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Preliminary communication

Favored direction of the isopropylidenation of 1-*C*-substituted L-*threo*-glycerol*

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Partial protection of the polyhydroxyalkyl moieties of *C*-nucleosides is needed in our laboratory, in connection with a program[1–5] devoted to the synthesis and modification of *C*-nucleosides and other heterocyclic compounds. In this report, the isopropylidenation of the glycerol-1-yl residue of **1** has been reinvestigated, and the product was found to have an α-T acetal ring, not an α-terminal one. Both the thermodynamic and kinetic products could be synthesized, and the factors governing their formation are discussed. When the progress of the reaction, under the experimental conditions of Ohle[6], was monitored by thin-layer chromatography, it became evident that the end-product that is isolated from the reaction is the thermodynamic product, and that it differs from the kinetic product, which is formed in the first stage of the reaction. One of the conventional factors governing the products of acetalation is the disposition of the hydroxyl groups available, where the relative free-energy of the conceivable products at equilibrium will be decisive.

The *threo* configuration of the hydroxyl groups provides a disposition favorable for the isopropylidene group to afford an α-T ring[†], the formation of which should lead to a ring more stable than that of the terminal α-ring, because of the more-symmetrical substitution on the ring[8]. Consequently, structure **3** for the isopropylidenation product isolated after equilibrium, which is the thermodynamically controlled product, should be favored over that reported earlier[5,6]. However, mechanistically, the product formed in the first stage of the reaction should have an α-terminal ring, as in **7**.

The structure of **3** was verified by a combination of chemical and spectroscopic tools. Acetylation and benzoylation of **3** respectively afforded the mono-acylated derivatives **4** and **5**, whose ^{1}H-n.m.r. spectra (see Table I) showed a pronounced, down-field shift of the terminal methylene protons compared to that of those of the parent isopropylidene derivative **3**, indicating their attachment to a carbon atom bearing an acyloxy group, com-

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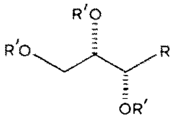
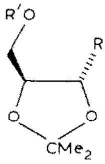
[*] Acetals, Part I.
[**] To whom enquiries should be addressed.
[†] The system of nomenclature used here for cyclic acetals was introduced by Barker and Bourne[7].

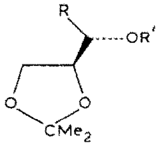




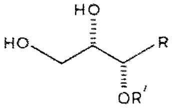
R = 1-phenyl-4-(phenylhydrazono)-4,5-pyrazolinedione-3-yl

1 R' = H
2 R' = Bz

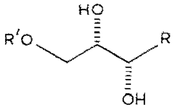
3 R' = H
4 R' = Ac
5 R' = Bz
6 R' = Ts



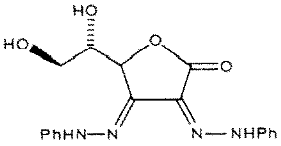
7 R' = H
8 R' = Ac
9 R' = Bz



10 R' = Bz



11 R' = Bz



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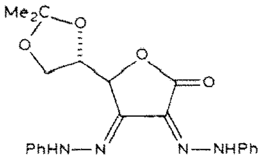

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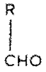

14

TABLE I

^{1}H-N.M.R.-SPECTRAL[a] AND OTHER PHYSICAL DATA

Compound	*Yield (%)*	*M.p. (degrees)*	*H-3'*	*H-3*	*H-2*	*H-1*
3	78	170–171	3.8	3.9	4.80	5.15
4	91	154–155	4.2	4.4	4.82	4.94
5	79	150–151	4.6		5.00	5.17
6	79	166–167	4.3		4.80	4.96
7	90	170–171	4.0	4.1	4.70	4.80
8	91	140–141	3.9	4.1	4.76	6.02
9	82	158–159	4.1	4.2	4.90	6.36
10	90	186–188	3.8		4.53	6.43
11	68	156–157	4.6			5.06
2	75	152–153	4.7	4.8	6.30	6.73
13	45	185–186	4.2		4.45	5.07

[a] Chemical shifts given in δ values, for solutions in $CDCl_3$, with Me_4Si as the internal standard.

parison with the tri-*O*-benzoylated derivative **2** confirmed the assignment. The resonances of the two methine protons, H-1 and H-2, did not suffer any appreciable change. Furthermore, *O*-deisopropylidenation of **5** with aqueous trifluoroacetic acid (90%) afforded **11**, whose per-*O*-benzoylation gave the corresponding tribenzoate **2**. On periodate oxidation, **11** underwent glycol cleavage, affording 3-formyl-1-phenyl-4,5-pyrazoledione 4-(phenylhydrazone) (**14**). This decisively indicated the location of the cyclic acetal ring on the two secondary hydroxyl groups, O-1 and O-2. Consequently, the isopropylidenation product was assigned the structure 3-(1,2-*O*-isopropylidene-L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazolinedione-4-(phenylhydrazone) (**3**), and the acyl derivatives must be **4**–**6**.

The synthesis of the other 1,3-dioxolane, namely, 3-(2,3-*O*-isopropylidene-L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**7**), which is presumably the kinetic product of the isopropylidenation of **1**, was achieved by starting with a precursor already having the isopropylidene group on O-2 and O-3. Isopropylidenation of L-*threo*-2,3-hexodiulosono-1,4-lactone 2,3-bis(phenylhydrazone) (**12**) afforded the 5,6-*O*-isopropylidene acetal **13** [$\nu_{\max}^{\mathrm{KBr}}$ 1750 cm^{-1} (COO)], whose rearrangement by the action of alkali, and acidification, resulted in opening of the lactone ring; acidification afforded the isopropylidene acetal **7** [$\nu_{\max}^{\mathrm{KBr}}$ 1660 cm^{-1} (OCN)]. Acetylation and benzoylation of **7** respectively furnished the acyl derivatives **8** and **9**. Acid hydrolysis of **9** afforded **10**. The ^{1}H-n.m.r. spectra of the latter series of derivatives (**7**–**10**) showed a down-field shift of the doublet due to the H-1 of the glycerol-1-yl side-chain, on acylation, and this was anticipated from its geminal attachment to acyl groups.

The isopropylidene acetal **7** was found to be the one formed at the first stage of the isopropylidenation; it undergoes migration of the isopropylidene group, affording **3**. Conversion of **7** into **3** was achieved by means of sulfuric acid in acetone, confirming that **3** must be the thermodynamic, and **7** the kinetic, product. Similar reactions have been extended[9] to various derivatives and analogs of **1** and **12**.

In conclusion, isopropylidenation of the 1-*C*-substituted L-*threo*-glycerol **1** affords the corresponding 1,2-isopropylidene acetal **3**, not the 2,3-isopropylidene acetal **7**, and derivatives thereof are those of **3**, not of **7**.

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