of diethylaminoethyl chloride hydrochloride in 80 ml. of acetone was treated with a solution of 8.4 g. of sodium hydroxide in 7.5 ml. of water. The mixture was heated under reflux for 3 hr. with continuous stirring, then diluted with 50 ml. of water and extracted with benzene. After removal of the solvent from the benzene solution the residual liquid was taken up in 250 ml. of ether. Dry hydrogen chloride was passed into the ethereal solution until precipitation of the crude hydrochloride was complete, yield 15.4 g. (83%). Recrystallization from isopropyl alcohol gave the pure hydrochloride, m.p. 147–148°.

Anal. Calcd. for $C_{16}H_{26}ClN_5O_3$: C, 51.7; H, 7.1; Cl, 9.5; N, 18.8. Found: C, 51.7; H, 7.0; Cl, 9.5; N, 19.1.

2-(3'-Dimethylaminopropyl)-5-(3',4',5'-trimethoxyphenyl)-tetrazole (III) *hydrochloride* was obtained in essentially the same way from I and 3-dimethylaminopropyl chloride hydrochloride, yield 50%, m.p. 162.5–163.5°.

Anal. Calcd. for $C_{15}H_{24}ClN_5O_3$: C, 50.3; H, 6.8; Cl, 9.9; N, 19.6. Found: C, 50.2; H, 6.9; Cl, 10.0; N, 19.4.

2-(3'-Diethylaminopropyl)-5-(3',4',5'-trimethoxyphenyl)-tetrazole (IV) *hydrochloride* was prepared similarly from I and 3-diethylaminopropyl chloride hydrochloride, yield 74%, m.p. 160–161°.

Anal. Calcd. for $C_{17}H_{28}ClN_5O_3$: C, 52.9; H, 7.3; Cl, 9.2; N, 18.2. Found: C, 52.9; H, 7.3; Cl, 9.4; N, 18.3.

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C1-C2 Acetyl Migration on Methylation of the Anomeric 1,3,4,6-Tetra-*O*-acetyl-D-glucopyranoses

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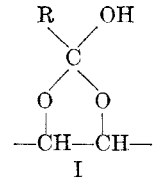
Received April 28, 1959

A need for the hitherto undescribed anomers of 2-*O*-methyltetra-*O*-acetyl-D-glucopyranose has prompted us to attempt their preparation by the direct methylation of the anomeric 1,3,4,6-tetra-*O*-acetyl-D-glucopyranoses with Purdies' reagent. When 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose was methylated with methyl iodide and silver oxide a quantitative yield of a clear sirup resulted, from which crystalline methyl tetra-*O*-acetyl-β-D-glucopyranoside could be isolated in a state of high purity in 81% yield. When 1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose was similarly methylated, the same acetylated methyl β-D-glucopyranoside was obtained crystalline in a yield of 51%. The identity of each reaction product was established by elemental analysis, optical rotation, melting point, mixed melting point, and comparison of its infrared absorption spectrum with that of an authentic sample of methyl tetra-*O*-acetyl-β-D-glucopyranoside.

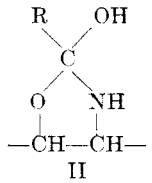
The facile migration of acyl groups in partially acylated polyhydroxylic compounds under mildly alkaline conditions is well known and has been the subject of numerous reports in the literature. Originally discovered and correctly interpreted in 1920 by E. Fischer[1] among partially acylated glycerol esters, acyl migration was apparently first noted in the carbohydrate series by Ohle[2] in 1924, who observed the conversion of 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose into the 6-*O*-benzoyl isomer under the influence of traces of alkali. Since this observation, subsequent investigators have noted migrations of acyl groups involving each carbon except C_6 of the hexose chain as the site of migration origin. Examples of known acyl migrations in the carbohydrate series as well as the conditions producing them are summarized in Table I.

Table I illustrates the variety of positions in the partially acylated aldose chain between which acyl migrations have been demonstrated to occur. In table I it is clear that the present acetyl migrations from C_1 to C_2 during methylation of the anomeric 1,3,4,6-tetra-*O*-acetyl-D-glucopyranoses with Purdies reagent (No. 1) represent acyl migrations of a type not hitherto observed, previous C_1-C_2 migrations having involved only aroyl groups in the ribofuranose (No. 2), glucopyranose (No. 3), and mannitol (No. 4) series under quite different reaction conditions. The present C_1-C_2 acetyl migration confirms in a sense the prediction, based on other considerations, by Lemieux[3] that 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose should possess a tendency to rearrange into the 2,3,4,6-tetra-*O*-acetyl isomer. It is interesting to note that the previously stated generalization[4] that acyl migrations invariably proceed *away* from C_1 and *towards* C_6 appears to be substantiated in most of the examples in Table I. Only in Nos. 7,8,9 and possibly 14 do the acyl migrations proceed in an opposite sense, *i.e.*, towards C_1.

In 1920 E. Fischer[1] suggested intuitively that the mechanism of acyl migration in partially acylated polyhydroxylic systems involved 1,2-ortho acid ester intermediates such as I. This concept was later expanded to include cyclic ortho acid ester intermediates spanning more than merely adjacent carbon atoms to account for acyl migrations over the longer carbon chain systems in the pyranose



I



II

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TABLE I. ACYL MIGRATIONS IN PARTIALLY ACYLATED ALDOSE DERIVATIVES

No.	Migration Origin	Migration Terminus	Acyl Group Migrating	Starting Material	Product	Reaction Conditions	Reference
1	C_1	C_2	Acetyl	1,2	3	4	*a*
2	C_1	C_2	Benzoyl	5	6	7	*b*
3	C_1	C_2	Mesitoyl	8	9	10	*c*
4	C_1	C_3 and/or C_2	Benzoyl	11	12,13	14	*d*
5	C_1	C_4	Acetyl	15	3	4	*e*
6	C_1	C_6	Acetyl	16	3	4	*f*
7	C_2	C_1	Acetyl	17	18	19	*g*
8	C_2	C_1	Acetyl	20	21	19	*b*
9	C_2	C_1	Benzoyl	22	5	19	*b*
10	C_2	C_3	Benzoyl	23	24	7	*h*
11	C_2	C_4	Benzoyl	25	26	27	*i*
12	C_2	C_5	Benzoyl	28	29	30	*j*
13	C_2	C_6	Acetyl	31	32	4	*k*
14	C_3	C_2	Trifluoroacetyl	33	34	35	*l*
15	C_3	C_5	Acetyl	36	37	4	*m*
16	C_3	C_6	Acetyl	38	39	7	*n*
17	C_3	C_6	Benzoyl	40	41	7	*o*
18	C_3 or C_4	C_6	Benzoyl	42	43	44	*p*
19	C_4	C_6	Acetyl	16	15	7	*q*
20	C_4	C_6	Acetyl	45	46	7	*r*
21	C_4	C_6	Acetyl	16	15	47	*s*
22	C_4	C_6	Acetyl	48	49	27	*t*
23	C_5	C_6	Acetyl	50	51	52	*u*

1. 1,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranose
2. 1,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranose
3. Methyl tetra-*O*-acetyl-β-D-glucopyranoside
4. Methylation with MeI, Ag_2O
5. 1,3,5-Tri-*O*-benzoyl-α-D-ribofuranose
6. 2,3,5-Tri-*O*-benzoyl-α-D-ribofuranose
7. Mild alkali
8. 1-*O*-Mesitoyl-tetra-*O*-acetyl-α-D-glucopyranose
9. 2-*O*-Mesitoyl-β-D-glucopyranose
10. NH_3, MeOH, 0°
11. 1,6-Di-*O*-benzoyl-D-mannitol
12. 2,6(or 3,6)-Di-*O*-benzoyl-1,4-anhydro-D-mannitol
13. Di-*O*-benzoyl-1,4:3,6-dianhydro-D-mannitol
14. Anhydride formation with *p*-toluenesulfonic acid catalyst
15. 1,2,3,6-Tetra-*O*-acetyl-β-D-glucopyranose
16. 1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranose
17. Heptaacetylceltrobiosyl chloride
18. 1,3,6-Tri-*O*-acetyl-4-*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-altropyranose
19. Hydrolysis
20. 2-*O*-Acetyl-di-*O*-benzoyl-D-ribofuranosyl bromide
21. 1-*O*-Acetyl-3,5-di-*O*-benzoyl-α-D-ribofuranose
22. Tri-*O*-benzoyl-β-D-ribofuranosyl bromide
23. Methyl 2-*O*-benzoyl-4 6-*O*-benzylidene-α-D-glucopyranoside
24. Methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside
25. Methyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside
26. Methyl 2-*O*-methyl-β-D-galactopyranoside
27. Methylation with MeI, Ag_2O followed by saponification
28. 2,3,4,6-Tetra-*O*-benzoyl-D-glucopyranose
29. 3,4,5,6-Tetra-*O*-benzoyl-D-glucose diethyl mercaptal
30. Mercaptalation with EtSH, HCl
31. Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside
32. Methyl 2-*O*-methyl-tri-*O*-acetyl-α-D-glucopyranoside
33. Methyl 3(?)-*O*-trifluoroacetyl-4,6-*O*-benzylidene-α-D-glucopyranoside
34. Methyl 3-*O*-acetyl-2-*O*-trifluoroacetyl-4,6-*O*-benzylidene-α-D glucopyranoside
35. (1) Ac_2O-pyridine, (2) alcoholysis, (3) $(F_3CCO_2)_2O$, F_3CCO_2Na; structure of 33 not firmly established
36. 3-*O*-Acetyl-6-*O*-trityl-1,2-*O*-isopropylidene-α-D-glucofuranose
37. 5-*O*-Acetyl-3-*O*-methyl-6-*O*-trityl-1,2-*O*-isopropylidene-α-D-glucofuranose
38. 3-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose
39. 6-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose
40. 3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose
41. 6-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose
42. Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-acetyl-β-D-glucopyranoside
43. Methyl 2,6-di-*O*-benzoyl-β-D-glucopyranoside
44. Partial hydrolysis
45. Methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside
46. Methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside
47. Lewis acid catalysts
48. Methyl 4-O-acetyl-2,3-di-*O*-methyl-α-D-glucopyranoside
49. 2,3,4-Tri-*O*-methyl-α-D-glucopyranose
50. Tetra-*O*-acetyl-6-deoxy-6-iodo-D-galactose diethyl mercaptal
51. 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranose
52. Ring closure on demercaptalation with $HgCl_2$

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series.[2,5-10] Fischer's suggested intervention of cyclic intermediates such as I has been substantiated by the isolation of trichloroacetyl derivatives of type I from ethylene glycol[11] and glycerol,[12] as well as by the carbon-14 tracer demonstration[13] that such acyl migrations are indeed *intra*molecular and not intermolecular in nature. Analogous ortho acid imides such as II have similarly been postulated as intermediates in the —O—COR⇌—NH—COR migrations which have been observed in partially acylated amino sugars[14-18] as well as aminophenols.[19]

Examination of molecular models of the single ortho acid ester intermediate which would be required in each of the acyl migrations listed in Table I indicates that in each case (with the somewhat ambiguous possible exceptions of Nos. 11 and 14) such an intermediate can be constructed provided that the ring system first assumes a proper unique conformation. It has been suggested[14,20] that those acyl migrations which span a large number of carbon atoms may proceed *via* a series of consecutive migrations each spanning fewer carbons (*e.g.*, $C_2 \rightarrow C_6$ *via* $C_4 \rightarrow C_6$, $C_3 \rightarrow C_4$, and $C_2 \rightarrow C_3$) and each involving ortho acid ester intermediates of smaller ring size. While there is no direct experimental evidence on this point and while factors of conformational stability or instability may require such a mechanism, the model examinations referred to above suggest at least that such consecutive acyl migrations are in general not of *geometrical* necessity. While ortho acid ester intermediates are now commonly accepted as being involved in acyl migrations[5-10,11-13] there appears to be no unambiguously established case of the isolation of a *stable* ortho acid ester in the carbohydrate series.[21]

In the present $C_1 \rightarrow C_2$ acetyl migration a model of the presumably most stable "C_1" chair conformation of the pyranose ring[22] permits the construction of a cyclic 1,2-ortho acid ester intermediate with almost equal ease from either anomer of 1,3,4,-6-tetra-*O*-acetyl-D-glucopyranose, thus rationalizing perhaps the essentially equivalent production of rearranged product from either of our anomeric starting materials.

EXPERIMENTAL

Anomers of 1,3,4,6-tetra-O-acetyl-D-glucopyranose. These were prepared by the action of silver acetate in acetic acid upon the two anomers of 3,4,6-tri-*O*-acetyl-D-glucopyranosyl chloride after the method of Lemieux.[23] The α-tetraacetate had m.p. 98.8° and $[\alpha]_D^{25}$ +142° (c, 1.8; $CHCl_3$) after two recrystallizations, while the β-tetraacetate showed m.p. 135.5–136° and $[\alpha]_D^{25}$ +18.4° (c, 1.5; $CHCl_3$) after one recrystallization. These physical properties are in substantial accord with those reported by Lemieux,[23] and the two products were methylated without further purification.

Methylation of 1,3,4,6-tetra-O-α-D-glucopyranose. 2.20 g. of the above α-tetraacetate was dissolved in methyl iodide (60 ml.). The solution was treated with silver oxide (12 g.), Drierite (10 g.), and glass beads. The mixture was shaken at room temperature for 24 hr., treated with additional silver oxide (10 g.) and shaken for another 20 hr. After filtration the cake was rinsed with acetone and ether, and the filtrate and rinsing were evaporated *in vacuo* to yield 2.34 g. (102%) of amber sirup which crystallized rapidly on addition of ether (15 ml.). Pentane (25 ml.) was added and the mixture was chilled, producing 1.76 g. of methyl tetra-*O*-acetyl-β-D-glucopyranoside, m.p. 103.8–104.3°, mixed m.p. with an authentic sample undepressed, $[\alpha]_D^{25}$ −17.85° (c, 1.7; $CHCl_3$), infrared spectrum in $CHCl_3$ solution identical with that of an authentic sample. From the mother liquors an additional 0.10 g. of product was obtained: total yield was 81.2%.

Methylation of 1,3,4,6-tetra-O-acetyl-β-D-glucopyranose. The above β-tetraacetate (5.0 g.), methyl iodide (100 ml.), silver oxide (20 g.), Drierite (20 g.), and glass beads were stirred under reflux for 4 hr., then at room temperature for 16 hr. Filtration and solvent removal yielded 5.50 g. (106%) of amber sirup, $[\alpha]_D^{25}$ −1.2° (c, 2.5; $CHCl_3$). This was dissolved in 2-propanol (10 ml.) and ligroin (10 ml.), producing 1.82 g. of sturdy prisms, m.p. 101.3–102°. The mother liquors were decolorized and stripped of solvent and the residue was redissolved in ether (15 ml.) and pentane (to turbidity). The chilled, seeded solution produced an additional 0.83 g. of product, m.p. 99.3–100.3°. The 2.65 g. (51%) of crystalline product was recrystallized twice from 2-propanol giving 2.30 g. of methyl tetra-*O*-acetyl-β-D-glucopyranoside of m.p. 102.3–103° and $[\alpha]_D^{25}$ −17.4° (c, 1.3; $CHCl_3$).

Anal. Calcd. for $C_{15}H_{22}O_9$. C, 49.72; H, 6.12. Found: C, 49.93, 50.02; H, 6.10, 6.16.

The above product showed no mixed m.p. depression with, and had an infrared absorption spectrum in chloroform identical with, that of an authentic sample.

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