hydrogenated directly to the desired guanine-type nucleosides without further purification.

**2-Methylamino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-one (9).**—A solution of 0.90 g (0.0024 mol) of crude **5** in 35 ml of EtOH and 70 ml of $H_2O$ was hydrogenated at 47 psi for 6.5 hr with 0.5 g of 5% palladium on charcoal. This mixture was treated as in the preparation of **8** above to yield 0.41 g [55% based on crude **5**, 17% based on starting 2-fluoro-6-benzyloxypurine (**1**)] of crystalline **9** hemihydrate: $[\alpha]^{26}D$ −15.2° (*c* 1.64, DMF); uv $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 13,400), $\lambda_{Sh}^{pH\ 1}$ 281 mμ (ε 7370), $\lambda_{max}^{pH\ 11}$ 258 mμ (ε 11,200), $\lambda_{Sh}^{pH\ 11}$ 270 mμ (ε 10,200), $\lambda_{max}^{MeOH}$ 254 mμ (ε 14,500), $\lambda_{Sh}^{MeOH}$ 273 mμ (ε 9150); nmr (DMSO-$d_6$, $D_2O$) δ 6.28 (t, 1, $J_{H_1'-H_2',H_2''}$ = 7 Hz, $H_1'$), 2.92 (s, 3, 2-NHCH$_3$); tlc $R_9/R_8$ (natural) = 1.0.

*Anal.* Calcd for $C_{11}H_{15}N_5O_4 \cdot 0.5H_2O$: C, 45.51; H, 5.56; N, 24.13. Found: C, 45.32; H, 5.58; N, 24.38.

**2-Methylamino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purin-6-one (11).**—A solution of 1.0 g (0.0027 mol) of crude **7** in 40 ml of EtOH and 80 ml of $H_2O$ was hydrogenated at 48 psi for 15 hr with 0.5 g of 5% palladium on charcoal. This mixture was treated as in the preparation of **8** above to yield 0.50 g (64% based on crude **7**, 21% based on starting **1**) of crystalline **11** hemihydrate: $[\alpha]^{26}D$ +94.1° (*c* 1.55, DMF); uv $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 11,400), $\lambda_{Sh}^{pH\ 1}$ 279.5 mμ (ε 6380), $\lambda_{max}^{pH\ 11}$ 257 mμ (ε 10,200), $\lambda_{Sh}^{pH\ 11}$ 269 mμ (ε 8980), $\lambda_{max}^{MeOH}$ 254 mμ (ε 13,100), $\lambda_{Sh}^{MeOH}$ 273 mμ (ε 8260); nmr (DMSO-$d_6$, $D_2O$) δ 6.27 (q, 1, $J_{H_1'-H_2',H_2''}$ = 3.5 and 8.0 Hz, $H_1'$), 2.91 (s, 3, 2-NHCH$_3$); tlc $R_9/R_{11}$ = 1.2.

*Anal.* Calcd for $C_{11}H_{15}N_5O_4 \cdot 0.5H_2O$: C, 45.51; H, 5.56; N, 24.13. Found: C, 45.38; H, 5.44; N, 24.17.

**Registry No.**—2,4,5-Triamino-6-benzyloxypyrimidine, 19916-72-4; 2-amino-6-benzyloxypurine, 19916-73-5; **1**, 19916-74-6; **6**, 19916-75-7; **8**, 961-07-9; **9**, 19916-77-9; **10**, 19916-78-0; **11**, 19916-79-1.

# Reactions of Carbohydrates with (Halomethylene)dimethyliminium Halides and Related Reagents. Synthesis of Some Chlorodeoxy Sugars[1]

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The reaction of (chloromethylene)- and (chloroethylidene)dimethyliminium chloride with selected carbohydrate derivatives containing hydroxyl, epoxide, and unsaturated functions has been investigated. Primary hydroxyl groups are converted into formate esters or are replaced by a chlorine atom, depending on the reaction conditions. Acetal and ketal groups migrate in certain cases, especially when the hydroxyl group is secondary. The reagent reacts with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside to give the *trans*-2-chlorodeoxy-3-formate derivative, as a result of nucleophilic attack of chloride ion on the epoxide function. At elevated temperature a second chlorine atom is incorporated into the molecule with acetal migration to give methyl 3,4-*O*-benzylidene-2,6-dichloro-2,6-dideoxy-α-D-altropyranoside. The mechanism of the reaction is discussed.

Relatively few methods are available for the direct replacement of a hydroxyl group (except at C-1) in a sugar derivative by a halogen atom.[3,4] Among the methods that are considered to be of synthetic utility are the reactions of suitably blocked sugars with sulfuryl chloride,[5,6] and with triphenyl phosphite halides.[7,8] In both of these methods the halogen atom is incorporated by SN2-type reactions leading to inversion of configuration in those cases where secondary hydroxyl groups are involved. Selective chlorination of the primary hydroxyl group in some methyl hexopyranosides has been accomplished with reagents such as sulfur monochloride[9] and *N,N*-dimethylformamide–methanesulfonyl chloride adducts.[10]

In a preliminary communication[11] we reported on the utility of halomethyleneiminium halide reagents[12] in the preparation of certain chlorodeoxy sugars. We now wish to disclose details of this work and to comment on some synthetic and mechanistic aspects of the reaction.

The strongly electrophilic character of amide halide reagents such as (chloromethylene)dimethyliminium chloride[13,14] **2** has been exploited in a wide variety of reactions.[12–15] Some applications which are pertinent to synthetic carbohydrate chemistry include the reaction of **2** with various alcohols to give formate esters[13,14a] and chlorodeoxy sugar derivatives.[11] The sequence of reactions leading to formylation and chlorination of alcohols is illustrated in Scheme I. The precise nature of the addition product from an alcohol and **2** cannot be readily established since an equilibrium such as A ⇌ B is possible. Only one case[13] is known where the primary adduct (type B) of *t*-butyl alcohol was actually isolated as the perchlorate salt. When solutions of the adducts of simple alcohols are heated in chlorinated hydrocarbons, the corresponding alkyl halides and presumably *N,N*-dimethylformamide are formed.[15] Although the reaction is of preparative significance, its application has not been extended to more complex systems. Furthermore, the stereochemical course of the reaction has not been established. Some analogy can be drawn from the pyrolysis of simple imino ester hydrochlorides to the corresponding alkyl halides, which has been shown[16] to proceed by a bimolecular mechanism. The conversion of optically

(1) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, D 16.

(2) To whom correspondence should be addressed at the University of Montreal.

(3) J. E. G. Barnett, *Advan. Carbohydrate Chem.*, **22**, 177 (1967).

(4) S. Hanessian, Advances in Chemistry Series, No. 74, American Chemical Society, Washington, D. C., 1968, p 159.

(5) B. Helferich, *Ber.*, **54**, 1082 (1921).

(6) H. J. Jennings and J. K. N. Jones, *Can. J. Chem.*, **43**, 2372 (1965), and previous papers.

(7) N. K. Kochetkov and A. I. Usov, *Tetrahedron*, **19**, 973 (1963).

(8) N. K. Kochetkov and A. I. Usov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 492 (1965); *Chem. Abstr.*, **63**, 1857 (1965).

(9) H. B. Sinclair, *J. Org. Chem.*, **30**, 1283 (1965).

(10) M. E. Evans, L. Long, Jr., and F. W. Parrish, *ibid.*, **33**, 1074 (1968).

(11) S. Hanessian and N. R. Plessas, *Chem. Commun.*, 1152 (1967).

(12) For a review, see, H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

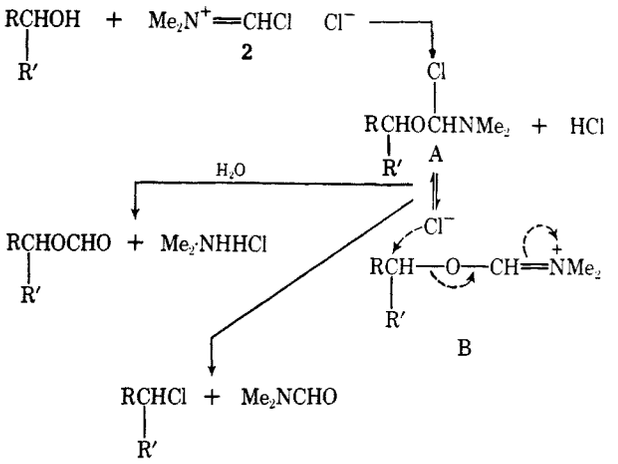
(13) Z. Arnold, *Collection Czech. Chem. Commun.*, **24**, 4048 (1959).

(14) (a) K. Morita, S. Noguchi, and M. Nishikawa, *Chem. Pharm. Bull.* (Tokyo), **7**, 896 (1959); (b) N. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

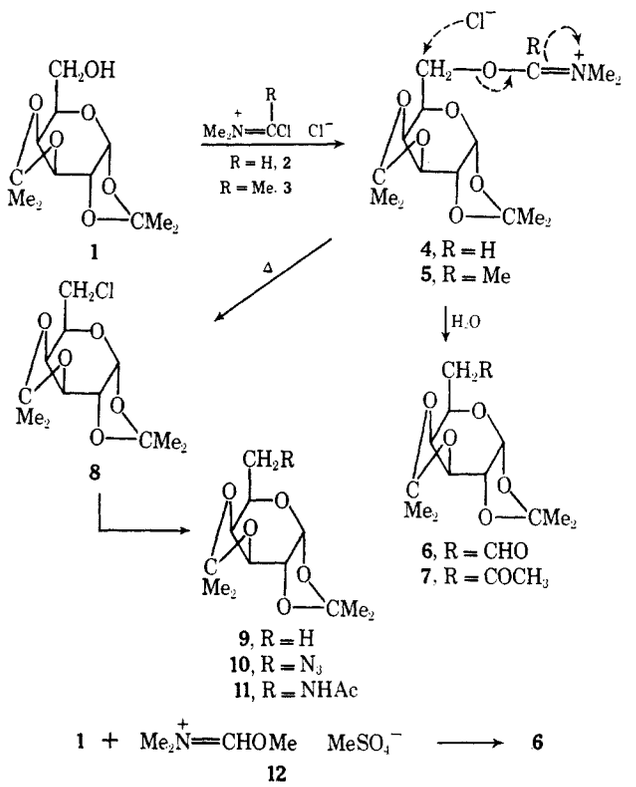
(15) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Chem. Ber.*, **96**, 2671 (1963).

(16) S. M. McElvain and B. E. Tate, *J. Amer. Chem. Soc.*, **73**, 2233 (1951).

SCHEME I



SCHEME II



active *sec*-butyl alcohol to the corresponding halide with inversion of configuration *via* the pyrolysis of the intermediate imino ester hydrochloride has also been reported.[17] Certain derivatives of carbohydrates containing an isolated hydroxyl group are converted into chlorodeoxy derivatives in good yield, by reaction with reagents of type **2**.[11] Recent observations in these laboratories indicate, however, that the replacement of a secondary hydroxyl group in derivatives containing cyclic acetals and ketals may be accompanied by a rearrangement of these groups to give chlorodeoxy derivatives which are different from those expected on the basis of simple replacement of the hydroxyl group.

Treatment of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**1**) with **2** in 1,1,2-trichloroethylene or a similar solvent resulted in almost complete conversion of **1** into the imino ester intermediate **4**[18] (Scheme II).

Treatment of the reaction mixture with aqueous bicarbonate afforded the formate ester **6**, in addition to small amounts of the 6-chlorodeoxy derivative **8**. The formation of the latter, even under mild conditions, reflects on the activated character of the imino ester group in the adduct **6**. Heating the reaction mixture afforded 6-chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**8**), in yields ranging from 85–98%. Compound **8** has been previously prepared in varying yields by other methods,[19–22] which require at least two steps starting with **1**. By conventional methods, **8** was converted into the known 6-deoxy[23,24] **9**, 6-azido[25] **10**, and 6-acetamido[25] **11** derivatives. Treatment of **1** with an excess of (chloroethylidene)dimethyliminium chloride[26] (**3**) followed by quenching of an aliquot with aqueous bicarbonate and examination by tlc, revealed the presence of the 6-*O*-acetate **7** as a preponderant product, in addition to small amounts of **1** and **8**. The reagent **3** could therefore be used as an acetylating agent in certain cases. Heating a solution containing the primary adduct **5** afforded the acetate **7** (tlc, ir) and the 6-chlorodeoxy derivative **8** in low yield (*ca.* 25%). While these results can be rationalized to some extent on the basis of steric hindrance to the attack of chloride ion at C-6, another factor which should be considered is the electronic effect exerted by the methyl group of the dimethylaminoethylidene group which would tend to stablize an intermediate such as **5**. The reaction of (methoxymethylene)dimethyliminium methylsulfate[27] (**12**) with **1** was found to be much slower than that of **2**; the formate ester **6** and unchanged **1** were the only products detectable on tlc.

As a model of a sugar derivative containing an isolated secondary hydroxyl group, we selected 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[28] (**13**).

When **13** was allowed to react with **2** at room temperature in 1,1,2,2-tetrachloroethane, the major product obtained was the 3-*O*-formate ester of **13**. Refluxing a solution containing **13** and **2** afforded a syrupy product which had spectral properties and an elemental analysis consistent with a product resulting from the loss of the hydroxyl group and the incorporation of a chlorine atom. However, the product was not the expected 3-chlorodeoxy derivative, which would have been formed by simple replacement[29] of the C-3 hydroxyl group in **13**, but rather, 6-chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose[30–32] (**14**) (Scheme III).

The structure of **14** was firmly established by comparison of optical rotation data and by appropriate

(17) C. L. Stevens, D. F. Morrow, and J. Lawson, *J. Amer. Chem. Soc.*, **77**, 2341 (1955).

(18) For simplicity, these primary adducts are represented as imino ester salts. It should be pointed out, however, that structures such as **4** could be part of an equilibrium involving related species.

(19) K. A. Petrov, E. E. Nifant'ev, A. A. Shchegolov, and V. G. Tevekhov, *J. Gen. Chem. USSR*, **34**, 1463 (1964).

(20) K. W. Buck and A. B. Foster, *J. Chem. Soc.*, 2217 (1963).

(21) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966).

(22) K. R. Wood, D. Fisher, and P. W. Kent, *J. Chem. Soc.*, 1994 (1966).

(23) K. Freudenberg and K. Raschig, *Ber.*, **60**, 1633 (1927).

(24) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949).

(25) W. A. Szarek and J. K. N. Jones, *Can. J. Chem.*, **43**, 2345 (1965).

(26) H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, **42**, 1659 (1959).

(27) H. Bredereck, F. Effenberger, and G. Simchen, *Chem. Ber.*, **96**, 1350 (1963).

(28) O. Th. Schmidt, *Methods Carbohydrate Chem.*, **2**, 318 (1963).

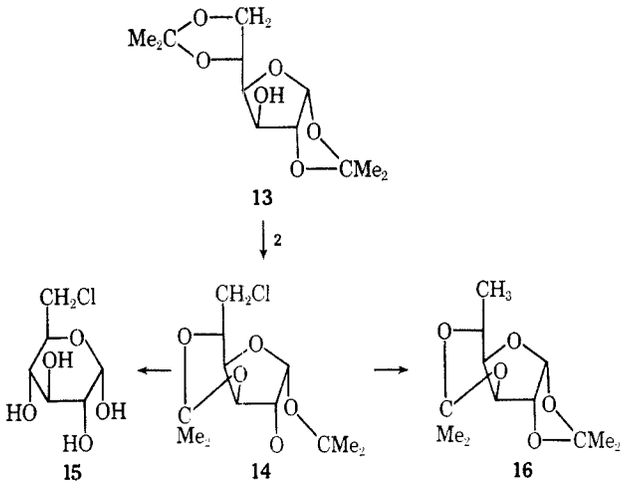
(29) It should be noted that the only example of a successful configurational inversion at C-3 in **13** involves treatment of the corresponding tosylate with refluxing hydrazine: M. L. Wolfrom, J. Bernsmann, and D. Horton, *J. Org. Chem.*, **27**, 4505 (1962), and references cited therein.

(30) J. B. Allison and R. M. Hixon, *J. Amer. Chem. Soc.*, **48**, 406 (1926).

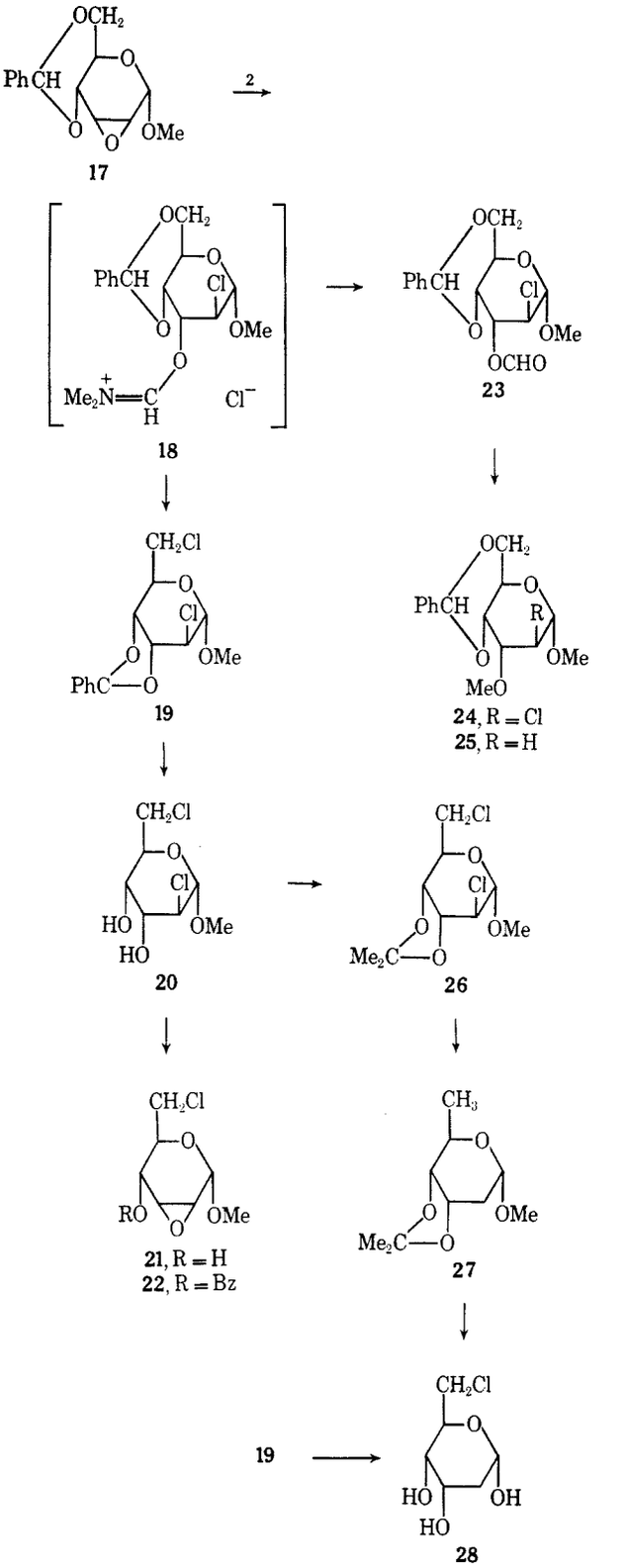
(31) D. C. C. Smith, *J. Chem. Soc.*, 1244 (1956).

(32) E. Hardegger, G. Zanetti, and K. Steiner, *Helv. Chim. Acta*, **46**, 282 (1963).

SCHEME III



SCHEME IV



conversions into the 6-deoxy derivative **16** and the crystalline free sugar, 6-chloro-6-deoxy-α-D-glucose[31] (**15**). The one-step conversion of **13** into **14** in yields exceeding 70% is particularly noteworthy, since previous preparations[30-32] utilizing phosphorus pentachloride as the chlorination agent have been accomplished at best in less than 15% yield.

Migration of the 5,6-*O*-isopropylidene group has also been observed[30-33] during the reaction of **13** with phosphorus pentachloride and with triphenyl phosphite dihalides[7] which afford the 6-halodeoxy derivatives corresponding to **14**. A possible pathway for the transformation of **13** to **14** by the method described herein has been suggested[4] and invokes the formation of an orthoester intermediate.

The reagent **2** reacts with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside[34] (**17**) to give monochlorodeoxy or dichlorodideoxy derivatives depending upon the reaction conditions.[11] At room temperature, the major product of the reaction is methyl 4,6-*O*-benzylidene-2-chloro-2-deoxy-3-*O*-formyl-α-D-altropyranoside (**23**) (Scheme IV). The latter is presumably formed by nucleophilic attack of chloride ion on the epoxide **17** or an activated form, in which the epoxide oxygen coordinated with the reagent, thus rendering it a good leaving group. Intermediate **18** which can be considered as the primary reaction product affords upon hydrolysis, the 2-chloro 3-formate derivative **23**. That the chlorine atom was situated at C-2 in the product isolated after chromatography was proved by conversion of **23** into the crystalline 3-*O*-methyl ether **24** and reduction of the latter to the known crystalline methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-*ribo*-hexopyranoside[35] (**25**). The conversion of the epoxide function in **17** into a vicinal *trans*-chloro formate system such as in **23**, under very mild conditions, demonstrates a further utility of halomethyleneiminium halide reagents in carbohydrate chemistry. Heating a solution of **17** and **2** in 1,1,2-trichloroethane afforded a methyl *O*-benzylidenedichlorodideoxyhexopyranoside in high yield. The incorporation of the second chlorine atom was originally assumed[11] to have taken place at C-3, according to mechanistic considerations,[16,17] to give a 2,3-dichlorodideoxy derivative. We have now found that the incorporation of the second chlorine atom is accompanied by a rearrangement of the benzylidene acetal, and the actual product is methyl 3,4-*O*-benzylidene-2,6-dichloro-2,6-dideoxy-α-D-altropyranoside (**19**). A direct proof in support of this is the conversion of **19** into 2,6-dideoxy-D-*ribo*-hexose (digitoxose)[36] (**28**). Mild

(33) J. Baddiley, J. G. Buchanan, and F. E. Hardy, *J. Chem. Soc.*, 2180 (1961).

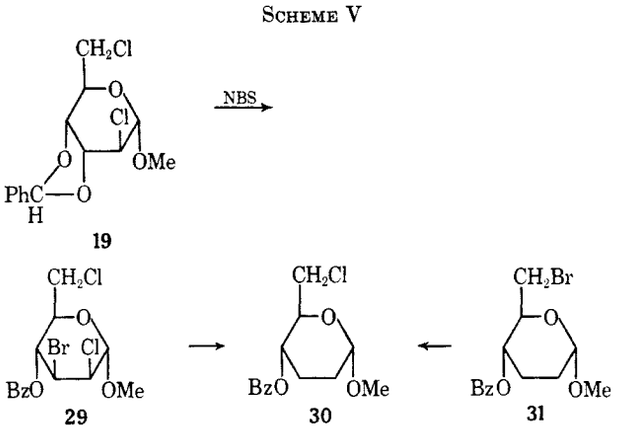
(34) G. J. Robertson and C. F. Griffith, *ibid.*, 1193 (1935); N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.*, **63**, 1727 (1941).

(35) R. W. Jeanloz, D. A. Prins, and T. Reichstein, *Helv. Chim. Acta*, **29**, 371 (1946).

(36) H. R. Bolliger and P. Ulrich, *ibid.*, **35**, 93 (1952), and references cited therein.

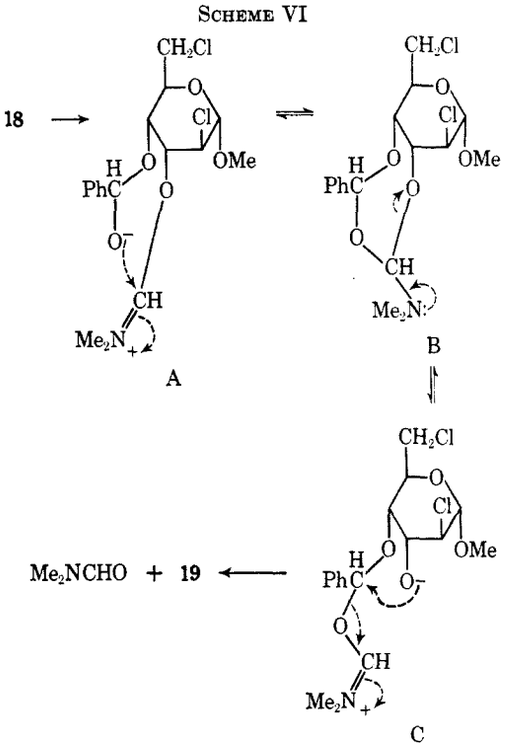
acid hydrolysis or catalytic hydrogenation removed the benzylidene group from **19** to give crystalline methyl 2,6-dichloro-2,6-dideoxy-α-D-altropyranoside (**20**). This substance was attacked by periodate, but the oxidation in unbuffered solutions proceeded slowly. Treatment of **20** with base afforded a crystalline epoxide **21** which on benzoylation gave the monobenzoate **22** as a homogeneous syrup. That the benzoate group was attached to a secondary carbon atom was evident from the nmr spectrum of the product which showed a quartet at low field corresponding to the C-4 proton in **22**. Compound **20** readily formed a crystalline acetonide **26**, which, when reduced with lithium aluminum hydride, afforded the 2,6-dideoxy derivative **27** as the major product. Mild acid hydrolysis of the latter gave crystalline digitoxose[36] (**28**). Although the vapor phase chromatograms of compounds **20**, **21**, and **26** indicated single peaks for the respective substances, the chromatogram of **19** showed two peaks in the approximate ratio of 1.3:1. Furthermore, the nmr spectrum of **19** showed two singlets for the benzylidene acetal proton, as well as two signals each for the anomeric proton and the methoxyl protons. From the integrated areas of these peaks it appeared that the product **19** was a mixture of diastereoisomers, differing in the configuration of the benzylidene acetal carbon atom. The nmr spectrum of methyl 2-*O*-benzoyl-3,4-*O*-benzylidene-β-D-arabinopyranoside[37,38] shows two singlets of the same relative frequency as in **19**, due to the presence of two diastereoisomers. Treatment of **20** with benzaldehyde and zinc chloride afforded a product which showed two peaks having the same retention time as those found in the chromatogram of the original product **19**. That the ratio of diastereoisomers obtained from the acetalation of **20** was changed (1.8:1) compared to **19** is not unexpected, since the mechanism of acetalation differs from the rearrangement reaction.[39] The structure of the rearranged product **19** was proved in a different manner (Scheme V). Treatment of **19** with *N*-bromo-

SCHEME V




succinimide[4,40] opened the acetal ring to give after chromatography a product which, based on its subsequent tranformations, can be designated as methyl-4-*O*-benzoyl-3-bromo-2,6-dichloro-2,3,6-trideoxy-α-D-mannopyranoside (**29**). Catalytic reduction of **29** gave a syrupy product, which was purified by chromatography and was obtained as a homogeneous syrup (purity >96% by vpc). The nmr spectrum of this product indicated the presence of a four-proton multiplet corresponding to two methylene groups and the absence of a C-methyl group. Since the ring-opening reaction with NBS is not expected[4,40] to be accompanied by rearrangement in this case, the absence of a C-methyl group in the reduced product is a clear indication that a 4,6-*O*-benzylidene acetal was not present in the starting material **29**. The preponderant incorporation of the bromine atom at C-3 in **29** can be explained on the basis of a stereoselectivity in the ring opening of the 3,4-*O*-benzylidene acetal in **19**. Similar results have been obtained with related acetals.[38] It is interesting to note that whereas the two chlorine atoms in **19** were inert to catalytic hydrogenation, the incorporation of a bromine atom at C-3 led to a selective reduction of the C-2 and C-3 halogen atoms, in preference to the C-6 chlorine atom. The identity of the reduced product **30** was further established by comparison of its nmr spectrum with that of **31**[41] and by converting the latter compound into **30** by reaction with lithium chloride in *N*,*N*-dimethylformamide. The sequence of reactions outlined in Scheme V thus provides additional proof for the location of the second chlorine atom at C-6, and also establishes the pyranose ring structure of the rearranged product **19**. A possible mechanism for the formation of **19** is outlined in Scheme VI. It invokes

SCHEME VI




the formation of an orthoester-type intermediate by a reversible reaction (A ⇄ B) and an irreversible acetal formation (C → **19**). The latter step explains the formation of diastereoisomeric benzylidene acetals.

(37) N. Baggett, K. W. Buck, A. B. Foster, and J. M. Webber, *J. Chem. Soc.*, 3401 (1965).

(38) S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 1053 (1969), paper IV in a series.

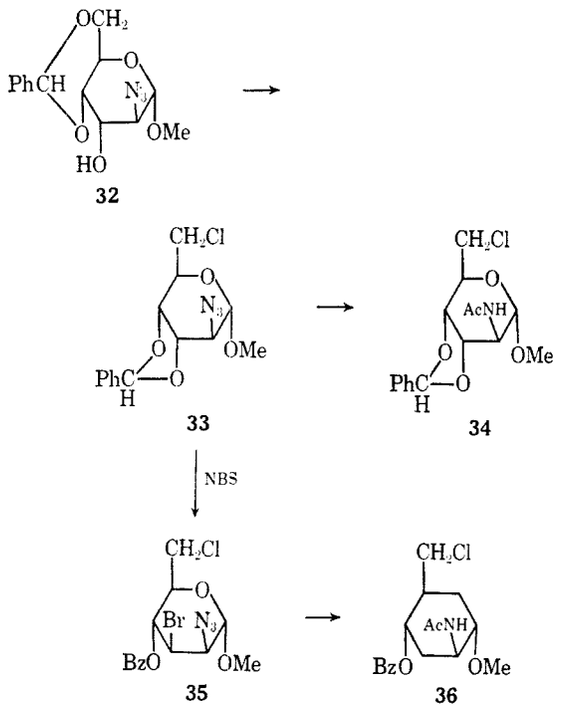
(39) The possibility of anomerization was also considered in an attempt to explain the chromatographic and nmr spectral behavior of **19**. The available data, and the transformations of **19** seem to favor the presence of diastereoisomers.

(40) S. Hanessian, *Carbohydrate Res.*, **2**, 86 (1966); S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 1035 (1969), paper II in a series.

(41) S. Hanessian and N. R. Plessas, *ibid.*, **34**, 1045 (1969), paper III in a series.

The reaction of methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside[42] (**32**) with **2** in refluxing 1,1,2,2-tetrachloroethane afforded a product whose analysis corresponded to the loss of a hydroxyl group and the incorporation of a chlorine atom in the molecule. On the basis of the transformations illustrated in Scheme VII this product is designated as methyl 2-

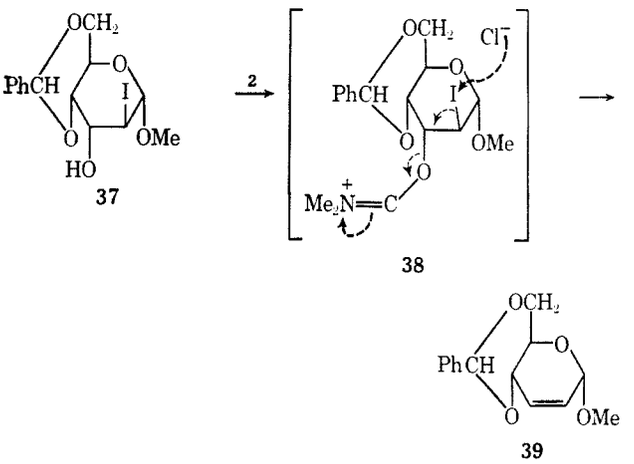
SCHEME VII



azido-3,4-*O*-benzylidene-6-chloro-2,6-dideoxy-α-D-altropyranoside (**33**).[43] The nmr spectrum of **33**, like that of **19**, showed evidence for the presence of two diastereoisomers differing in the configuration of the benzylic carbon atom. Treatment of **33** with *N*-bromosuccinimide[40] afforded a product, presumably **35**, which was catalytically reduced and N-acetylated. The nmr spectrum of the product contained a two-proton multiplet corresponding to a methylene group, but no signal for a C-methyl group. In analogy with the results obtained with **19** (Scheme IV), this reduced and N-acetylated product is designated as methyl 2-acetamido-4-*O*-benzoyl-6-chloro-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (**36**). Selective reduction of the azido group in **33** and subsequent N-acetylation afforded crystalline methyl 2-acetamido-3,4-*O*-benzylidene-6-chloro-2,6-dideoxy-α-D-altropyranoside (**34**). The nmr spectrum of this product in pyridine-$d_5$ exhibited only one singlet for the benzylidene acetal proton, and it is not unlikely that, in the crystallization process, only one of the diastereoisomers was isolated.[37,38]

Whereas the chlorination of **17** and **32** (*via* the intermediate 3-imino ester) proceeded with rearrangement, but with no accompanying side reactions, the reaction of **2** with methyl 4,6-*O*-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside[44] (**37**) led to a complex mixture of products. One of these products was isolated and identified as methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[44,45] (**39**). The formation of **39** can be explained by attack of chloride ion on the iodine atom as in intermediate **38**, with concomitant elimination of the C-3 substituent (Scheme VIII). It is of interest to note that a preparative route[44] to **39** consists of treating the 3-*O*-tosyl derivative of **37** with pyridine hydrochloride, which follows an analogous pathway, with expulsion of the tosyloxy function. Since the product **39** reacts with the reagent **2**, the sequence shown in Scheme VIII is not of preparative significance at this time.

SCHEME VIII



## Experimental Section

Melting points are uncorrected. Nmr spectra were obtained in chloroform-*d* unless otherwise stated on a 60-MHz spectrometer using tetramethylsilane as reference. Optical rotations were measured with a Perkin-Elmer photoelectric polarimeter at 25°. Thin layer chromatography was performed on silica gel HF plates and the spots were detected with a spray containing 5% each of ammonium molybdate, sulfuric acid, and phosphoric acid after heating the plate for 10 min at 110°, and with a 1% potassium permanganate solution in 0.1 *N* sulfuric acid. Solvent systems and mobilities (slow, medium, fast) are given. Chlorinated hydrocarbons were dried by passage over neutral alumina (Woelm) prior to use. Processed solutions of chloroform and ether were dried over anhydrous sodium sulfate. Vapor phase chromatography was done on columns containing 5% SE-30 (Analabs, Inc.) or 3% OV-17 (Applied Science Labs, Inc.) depending on the derivative.

**6-Chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (8).**—To a solution containing 0.77 g (6 mmoles) of (chloromethylene)dimethyliminium chloride[14] (**2**) in 6 ml of 1,1,2-trichloroethane was added a solution of **1** (1.3 g, 5 mmoles) in 12 ml of the same solvent. After stirring for 1–2 hr an aliquot (1 ml) was taken from the yellow solution and treated with aqueous bicarbonate. Examination of the organic layer by tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:1) revealed the presence of the 6-formate ester **6**, in addition to a small amount of **8**. The reaction mixture was refluxed with stirring for 3 hr and the dark solution was cooled and treated with aqueous sodium bicarbonate solution. Processing in the usual way afforded a pale yellow solution which was decolorized and evaporated to dryness to give the product **8**, as a colorless chromatographically homogeneous syrup; yield 1.32 g, 95%. The yield varied between 85 and 98%. A portion was distilled 95–100° (bath temperature) (0.1 mm), and showed $[\alpha]_D$ −66° (*c* 0.78, chloroform); nmr data, τ 4.55 (center of a doublet, $J_{12}$ = 5 Hz, C-1 proton), 5.36 (center of a quartet, C-2 proton), 8.45, 8.58, 8.66 (ketal methyl protons), etc.; vpc, singlet peak, >98% pure.

(42) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 5288 (1963); Y. Ali and A. C. Richardson, *Carbohydrate Res.*, **5**, 441 (1967).

(43) Based on mechanistic considerations,[16,17] this product was previously assumed[11] to be methyl 2-acetamido-4,6-*O*-benzylidene-3-chloro-2,3-dideoxy-α-D-mannopyranoside.

(44) R. U. Lemieux, E. Fraga, and K. A. Watanabe, *Can. J. Chem.*, **46**, 61 (1968).

(45) E. Albano, D. Horton, and T. Tsuchiya, *Carbohydrate Res.*, **2**, 349 (1966), and references cited therein.

*Anal.* Calcd for $C_{12}H_{19}O_5Cl$: C, 51.70; H. 6.87; Cl, 12.72. Found: C, 51.82; H, 6.73; Cl, 12.54.

**6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (9).**—A solution of **8** (0.45 g) in 30 ml of ether was added dropwise to a suspension of lithium aluminum hydride (0.5 g) in 50 ml of tetrahydrofuran. After stirring under reflux overnight, excess reagent was decomposed by cautious addition of water and the salts were removed by filtration. Evaporation of the filtrate gave a syrup which was dissolved in ether, and the solution was washed once with a small volume of water and dried. Evaporation gave a colorless syrup which was homogeneous on tlc and had a mobility slightly slower than **8**. It gave a characteristic green color with the molybdate spray. A portion of the syrup was distilled at 68–70° (0.5 mm) to give the product as a pure liquid: $[\alpha]_D$ −47.5° (*c* 2.67, chloroform), lit.[23,24] $[\alpha]_D$ −47.1° (chloroform); nmr data, $\tau$ 4.45 (center of a doublet, $J_{12}$ = 5 Hz, C-1 proton), 5.40 (center of a quartet, C-2 proton), 8.62 (center of a 15-proton multiplet, ketal and C-6 methyl protons), etc.

**6-Azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (10).**—To a solution of **8** (0.46 g) in 15 ml of *N*,*N*-dimethylformamide was added sodium azide (0.46 g) and the mixture was refluxed with stirring during 36 hr. The solution was evaporated to dryness in the presence of butyl alcohol and the residue was suspended in ether and filtered. This was repeated several times to give finally a yellow syrup which was homogeneous on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.5, medium); ir data, 2100 $cm^{-1}$ (azide). A portion was purified by preparative tlc; $[\alpha]_D$ −91° (*c* 0.97, chloroform), lit.[25] $[\alpha]_D$ −92.1° (chloroform) as a syrup.

A portion of the syrup was dissolved in methanol and treated with acetic anhydride and excess Raney nickel. After stirring overnight at room temperature the mixture was filtered and the filtrate was processed to give 6-acetamido-6-deoxy-1,2:3,4-*O*-isopropylidene-α-D-galactopyranose as a chromatographically homogeneous syrup: ir data, 1660 (amide I), 1550 $cm^{-1}$ (amide II); $[\alpha]_D$ −5.4° (*c* 1.425, chloroform containing 1% ethanol), lit.[25] $[\alpha]_D$ −8.3° (chloroform–ethanol) as a syrup.

**6-Chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (14).**—To a solution of **13** (4.4 g) in 30 ml of 1,1,2,2-tetrachloroethane was added **2** (6.5 g) in 60 ml of the same solvent. After 2–3 hr at room temperature an aliquot (2 ml) was withdrawn from the solution and treated with aqueous sodium bicarbonate. Investigation of the organic layer by tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.4, medium) revealed the presence of the formate ester as the major product. The reaction mixture was refluxed for 3.5 hr with stirring, and the dark solution was cooled and treated with cold aqueous sodium bicarbonate. Processing of the organic layer in the usual way afforded 5.1 g (70%) of a pale yellow syrup which was homogeneous by tlc. A portion was distilled at 84–85° (0.05 mm); $[\alpha]_D$ +36° (*c* 2.64, chloroform); nmr data, $\tau$ 4.0 (center of a doublet, $J_{12}$ = 3.5 Hz, C-1 proton), 5.42 (center of a doublet $J_{21}$ = 3.5 Hz, C-2 proton), etc.; vpc analysis, >98% pure.

*Anal.* Calcd for $C_{12}H_{19}O_5Cl$: C, 51.70; H, 6.87; Cl, 12.72. Found: C, 51.44; H, 6.80; Cl, 13.22.

A portion of **14** was hydrolyzed essentially according to Smith[31] to give crystalline **6-chloro-6-deoxy-α-D-glucopyranose (15)**, mp 135–136°, $[\alpha]_D$ +95.8° → +51.1° (18 hr, in water); lit.[31] mp 135–136°, $[\alpha]_D$ +92.5° → +46.6° (at equilibrium, in water).

A portion of **14** (0.2 g) was reduced with lithium aluminum hydride in ether in the usual way. Processing of the reaction mixture gave **6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (16)**, as a pale yellow syrup (0.1 g): nmr data, $\tau$ 4.0 (center of a doublet, $J_{12}$ = 3.5 Hz, C-1 proton), 5.42 (center of a doublet $J_{21}$ = 3.5 Hz, C-2 proton), 8.60 (center of a 15-proton multiplet, ketal and C-6 methyl protons), etc.

**Methyl 3,4-*O*-Benzylidene-2,6-dichloro-2,6-dideoxy-α-D-altropyranoside (19).**—To a solution containing 0.64 g of **2** in 15 ml of 1,1,2,2-tetrachloroethane was added dropwise a solution of **17** (1.32 g) in 25 ml of the same solvent. After stirring overnight at room temperature, an aliquot treated with aqueous bicarbonate and examined by tlc showed the virtual absence of starting material (see below). The pale yellow solution was heated at 110° for 2–2.5 hr, the resulting dark-colored solution was cooled and treated with aqueous bicarbonate, and the processed organic layer was evaporated in the presence of butyl alcohol. The resulting tan-colored syrup was dissolved in chloroform and decolorized, and the processed solution was evaporated to an almost colorless syrup, 1.55 g (97%). The product showed essentially a fast-moving major double spot in addition to one or two slower moving components of minor intensity (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.5). In the case of larger runs, the yield varied between 75 and 95% depending on the purity of the reagent and the quantitative formation of the chloro ester **18**. A portion was further purified by distillation: bp 157–160° (0.25 mm); $[\alpha]_D$ +41.5° (*c* 1.47, chloroform); vpc analysis showed two major closely spaced peaks in an approximate ratio of 1.3:1; nmr data, $\tau$ 2.58 (aromatic protons, apparent singlet), 3.84, 4.10 (benzylic protons, 1:1.25 approximate ratio, integrate for one proton), 5.15, 5.21 (anomeric proton, 1:1.25 approximate ratio, integrate for one proton), 6.5, 6.51 (C-1 methoxyl protons, integrate for three protons).

*Anal.* Calcd for $C_{14}H_{16}O_4Cl_2$: C, 52.67; H, 5.05; Cl, 22.21. Found: C, 53.18; H, 5.12; Cl, 22.38.

An aliquot from the reaction of **17** with **2** taken after 18–24 hr showed essentially a major component on tlc which gave a postive test with the hydroxylamine spray. Purification of this product by preparative tlc gave **methyl 4,6-*O*-benzylidene-2-chloro-2-deoxy-3-*O*-formyl-α-D-altropyranoside (23)** as a colorless syrup: $[\alpha]_D$ 51.1° (*c* 3.94, chloroform); ir data, 1730 $cm^{-1}$ (ester). Attempted purification of **23** by chromatography over neutral alumina (Merck) or storage at room temperature resulted in partial deformylation.

**Methyl 2,6-Dichloro-2,6-dideoxy-α-D-altropyranoside (20). A. By Hydrogenolysis of 19.**—A solution of **19** (3 g) in 100 ml of methanol was stirred in the presence of 20% palladium on carbon (1 g) and hydrogen during 5.5 hr. Filtration and evaporation afforded a colorless syrup which was homogeneous on tlc (benzene–methanol, 10:1.5) and showed a single peak by vpc analysis. The syrup crystallized in a few hours and the crystals were triturated with a mixture of ether and petroleum ether (bp 30–60°) to give 0.55 g of colorless crystals, mp 70–72°. Recrystallization from the same solvent gave colorless crystals showing a purity of over 99% by vpc analysis: mp 78–80°; $[\alpha]_D$ +118° (*c* 1, methanol); nmr data, $\tau$ 5.15 (C-1 anomeric proton, apparent singlet), 6.54 (C-1 methoxyl protons, singlet), etc. The mother liquors remaining after the filtration of the crystalline product were evaporated to a syrup which showed essentially one spot on tlc corresponding to **20**; yield 1.38 g (combined yield, 94%). A portion of this product was purified by preparative tlc to give a crystalline product which was identical (nmr, tlc, vpc) with material obtained from the first crop, mp 78–80°.

*Anal.* Calcd for $C_7H_{12}O_4Cl_2$: C, 36.59; H, 5.22; Cl, 30.68. Found: C, 36.81; H, 5.68; Cl, 30.78.

A portion of the product was treated with benzaldehyde and zinc chloride and the mixture was stirred for 5 hr. Processing of the reaction mixture in the usual way afforded a syrup which was indistinguishable from the original **19** by tlc, ir, and nmr. Vpc analysis revealed the presence of the same two components found in the original mixture; however, the ratio of the faster to the slower components was now about 1.8:1 respectively.

**B. By Acid Hydrolysis of 19.**—An amount of **19** (0.8 g) was dissolved in 10 ml of methanol and the solution was treated with 10 ml of 0.1 *N* sulfuric acid. After stirring at 45–50° overnight the solution was neutralized with barium carbonate and processed to give a syrup which showed a major component corresponding to **20** on tlc, in addition to some minor more slowly moving components. A portion of the syrup was purified by preparative tlc to give a crystalline product, identical (nmr, vpc) with **20** obtained by procedure A; mp 70–72°, $[\alpha]_D$ +118° (*c* 1, methanol)

**Methyl 2,3-Anhydro-6-chloro-6-deoxy-α-D-allopyranoside (21).**—To a solution of **20** (0.24 g) in 7 ml of ethanol was added 1.2 ml of 1 *N* sodium hydroxide and the resulting solution was refluxed for 20 min. Neutralization of the solution with dilute acetic acid, extraction with ether, and processing of the ethereal extract in the usual way afforded a colorless syrup which exhibited a single spot on tlc with a mobility very slightly slower than **20** (chloroform–methanol, 10:0.7, fast). The syrup was taken up in acetone, filtered, and evaporated to a syrup which crystallized. Trituration with ether–petroleum ether and filtration gave 0.1 g (50%) of **21**, mp 90–92°. Two recrystallizations from the same solvent mixture gave pure material: mp 93–94°; $[\alpha]_D$ +155° (*c* 0.59, chloroform); vpc, >99% pure. Investigation of the mother liquors from the crystallization of **21** by vpc and tlc indicated the presence of the epoxide mainly.

*Anal.* Calcd for $C_7H_{11}O_4Cl$: C, 43.19; H, 5.69; Cl, 18.22. Found: C, 43.04; H, 5.52; Cl, 18.60.

A portion of crude **21** (90 mg) was benzoylated in pyridine in the usual way to give **methyl 2,3-anhydro-4-*O*-benzoyl-6-chloro-6-deoxy-α-D-allopyranoside (22)** as a syrup. This product was

purified by preparative tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:1); nmr data, $\tau$ 4.68, 4.74 (centers of two doublets, $J_{45}$ = 9.5 Hz, $J_{43}$ = 1.5 Hz), 5.68 (center of a multiplet, C-3 proton), 6.35 (center of a four-proton multiplet, C-2, C-5, C-6 protons), 6.45 (C-1 methoxyl protons), etc. Treatment of **22** with a dilute solution of sodium methoxide in methanol, either at room temperature or at reflux for 30 min, gave the epoxide **21** as the sole product.

**Methyl 4,6-*O*-Benzylidene-2-chloro-2-deoxy-3-*O*-methyl-α-D-altropyranoside (24).**—A portion (1 g) of the crude formate ester **23** was dissolved in chloroform and passed through a chilled column containing neutral alumina. The column was washed with chloroform and the fractions were examined by tlc. It appeared that extensive deformylation had taken place. The first eluates containing mostly the deformylated product were combined and processed to a colorless syrup (0.5 g). The latter was dissolved in 50 ml of methyl iodide and 2 g of silver oxide was added in portions to the refluxing solution. After refluxing overnight, the suspension was filtered and the filtrate was evaporated to dryness. The resulting crystalline solid was triturated with cold ether and filtered to give the product in two crops, yield 0.35 g, mp 120–122°. Recrystallization from a mixture of acetone–ether and petroleum ether gave an analytical sample: mp 121–122°; $[\alpha]_D$ +68° (*c* 0.82, chloroform); nmr data, $\tau$ 4.42 (benzylic proton, singlet), 5.26 (C-1 proton, singlet), 6.45 (C-1 methoxyl proton, singlet), 6.60 (C-3 methoxyl protons).

*Anal.* Calcd for $C_{15}H_{19}O_5Cl$: C, 57.23; H, 6.08; Cl, 11.26. Found: C, 57.03; H, 6.10; Cl, 11.04.

**Methyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-methyl-α-D-*ribo*-hexopyranoside (25).**—A solution of **24** (0.1 g) in 30 ml of ether was added dropwise to a suspension of lithium aluminum hydride (1 g) in ether and the mixture was refluxed for 3 days with stirring. After the addition of water to the cooled reaction mixture, and processing in the usual way, the ethereal solution was dried and evaporated to dryness. The crystalline residue consisted of three products which were separated by preparative tlc. The component with medium mobility (25 mg) was crystallized from a mixture of ether and petroleum ether, mp 95–97°, $[\alpha]_D$ 136° (*c* 0.28, chloroform), and was found to be identical (ir, vpc) with the title compound; lit.[35] mp 100°, $[\alpha]_D$ +127° (chloroform). The faster (15 mg) and slower (12 mg) components were isolated as syrups which were oxidized by aqueous permanganate and exhibited signals for vinyl-type protons in their respective nmr spectra, but no signals for methylene protons indicating that they were unsaturated by-products.

**Methyl 2,6-Dichloro-2,6-dideoxy-3,4-*O*-isopropylidene-α-D-altropyranoside (26).**—An amount of **20** (0.3 g) was dissolved in 50 ml of acetone containing 0.01 ml of concentrated sulfuric acid. The solution was stirred at room temperature overnight after which another 0.01 ml of acid was added. After a total time of 36 hr tlc showed the virtual absence of starting material. The acid was neutralized with barium carbonate, the salts were filtered and the filtrate was evaporated to dryness. The mobile liquid containing acetone condensation products was subjected to repeated evaporation from an aqueous solution and the final syrup was dissolved in petroleum ether, dried, and evaporated to a syrup which crystallized. Trituration with cold petroleum ether and filtration gave 0.22 g of product, mp 63–65°, >99% pure by vpc analysis. Recrystallization from the same solvent afforded material with mp 65–66°; $[\alpha]_D$ +63° (*c* 0.5, chloroform); nmr data, $\tau$ 5.22 (center of a doublet, $J_{12}$ = 4.5 Hz, C-1 proton), 5.72 (center of a two-proton multiplet, C-3, C-4 protons), 6.51 (singlet, methoxyl protons), 8.54 (center of a doublet, ketal methyl protons).

*Anal.* Calcd for $C_{10}H_{16}O_4Cl_2$: C, 44.50; H, 5.94. Found: C, 44.54; H, 5.87.

**Reduction of 26 with Lithium Aluminum Hydride and Isolation of D-Digitoxose.**—A solution of **26** (0.1 g) in 10 ml of tetrahydrofuran was added to a suspension of lithium aluminum hydride (35 mg) in 15 ml of the same solvent. The mixture was refluxed for 48 hr and excess reagent was decomposed by cautious addition of water. Filtration of the salts and evaporation of the filtrate gave a syrup which showed a major spot and another spot of minor intensity corresponding to unreacted **26** (chloroform–2,2,4-trimethylpentane–methanol, 100:40:0.1). The major component, **methyl 2,6-dideoxy-3,4-*O*-isopropylidene-α-D-*ribo*-hexopyranoside**, was separated by preparative tlc and was obtained as a syrup (35 mg): nmr data, $\tau$ 5.22 (center of a triplet, $J$ = 4.5 Hz, C-1 proton), 7.92 (center of a two-proton multiplet, C-2 protons), 8.62 (center of a nine-proton triplet, ketal and C-6 methyl protons).

The product was hydrolyzed with 0.02 *N* aqueous sulfuric acid at 60° during 20 min and the solution was neutralized with barium carbonate. Filtration and evaporation of the filtrate gave a syrup which showed essentially one spot corresponding to digitoxose on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:20). Purification by preparative tlc gave 8 mg of crystalline D-digitoxose (**2,6-dideoxy-D-*ribo*-hexose**) which was identical (melting point, ir) with an authentic sample.[36,46]

A similar sequence of reactions was performed starting with **19**, and digitoxose was the major product identified by tlc. In this case the hydride reduction led, in addition to the expected 2,6-dideoxy derivative, to a mixture of products. The nmr spectra of these products lacked the benzylidene acetal proton, and they could presumably be benzyl ethers.

**Reaction of 19 with N-Bromosuccinimide.**—To a solution of **19** (3.0 g) in 150 ml of carbon tetrachloride were added 5 g of barium carbonate and 2 g of NBS, and the mixture was refluxed with stirring for 2.5 hr. Filtration, evaporation of the filtrate, and processing of the resulting syrup afforded a dark yellow syrup (3.9 g) which contained some starting material (tlc, chloroform–2,2,4-trimethylpentane–methanol, 100:40:0.1) in addition to the expected ring-opening product (major product). A portion (0.38 g) of this syrup was purified by preparative tlc to give a syrupy product which, based on subsequent transformations, consisted mainly of **methyl 4-*O*-benzoyl-3-bromo-2,6-dichloro-2,3,6-trideoxy-α-D-mannopyranoside (29)** (0.2 g): ir data, 1720 $cm^{-1}$ (ester).

*Anal.* Calcd for $C_{14}H_{15}O_4BrCl_2$: C, 42.23; H, 3.79; Br, 20.07; Cl, 17.81. Found: C, 42.75; H, 4.24; Br, 19.49; Cl, 17.70.

**Methyl 4-*O*-Benzoyl-6-chloro-2,3-*O*-dideoxy-α-D-*erythro*-hexopyranoside (30). A. From 29.**—A mixture of **29** (0.19 g), 20% palladium on carbon (0.2 g), and barium carbonate in 70 ml of methanol was hydrogenated during 8 hr. The suspension was filtered, and the filtrate was evaporated to a syrup which showed a major spot on tlc, in addition to traces of **29**. Purification by preparative tlc gave the product (80 mg) as a chromatographically homogeneous syrup: ir data, 1730 $cm^{-1}$ (ester); vpc, >94% pure; nmr data, $\tau$ 5.04 (centr of a multiplet, C-4 proton), 5.20 (center of a broad triplet, C-1 proton), 6.65 (singlet, methoxyl protons), 8.05 (center of a two-proton multiplet, C-3, C-4 protons).

*Anal.* Calcd for $C_{14}H_{17}O_4Cl$: Cl, 12.40. Found: Cl, 12.59.

**B. From Methyl 4-*O*-Benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (31).**—An amount of **31**[41] (75 mg) was dissolved in 5 ml of *N*,*N*-dimethylformamide containing 0.1 g of lithium chloride. After refluxing the solution for 1 hr, it was evaporated to dryness, the residue was dissolved in water, and the solution was extracted with ether. Processing the organic phase afforded a pure yellow syrup which was purified by preparative tlc to give **30** as a colorless syrup. This product was found to be >99% pure by vpc analysis and it had the same retention time as **30** obtained above and had emerged from the column before **31**.

**Methyl 2-Azido-3,4-*O*-benzylidene-6-chloro-2,6-dideoxy-α-D-altropyranoside (33).**—A solution of **32** (0.96 g) in 20 ml of 1,1,2,2-tetrachloroethane was added to **2** (0.45 g) in 10 ml of the same solvent. After stirring for 1 hr at room temperature, the pale yellow solution was refluxed for 3 hr. The dark solution was cooled and poured into aqueous sodium bicarbonate and the organic layer was processed as usual. Evaporation gave a light brown syrup which was decolorized from chloroform and evaporated to a dark yellow syrup which showed essentially one major component on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.2, fast); yield 0.95 g. This product was dissolved in ether and passed through a column containing neutral alumina. Evaporation of the first few fractions after the holdup volume gave **33** as a colorless syrup (0.44 g, 47% over-all). Another portion purified further by preparative tlc showed $[\alpha]_D$ + 38.8° (*c* 0.216, chloroform); ir data, 2100 $cm^{-1}$ (azide), no hydroxyl absorption; nmr data, $\tau$ 3.82, 4.11 (benzylic protons, approximate ratio, 1:1, integrate for one proton), 5.38, 5.47 (centers of two doublets, $J_{12}$ = 1 and 1.5 Hz, respectively, integrate for one proton, C-1 proton), 6.51 (singlet, methoxyl

(46) We thank Professor T. Reichstein for a generous sample of D-digitoxose.

protons), etc. The product decomposed on attempted vpc analysis.

*Anal.* Calcd for $C_{12}H_{16}N_3O_4Cl$: Cl, 10.88. Found: Cl, 11.25.

A mixture of this product (0.3 g) in 20 ml of carbon tetrachloride containing 0.18 g of NBS and 0.2 g of barium carbonate was refluxed for 2 hr. The suspension was filtered, and the filtrate was evaporated to a syrup which exhibited a major spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.2). The product (0.3 g) was separated by preparative tlc and the zone corresponding to the major product was isolated and processed to give **methyl 2-azido-4-*O*-benzoyl-3-bromo-6-chloro-2,3,6-trideoxy-α-D-mannopyranoside** (**35**) as a syrup. Catalytic hydrogenation of this product in the presence of palladium on carbon and barium carbonate in methanol afforded a syrup which was dissolved in methanol and treated with acetic anhydride. Evaporation of the solution and purification of the syrupy product by preparative tlc gave **methyl 2-acetamido-4-*O*-benzoyl-6-chloro-2,6-dideoxy-α-D-*arabino*-hexopyranoside** (**36**) (49 mg): ir data, 1718 (ester), 1660 (amide I), 1560 $cm^{-1}$ (amide II); nmr data, $\tau$ 5.40 (singlet, C-1 proton), 7.85 (center of a two-proton multiplet, C-3 proton), 7.96 (singlet, N-acetyl protons), etc.

*Anal.* Calcd for $C_{16}H_{20}ClNO_5$: N, 4.42. Found: N, 4.21.

**Methyl 2-Acetamido-3,4-*O*-benzylidene-6-chloro-2,6-dideoxy-α-D-altropyranoside** (**34**).—To a solution of **33** (0.4 g) in 50 ml of methanol were added excess Raney nickel (previously washed with methanol by decantation) and 5 ml of acetic anhydride. After stirring overnight at room temperature, the catalyst was filtered, the filtrate was evaporated to dryness, the residue was taken up in ether, and some insoluble matter was removed by filtration. Evaporation of the filtrate gave the crystalline product **34**, contaminated with some inorganic salts which were removed by washing the solid with cold 0.1 *N* acetic acid, followed by water. The insoluble crystalline product was homogeneous by tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.4, medium); yield 0.11 g; mp 209–210°; ir data, 1660 (amide I), 1560 $cm^{-1}$ (amide II). Recrystallization of a portion from a small volume of methanol gave an analytical sample; mp 211–212° dec, $[\alpha]_D$ +95° (*c* 0.26, chloroform). This compound was previously reported[11] to have mp 179°, $[\alpha]_D$ + 72° (chloroform).

*Anal.* Calcd for $C_{16}H_{20}NO_5Cl$: C, 56.22; H, 5.89; N, 4.09; Cl, 10.37. Found: C, 55.93; H, 5.83; N, 3.81; Cl, 10.28.

**Attempted Reaction of 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose with (Chloroethylidene)dimethyliminium Chloride.**—A solution of 1 (1.3 g) in 15 ml of 1,1,2,2-tetrachloroethane was added to a cooled suspension of **3** (1 g) in 5 ml of the same solvent. After stirring for 1 hr at room temperature 1 g of **3** was added and the yellow solution was stirred for an additional 24 hr. A 2-ml aliquot was treated with aqueous bicarbonate and the organic layer was processed to give a syrup which exhibited essentially one spot on tlc (hydroxylamine positive) corresponding to the 6-*O*-acetyl derivative **7**: ir data, 1742 $cm^{-1}$ (ester). A small amount of the 6-chloro derivative **8** was also present. The remainder of the reaction mixture was heated under reflux during 3 hr and the dark solution was processed as described for **8**. A syrup was obtained which was identical in all respects with **8** obtained *via* reaction with **2**; yield 0.36 g (25%).

**Attempted Reaction of 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose with (Methoxymethylene)dimethyliminium Methylsulfate.**—A solution of 1 (1.3 g) in 15 ml of chloroform was added to a solution of **12** (5 g) in 5 ml of chloroform. After stirring at room temperature for 4 hr, a portion was treated with aqueous sodium bicarbonate and the organic layer was processed to a colorless syrup which consisted of a mixture of starting material (preponderant) and the 6-*O*-formate ester **6**, as evidenced by tlc. Refluxing the remaining solution for 4 hr, followed by processing in the usual manner, gave a syrup which also consisted mostly of starting material and a small amount of the ester **6** (tlc, ir data).

**Attempted Reaction of Methyl 4,6-*O*-Benzylidene-2-deoxy-2-iodo-α-D-altropyranoside with (Chloromethylene)dimethyliminium Chloride.**—To a solution of **2** (0.39 g) in 6 ml of 1,1,2-trichloroethane was added 0.15 g of **37** in portions at 0°. An aliquot was processed after stirring at room temperature for 3 hr. Examination by tlc revealed the presence of the unsaturated derivative **39**, and two slow-moving components, in addition to some starting material, (chloroform–2,2,4-trimethylpentane–methanol 100:30:1). Prolonged reaction periods led to extensive decomposition (tlc) and no definite products could be isolated. The unsaturated derivative **39**, mp 116–118° (lit.[44,45] 119–129°), could be isolated in about 10–15% yield by preparative tlc of the product after a reaction time of 3–4 hr. The ir spectrum and vpc characteristics of **39** were identical with those of an authentic sample.

Treatment of **39** with stoichiometric amounts of **2** even at temperatures as low as −10° led to the formation of several products and eventual decomposition as evidenced by tlc. At −70°, compound **39** remained mostly unchanged during a few hours in the presence of an equimolar amount of **2**.

**Registry No.**—**8**, 13454-63-2; **14**, 19685-14-4; **19**, 19685-15-5; **20**, 19685-16-6; **21**, 19685-17-7; **24**, 19685-18-8; **26**, 19684-26-5; **29**, 19684-27-6; **30**, 19684-28-7; **33**, 19684-23-2; **34**, 19684-24-3; **36**, 19684-25-4.

# Bile Acids. XXVII. Mechanism of Allomerization of Steroids with Raney Nickel[1]

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The transformation of 3-hydroxy 5β-steroids to 5α compounds by heating with Raney nickel in boiling *p*-cymene proceeds by dehydrogenation to the 3-keto 5β derivative and desaturation to the 3-keto $\Delta^4$-steroids. An equilibrium is established between the 3-keto 5β-, 3-keto $\Delta^4$-, and 3-keto 5α-steroid with the latter predominating. The 4α hydrogen of the steroid is transferred to the *p*-cymene. *p*-Cymene can be replaced with similar aromatic or cycloalkyl hydrocarbons.

Previously[2] it was reported that 3-hydroxy steroids and steroidal sapogenins with *cis*-A/B configuration (5β) undergo epimerization at the 5 position to provide 3-keto-*trans*-A/B (5α) compounds on heating under reflux with freshly prepared Raney nickel in a solvent such as *p*-cymene. This procedure has been successfully applied to normal (5β) cholanoates with various substituents for the preparation of allo-(5α) cholanoates like allodeoxycholic acid,[3] allochenodeoxycholic acid,[4] 3β,7α,12α-trihydroxy-5α-cholanoic acid,[5,6] and allo-

(1) (a) This investigation was supported in part by N.I.H. Grant HE-07878 and AM-09992. (b) The following abbreviations have been used: tlc, thin layer chromatography; glpc, gas–liquid partition chromatography; plc, preparative layer chromatography; ORD, optical rotatory dispersion; unless otherwise mentioned, $R_t$, retention time relative to methyl deoxycholate (methyl 3α,12α-dihydroxy-5β-cholanoate; absolute time, 30 min on QF-1, 36 min on OV-17). $R_f$ and $R_t$ values of different compounds reported in this manuscript have been compared with those of authentic samples and found to be identical.

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