The Swamping Catalyst Effect. VIII.
The Rearrangement of Methylated and Brominated Phenols[1]

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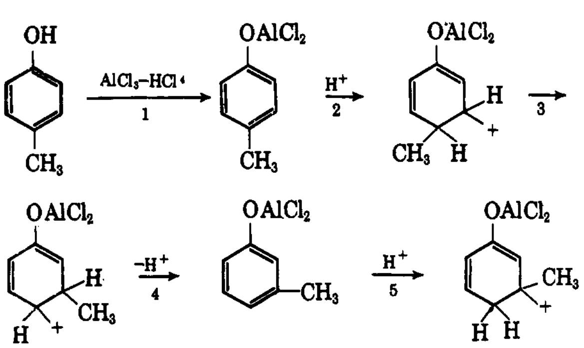
In the presence of aluminum chloride and the co-catalyst, hydrogen chloride, *p*-cresol has been rearranged to an equilibrium mixture of 80% *m*- and 20% *p*-cresol; 2,4-, 3,4-, and 2,5-dimethylphenols to 3,5-dimethylphenol; 2,4,5-, 3,4,5-, and 2,4,6-trimethylphenols to 2,3,5-trimethylphenol; and 2,3,4,6-tetramethylphenol to 2,3,5,6-tetramethylphenol. It is notable that the alkyl group in the 4-position is absent from these thermodynamically favored phenols (as aluminum chloride–hydrogen chloride complexes). *p*-Bromophenol has been shown to rearrange similarly to about 54% of the *meta* isomer. Furthermore, bromination of phenol in the aluminum chloride–hydrogen chloride environment has been shown to take place in the *para* position followed by rearrangement in a slower step to *m*-bromophenol. *p*-Toluidine does not rearrange in the aluminum chloride–hydrogen chloride system.

This paper attempts to emphasize the importance of the presence of hydrogen ions in bringing about rearrangements in methylated or brominated phenols. These reactions are reversible and depend on protonic attack at the substituted position as shown for step 2 below. Furthermore, the reactions involving methyl migrations are free of disproportionation products because the methyl group is unique among alkyl groups in rearranging in Friedel–Crafts reactions by an intramolecular process under proper conditions.[5] Previous to the present work on phenol rearrangements, the presence of hydrogen chloride in aluminum chloride has been adventitious—being derived from moisture contamination of aluminum chloride or purposeful addition of a few drops of water to "activate" the aluminum chloride. Baddeley[6] and Meissner and French[7] studied the rearrangement of *p*-cresol with excess aluminum chloride in this way and obtained an equilibrium mixture of about 60% *m*- and 40% *p*-cresol. Baddeley, in a later paper,[8] recognized the importance of hydrogen chloride by observing that removal of hydrogen chloride gave much less rearrangement, but he did not perform the *coup de grace* of adding hydrogen chloride to the *p*-cresol–aluminum chloride complex. Thus, since 1950 the impression has remained that the cresols with aluminum chloride form an equilibrium mixture of 60% *m*- and 40% *p*-cresol.



In our initial studies on the addition of hydrogen chloride to the cresol–aluminum chloride complex, it was apparent from the beginning that the reaction was different. A more homogeneous solution was formed, and the rate of rearrangement was faster. Indeed, with polymethylphenols and excess aluminum chloride, introduction of hydrogen chloride gave completely homogeneous solutions. The equilibrium position for the cresol–aluminum chloride complex saturated with hydrogen chloride was 80% *m*- and 20% *p*-cresol, requiring about 15 hr. at 120° to reach this state starting with either pure *p*- or *m*-cresol. These conditions for rearrangement are quite drastic in comparison with hydrocarbon rearrangement and suggest strong deactivation of the ring by complexation of the hydroxyl group. Indeed, boron trifluoride and liquid hydrogen fluoride fail to give any rearrangement of *p*-cresol. It is our opinion from this work that many different "equilibrium" positions exist for the *p*- and *m*-cresol–acid systems depending on the strength and concentration of the acid. The aluminum chloride–hydrogen chloride system has been found to yield the most *m*-cresol.

The *o*-cresol–aluminum chloride–hydrogen chloride complex at 120° showed rearrangement but at the same time was converted to resinous products which detracted from the usefulness of the reaction. The polymethylphenols in the presence of excess aluminum chloride and hydrogen chloride rearranged more rapidly and more completely than the cresol complexes as shown schematically (see Table I for details). It is

2,4-, 3,4-, 2,5-dimethylphenols ⟶ 3,5-dimethylphenol

2,4,5-, 3,4,5-, 2,4,6-trimethylphenols ⟶ 2,3,5-trimethylphenol

2,3,4,6-tetramethylphenol ⟶ 2,3,5,6-tetramethylphenol

significant that the thermodynamically stable products in these rearrangements have no methyl groups in the 4-position. The interpretation is that protonation occurs more extensively in the 4-position, favoring removal of the methyl group from this position (see step 2 of earlier equations). Furthermore, *m*-cresols, in contrast to *o*- and *p*-cresols, in the aluminum chloride–hydrogen chloride medium, are more stable as cations since tertiary carbonium ions are present as shown for 3,5-dimethylphenol. The fact that 3,4-dimethyl-

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[1] Paper VII: D. E. Pearson and C. R. McIntosh, *J. Chem. Eng. Data*, **9**, 245 (1964).

[2] Tennessee Eastman Fellow in 1964 and Socony Mobil Oil Fellow in 1963. This paper was abstracted from the Ph.D. Thesis of L. F. in which considerably more experimental detail is to be found.

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[4] When phenol is added to aluminum chloride without cooling, hydrogen chloride is evolved yielding the product of step 1. The hydrogen chloride evolved is not easily absorbed by the reaction mixture in this step, but, by passing hydrogen chloride continuously through the molten mixture, 1 equiv. is absorbed.

[5] G. A. Olah, M. W. Meyer, and N. A. Overchuk, *J. Org. Chem.*, **29**, 2313 (1964). Under more strenuous conditions, methyl groups do undergo intermolecular rearrangements.

[6] G. Baddeley, *J. Chem. Soc.*, 527 (1943).

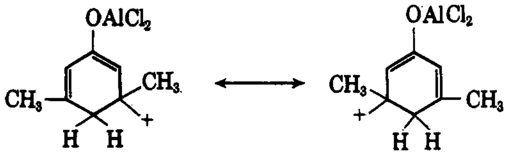
[7] H. P. Meissner and R. E. French, *J. Am. Chem. Soc.*, **74**, 1000 (1952).

[8] G. Baddeley, *J. Chem. Soc.*, 994 (1950).

TABLE I

REARRANGEMENT OF METHYLATED PHENOLS

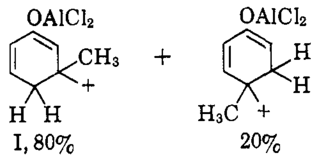
Expt.	Phenol	Temp., °C.	Time, hr.	Cresol, % *m*	*p*	*o*
1	4-Methyl	120	12	85	15	
			22	82	18	
2	3-Methyl	105	12	86	14	
			36	80	20	
			60	78	22	
3	2-Methyl	120	5	13	2	85
			8	31	4	65
			11	39	7	54
				Xylenol, % 3,5-	Others	
4	2,5-Dimethyl	130	12	91	2,5-, 9	
5		105	10	34	65	
6	2,4-Dimethyl	130	14	93	2,4-, 7	
7		105	20	50	50	
8	3,4-Dimethyl	105	10	87	3,4-, 5; 2,4- or 2,5-, 4 3-, 2; 2,3,5-, 2	
				Trimethylphenol, % 2,3,5-	Others	
9	3,4,5-Trimethyl	105	10	90	3,5-, 5; 2,3,5,6-, 5	
10	2,4,6-Trimethyl	105	20	100		
11	2,4,5-Trimethyl	105	15	78 by actual isolation		



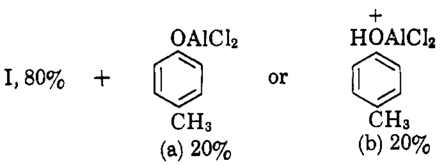
phenol rearranges faster than 2,5-dimethylphenol supports this view also. In the former phenol, a *p*-methyl group migration takes place in which *para* protonation is more prevalent than *ortho;* in the latter an *o*-methyl group migration occurs.

The question arises in methylation of phenol in excess aluminum chloride whether substitution of the phenol takes place *para* and then migration follows to the *meta* position, or whether direct *meta* substitution occurs. This question could not be answered because polymethylation could not be suppressed. Under conditions where substantial amounts of phenol remained, over 50% of the product was 3,5-dimethyl- and 2,3,5-trimethylphenols. This question could be answered, however, by study of the bromination of phenol, where polybrominated phenols do not form. The rearrangement of bromine in bromophenols has not been studied previously although many references are recorded on the rearrangement and disproportionation of halogen in other compounds.[9] It was found that an equilibrium mixture of 54% *m*- and 46% *p*-bromophenol was formed from the *p*-bromophenol-aluminum chloride complex saturated with hydrogen chloride in 9 hr. at 130°. Bromination of phenol–aluminum chloride–hydrogen chloride under identical conditions except for a 1-hr. time lapse gave 81% *p*-, 12% *m*-, and 7% *o*-bromophenol (8% of the *m*- would have originated from the *p*-bromophenol by migration within this time). Thus, it is apparent that the bromine atom enters the *para* position, at least to the extent of 89%, and migrates to the *meta* position in a slower reaction.

A more subtle question to answer is whether the protonation is complete where, for example, in the cresol–aluminum chloride-hydrogen chloride complex, 80% of the protonation is in the *para* position and 20% in the *meta* position as in (1) below, thus yielding the inverse ratio of products (*i.e.*, *para* protonation yielding *meta* product) or where 80% of the complex is protonated and 20% is free from protonation as a simple cresol–aluminum chloride complex as in (2a) or is protonated at the oxygen atom as in (2b). The implication of the first view where products in (1) are shown is that any excess acid or any stronger acid will not change the equilibrium beyond the 80% *meta*, 20% *para* mixture while the implication from the latter view [products (2)] is that the *p*-cresol (and *p*-bromophenol) rearrangement can be carried to completion. One argument in favor of viewpoint 1 is that the amount of hydrogen chloride absorbed seems to be exactly equivalent to the amount of the phenol–aluminum chloride complex. On the other hand, the result with *p*-bromophenol in which the equilibrium lies closer to the starting materials is an argument in favor of viewpoint 2, since *p*-bromophenol is less basic than *p*-cresol and should be protonated to a lesser extent. Furthermore, the cresol–aluminum chloride-hydrogen chloride complex is the only nonhomogeneous mixture encountered in this study, indicating incomplete protonation. If viewpoint 2 is correct, therefore, the complex under increased hydrogen chloride pressure should yield more *m*-cresol. This experiment remains to be done.



(1)



(2)

We have pointed out that the phenol-aluminum chloride complex protonates at a position other than the oxygen atom and most frequently at the *para* position of the ring. A confirmation of this view comes from another experiment on the attempted rearrangement of *p*-toluidine. Alkylation was assumed to be a reversible reaction for all aromatic nuclei including the toluidine nucleus. Much to our surprise *p*-toluidine in the presence of excess aluminum chloride and hydrogen chloride did not rearrange at all at 130° over a 24-hr. period of time. Protonation in the aniline and phenol systems, then, must be quite different, the former occurring at the nitrogen atom where rearrangement is not facilitated and the latter at the nuclear positions where rearrangements are brought about.

Experimental

General Rearrangement Procedure.—The reaction vessel was a round-bottom, three-neck flask equipped with ball and socket seal stirrer having high-torque motor and with off-set adapter

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[9] References in paper by J. W. Crump and G. A. Gornowicz, *J. Org. Chem.*, **28**, 949 (1963). In these papers, the rearrangement reaction is treated as intermolecular, where free bromine or a bromine cation is formed. We wish to point out that in rearrangement of *p*-bromophenol only traces of disproportionation products were found, which suggests an intramolecular migration.

holding thermometer and condenser. The apparatus was assembled while hot and protected by drying tubes. The hydrogen chloride evolved was led to a water trap *via* the condenser. About 0.2 mole of anhydrous aluminum chloride (resublimed grade) was introduced directly from container to flask (the container being weighed before and after) and 0.1 mole of phenol was added rapidly with stirring to dissipate heat. The slurry was warmed to the desired temperature (usually 60°) while dry hydrogen chloride was passed underneath the surface of the reaction mixture. The mixture, except in the case of the cresols, became homogeneous as the solution became saturated with hydrogen chloride. The color varied from light yellow to dark red. After being held at selected temperatures for the desired length of time with very slow addition of hydrogen chloride, the mixture was allowed to cool to room temperature and poured onto a slurry of ice and water with vigorous stirring. Large volumes of hydrogen chloride were evolved in this operation. The organic phase was extracted carefully with ether (to minimize losses), the ether extract being washed with aqueous sodium bicarbonate solution and dried with anhydrous sodium sulfate. The ether then was evaporated using a Rinco rotary evaporator. The residue was weighed; a 2-g. aliquot was converted quantitatively to the methyl ether by a published procedure[10] modified by increasing the dimethyl sulfate equivalent by 50%. The sodium salt of 2,3,5,6-tetramethylphenol was too insoluble in water to convert to the methyl ether so that 10% methanolic sodium hydroxide was used in this case. The methyl ethers were extracted with ether, dried, and concentrated to about a 10-ml. vol. An aliquot (about 1–4 μl.) of the ether solution was injected into the gas chromatograph for analysis.

Gas Chromatographic Procedure.—A thermal conductivity apparatus with injection port and detector temperatures at about 250° was used. *m*- and *p*-methylanisoles could not be separated with ordinary columns so that a special column using Bentone-34 was devised to separate these isomers.

Column 1 was Bentone-34 (5%), 5% dinonylphthalate impregnated from benzene on Chromosorb P (35–80 mesh) pretreated with hexamethylsilazane in 6 ft. × 0.25 in. o.d. copper tubing, oven temperature 160°, flow rate of helium 60 cc./min., 150-ma. current, attenuation 4, sample size 2 μl. Retention time in seconds follow: anisole 138, *o*-methyl- 190, *m*-methyl- 260, *p*-methylanisole 190.

Column 2 was dinonylphthalate (5%) (all other factors the same as those of column 1). Retention time in seconds follow: anisole 128; *o*-methyl- 177; *m*-methyl- 197; *p*-methyl- 197; 2,6-dimethyl- 225; 2,4- 273, 2,5- 273, 2,3- 317, 3,5- 317, 3,4- 360, 2,4,6-trimethyl- 375; 2,4,5- 525, 2,3,5- 531, 3,4,5- 705, 2,3,5,6-tetramethylanisole 750.

Column 3 was XF-1150 (15%) (all other factors the same as those of column 1 except oven temperature of 140° and flow rate of 90 cc./min.) Retention time in seconds follow: *o*-bromo- 530, *m*-bromo- 600, *p*-bromoanisole 710. Previous reports of cresol isomer separations in g.l.c. utilize the free cresols not the methyl ethers.[11–13]

The area normalization method was employed in determining the relative percentage of each anisole in a mixture.[14] The yield was obtained by weighing the crude phenol residue from ether extraction of reaction mixture. The determination of *m*-methylanisole on the Bentone-34 column tended to be high by several per cent because of strong retention which made the Gaussian curve more diffuse. This isomer was determined on the Bentone-34 column; the *ortho* isomer, on the dinonyl phthalate column; and the *para* isomer, by difference. Five known mixtures of the cresols and phenol were carried through the methylation procedure and analyzed by gas chromatography. The average absolute error was as follows: phenol +1%, *m*-cresol +4%, *p*-cresol −4%, *o*-cresol −4%. Corrections could have been made but were not considered large enough to alter conclusions of the results. Furthermore, in a mixture containing only *m*- and *p*-cresol, the error was much less than 4%. Analysis on the dinonyl phthalate column was more accurate as shown from a typical mixture (true per cent first, analyzed per cent second): phenol 10.2, 11; *o*-cresol 7.6, 6.7; *m*- and *p*-cresol 45, 46.3; 2,6-xylenol 2.3, 2.3; 2,4-xylenol 5.0, 4.3; 3,5-xylenol 19.9, 20.4; 3,4-xylenol 10, 9.

Rearrangement of Methylated Phenols.—The results from gas chromatography are shown in Table I. The yields of crude products in all experiments except no. 3 (*o*-cresol) were above 90%. *o*-Cresol polymerized in the aluminum chloride–hydrogen-chloride mixture to such an extent that analysis of monomeric material was impossible after 11 hr. In expt. 4, the crude product was steam distilled and the solid in the distillate was recrystallized from hexane yielding 73% 3,5-xylenol, m.p. 63–64°. In expt. 6, a 79% yield of 3,5-xylenol was obtained similarly. In expt. 10, 2,3,5-trimethylphenol, m.p. 94°, was isolated in 94% yield after recrystallization from hexane. In expt. 11, the reaction was run with 0.5 mole of 2,4,5-trimethylphenol and 1.0 mole of aluminum chloride. The hydrogen chloride absorbed after the system was first flushed with nitrogen was 17.5 g. (calculated for 0.5 mole, 18.2 g.). The crude product from ice decomposition was filtered, washed, dried, and recrystallized from hexane yielding 53 g. (78%) of 2,3,5-trimethylphenol, m.p. 94–94.5°. From the mother liquors, 10 g. (15%) of 2,4,5-trimethylphenol, m.p. 70–71°, was isolated.

Rearrangement of 2,3,4,6-Tetramethylphenol.—This phenol (0.067 mole) was rearranged in the usual manner at 105° for 10 hr. The reaction mixture was decomposed with water, washed, dried, and recrystallized from hexane, yielding 8.5 g. (85%) of 2,3,5,6-tetramethylphenol, m.p. 216°, methyl ether m.p. 59–60°.

Methylation of Phenol Using Methyl Bromide as a Limiting Reagent.—Attempts were made to obtain a maximum yield of *m*-cresol from phenol. Methyl bromide (0.2 mole) was added as a vapor to the complex of phenol (0.22 mole) and aluminum chloride (0.4 mole), saturated with hydrogen chloride, and held at 105°. Four hours was taken for the addition and an additional 3 hr. for recycling the unreacted methyl bromide which was recovered in a Dry Ice trap. After the usual work-up, 21.0 g. of crude phenols was obtained (calcd., 21.6 g.) of the following composition determined by g.l.c.: 32% phenol, 2% *p*- and 6% *m*-cresol, 2% 2,4- and 2,5-xylenol, 27% 3,5-xylenol, 24% 2,3,5-trimethylphenol, and 7% 2,3,5,6-tetramethylphenol.

Rearrangement of *p*-Bromophenol to a Mixture of *m*- and *p*-Bromophenol.—*p*-Bromophenol (0.1 mole) and aluminum chloride (0.2 mole) were complexed and saturated with hydrogen chloride at 130°. Aliquots were removed each hour and analyzed by g.l.c. after the usual work-up consisting of decomposition with water, washing, drying, and conversion to the methyl ethers (Table II). No disproportionation products were present and only a trace of *o*-bromophenol could be detected.

TABLE II

Time, hr.	*p*-Bromophenol, %	*m*-Bromophenol, %
1	92	8
2	84	16
3	75	25
4	67	33
5	63	37
6	54	46
7	49	51
8	49	51
9	46	54

The identical experiment was run except that the free hydrogen chloride was swept out with dry nitrogen. At the end of 8 hr. at 130°, the mixture contained 94% *p*- and 6% *m*-bromophenol.

When the original reaction was run with 0.1 mole in place of 0.2 mole of aluminum chloride, the final product consisted of 72% *p*-, 23% *m*-, and 5% *o*-bromophenol.

Bromination of Phenol–Aluminum Chloride Complex.—The complex of phenol (0.1 mole) and aluminum chloride (0.2 mole), saturated with hydrogen chloride, was maintained at 130° while bromine (0.1 mole) was added dropwise over a period of 35 min. The mixture was maintained an additional 30 min. at 130°, cooled, poured onto ice, and extracted with ether. The ether solution was washed with water, dried, and concentrated yielding 17.0 g. of crude bromophenols (calcd., 17.3 g.), the composition of which by g.l.c. analysis was 81% *p*-, 12% *m*-, and 7% *o*-bromophenol with traces of phenol.

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(10) G. S. Hiers and F. D. Hager, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 58.

(11) R. H. Crouse, J. W. Garner, and H. J. O'Neill, *J. Gas Chromatog.*, **1**, 18 (1963).

(12) T. A. Rudol'fi, R. I. Sharapova, and V. I. Lushchik, *Zh. Analit. Khim.*, **19**, 903 (1964); *Chem. Abstr.*, **61**, 10048 (1964).

(13) J. V. Mortimer and P. L. Ghent, *Anal. Chem.*, **36**, 754 (1964).

(14) S. Del Nogare and R. S. Juvet, "Gas-Liquid Chromatography," Interscience Publishers, Inc., New York, N. Y., 1962, p. 257.

Attempted Rearrangement of *p*-Toluidine.—*p*-Toluidine (0.05 mole) and aluminum chloride (0.11 mole) were complexed, saturated with hydrogen chloride, and maintained at 127–133° for 24 hr. The mixture was poured carefully into an ice slurry of 40 g. of sodium hydroxide in water, and the amine was extracted with ether. Concentration of the ether solution gave a quantitative yield of crude amine which by g.l.c. analysis was at least 99% *p*-toluidine. The column for separation of *m*- and *p*-toluidine was 5% Bentone-34 and 0.5% XF-1150 at 160° and flow rate of 90 cc./min., attenuation 2. Retention time for *p*-toluidine was 279 sec., for *m*-toluidine 378 sec.

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Synthetic Nucleosides. LXIII.[1,2] Synthesis and Reactions of Some α-Sulfonyloxy Oxo Sugars

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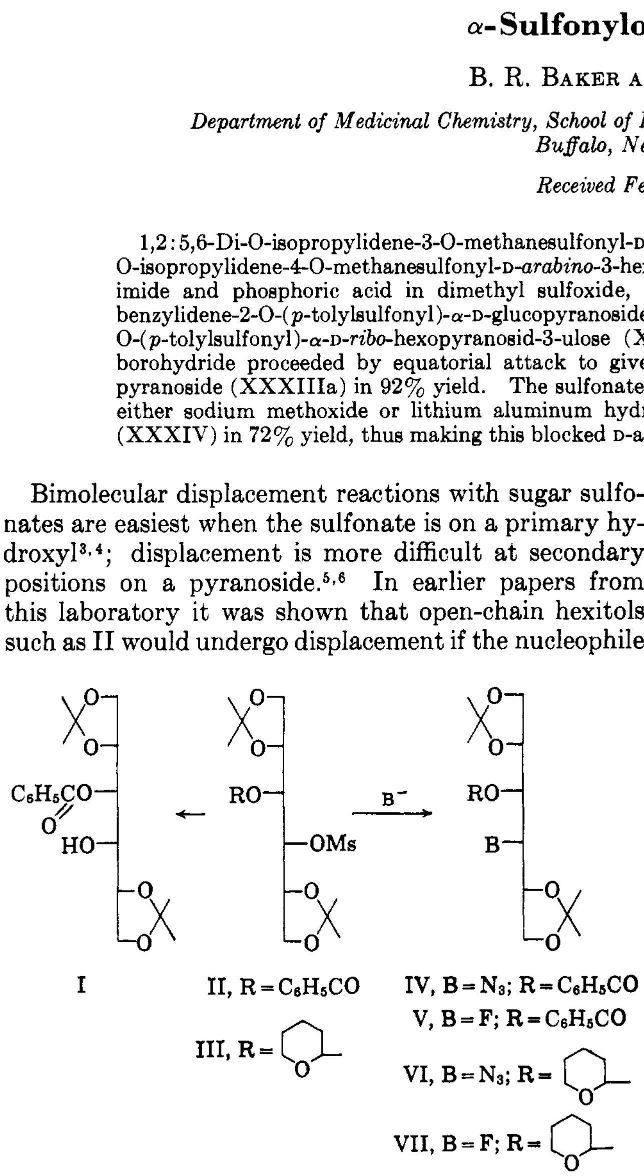
1,2:5,6-Di-O-isopropylidene-3-O-methanesulfonyl-D-mannitol (XVI) was smoothly oxidized to 1,2:5,6-di-O-isopropylidene-4-O-methanesulfonyl-D-*arabino*-3-hexulose (XVIII) in 74% yield by dicyclohexylcarbodiimide and phosphoric acid in dimethyl sulfoxide, the Pfitzner–Moffatt reagent. Similarly, methyl 4,6-O-benzylidene-2-O-(*p*-tolylsulfonyl)-α-D-glucopyranoside (XXVII) was oxidized to methyl 4,6-O-benzylidene-2-O-(*p*-tolylsulfonyl)-α-D-*ribo*-hexopyranosid-3-ulose (XXIX) in 80% yield. Reduction of XXIX by sodium borohydride proceeded by equatorial attack to give methyl 4,6-O-benzylidene-2-O-(*p*-tolylsulfonyl)-α-D-allopyranoside (XXXIIIa) in 92% yield. The sulfonate group of XXXIIIa was removed by O–S cleavage with either sodium methoxide or lithium aluminum hydride to give methyl 4,6-O-benzylidene-α-D-allopyranoside (XXXIV) in 72% yield, thus making this blocked D-allose derivative readily available for other transformations.

Bimolecular displacement reactions with sugar sulfonates are easiest when the sulfonate is on a primary hydroxyl[3,4]; displacement is more difficult at secondary positions on a pyranoside.[5,6] In earlier papers from this laboratory it was shown that open-chain hexitols such as II would undergo displacement if the nucleophile were sufficiently active; for example II could be converted to the azido hexitol (IV) with azide in N,N-dimethylformamide.[7] However, with the weakly nucleophilic fluoride ion, V was not formed, but the product was I formed *via* an ortho ester ion derived from the O-benzoate.[3] When the nonparticipating tetrahydropyranyl blocking group was employed, as in III, displacement of the sulfonate with azide became slower, but an azido derivative (VI) was still obtained[8]; however, displacement of the sulfonate of III with fluoride ion to give VII failed to take place below decomposition conditions.



If a displacement reaction of a hexitol methanesulfonate by fluoride ion was to be successful, it was clear that a more activated methanesulfonate would be required as a leaving group; such a more active system would be the oxo-α-methanesulfonate XVIII. Sugihara and Yuen[9] have successfully oxidized the monobenzoyl-D-mannitol derivative (X) to the oxo sugar VIII with chromium trioxide in pyridine; that the benzoyloxy group of VIII had not epimerized was clearly demonstrated by their reduction of VIII with lithium aluminum hydride to the mannitol (IX) and altritol (XI) derivatives.

A study of the oxidation of the monomesyl mannitol (XVI)[8] with the chromium trioxide–pyridine reagent under various conditions gave 0–5% yields of a crystalline oxo mesylate which could have structure XVIII or XIX; in contrast, the previously described[9] oxidation of the monobenzoylmannitol X was readily duplicated. Attempts to debenzoylate VIII to the ketol XII with cold methanolic sodium methoxide or ammonia apparently gave an equilibrated mixture of isomers since none of the D-*arabino*-3-hexulose monobenzoate (VIII) could be reisolated after rebenzoylation, nor could a crystalline oxo mesylate (XVIII or

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[2] For the previous paper of this series, see B. R. Baker, R. Harrison, and A. H. Haines, *J. Org. Chem.*, **29**, 1068 (1964).

[3] B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 438 (1963), paper LIV of this series.

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[6] C. L. Stevens and co-workers [*J. Am. Chem. Soc.*, **86**, 2937, 2939 (1964)] have used the methods devised in ref. 5a–c for synthesis of sugars and nucleosides related to amicetin.

[7] B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 442 (1963), paper LV.

[8] B. R. Baker and H. S. Sachdev, *ibid.*, **28**, 2132 (1963), paper LVI.

[9] J. M. Sugihara and G. U. Yuen, *J. Am. Chem. Soc.*, **79**, 5780 (1957).