueous layer is made basic with 50% aqueous sodium hydroxide and extracted three times with 15-ml portions of ethyl ether. The ether layers are combined and washed with 5 ml of water and then dried over anhydrous magnesium sulfate. The ether is removed under vacuum giving 5.8 g of basic material.

Methylenebenzylamine (**2**).—To 10.0 g (0.09 mol) of benzylamine was added 0.2 mol of 36% formaldehyde, and the mixture was heated for 24 hr at 80°. An acid–base extraction of the product gave 0.6 g of nonbasic material and 11.1 g of basic material: bp 94° (1.1 mm) [lit.[11a] bp 100–130° (1 mm)]; nmr ($CDCl_3$) δ 3.38 (s, 2, $N{=}CH_2$),[17] 3.60 (s, 2, $C_6H_5CH_2$),[17] 7.23 (m, 5, C_6H_5).

***N*-Methyl-*N*-benzylformamide** (**8**).—To 5.0 g (0.04 mol) of *N*-methylbenzylamine was added 6.5 g (0.12 mol) of 88% formic acid, and the mixture was heated for 24 hr at 80°. The product was recovered by ether extraction to give 6.0 g (99%) of **8**: bp 133° (750 mm); ir (CCl_4) 3000 (amide CH), 1680 (C=O); nmr (CCl_4) δ 2.70 (d, 3, $=CH_3$), 4.37 (d, 2, $C_6H_5CH_2$), 7.20 (m, 5, C_6H_5), 8.10 (d, 1, HC=O).

***N*-Benzylformamide** (**7**) was prepared from 88% formic acid and benzylamine as above: mp 59–60° (lit.[18] mp 59.8–60.4°);

(17) Assignments based on the assumption that **2** is a cyclic trimer.[11a]

(18) C. A. Buehler and C. A. Mackenzie, *J. Amer. Chem. Soc.*, **59**, 421 (1937).

ir (CCl_4) 3570 (NH), 3050 (amide CH), 1700 (C=O); nmr (CCl_4) δ 4.30 (d, 2, $C_6H_5CH_2$), 7.27 (m, 6, C_6H_5 and NH), 8.12 (s, 1, HC=O).

N-**Methyldibenzylamine** (**9**).—To 5.0 g (0.025 mol) of dibenzylamine was added 0.037 mol of 88% formic acid and 0.025 mol of 36% formaldehyde. The mixture was allowed to react for 24 hr at 80° and worked up under typical methylation conditions (see above) to give 4.5 g (84%) of **9**: bp 277° (750 mm) [lit.[19] bp 304–305° (765.5 mm)]; nmr (CCl_4) δ 2.05 (s, 3, CH_3), 3.42 (s, 4, $C_6H_5CH_2$), 7.23 (s, 10, C_6H_5).

Benzylidenemethylamine (**10**) was obtained commercially from Aldrich: nmr (CCl_4) δ 3.39 (d, 3, J = 1.5 Hz, NCH_3), 7.3–7.7 (m, 5, C_6H_5), 8.13 (m, 1, C_6H_5CH).

Registry No.—**2**, 4393-14-0; **7**, 6343-54-0; **8**, 17105-71-4; **9**, 102-05-6; formic acid, 64-18-6; formaldehyde, 50-00-0.

(19) Dictionary of Organic Compounds, Oxford University Press, London, 1965, p 2181.

Studies in the Ganglioside Series. VI. Synthesis of the Trisaccharide Inherent in the Tay–Sachs Ganglioside[1]

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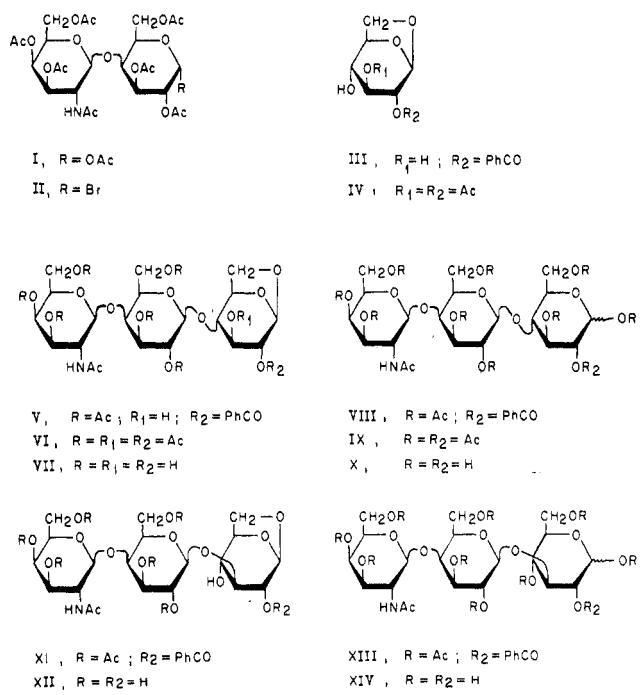
The synthesis of 2-acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→4)-D-glucopyranose (X) is reported. It involves the Koenigs–Knorr reaction of 2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-α-D-galactopyranosyl bromide (II) with 1,6-anhydro-2,3-di-*O*-acetyl-β-D-glucopyranose (IV). Opening of the anhydro ring of the resulting 1,6-anhydro-2,3-di-*O*-acetyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranose (VI) followed by catalytic de-*O*-acetylation gave the trisaccharide X. The use of 1,6-anhydro-2-*O*-benzoyl-β-D-glucopyranose (III) as aglycon led, in addition, to the 1→3 isomer, 2-acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→3)-D-glucopyranose (XIV).

The linear carbohydrate chain inherent in the molecule of the abnormal ganglioside which accumulates in the brain with Tay–Sachs disease[2,3] was shown to have the structure X.[4–6] The trisaccharide has also been obtained by hydrolytic degradation of normal gangliosides and was named "ganglio-N-triose II."[7]

A prerequisite material for the chemical approach to this carbohydrate moiety is the amino disaccharide I, whose synthesis has been recently accomplished.[8] The establishment of a glycosidic linkage at C-4 of glucopyranose posed a problem on account of the well-known low reactivity of the hydroxyl group in this position. However, in the *1C* conformation of 1,6-anhydroglucopyranose the C-2 and C-4 hydroxyls react preferentially,[9–11] since the hydroxyl in position 3 is sterically hindered by the anhydro ring and by the C–C linkage at C-5.[9] The 2-benzoyl derivative III, which can be conveniently prepared by selective benzoylation of 1,6-anhydroglucose,[10] appeared to be a suitable aglycon. Surprisingly, its condensation with the bromide II gave rise to the formation of both isomers V and XI in about equal amounts. Their separation proved to be difficult and time consuming but was eventually achieved by a combination of silica gel and silica gel G columns. Even so, part of the products was eluted as a mixture. The chromatographically pure oily isomers were eventually obtained in crystalline form and showed in the nmr spectrum the correct ratio of acetyl to phenyl protons.

During the course of our studies we found that 2,3-di-*O*-acetyl-1,6-anhydroglucose (IV) is an excellent aglycon for the unambiguous synthesis of oligosaccharides involving glycosidation at C-4 of glucose.[12] Thus,



lactose may be obtained in good yield. Likewise satisfactory was the synthesis of an amino disaccharide as a model, *viz.*, 2′-deoxy-2′-acetamidocellobiose.[13] Similarly, it was now found that the Koenigs–Knorr reaction of IV with II afforded the desired 1→4 isomer VI in a 56% yield.

The continuation of the synthesis involved opening of the 1,6-anhydro ring by means of acetic anhydride

(1) This work was supported by the U. S. National Institutes of Health, PL 480, Agreement No. 425115.

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