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AN APPROACH TO BI-TETRAHYDROFURANS FROM GLUCOSE AND A CORRECTION OF THE LITERATURE

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Abstract: The condensation of glucose with acetylacetone in the presence of zinc chloride has been found to yield the tetrahydrofuranylfuran **4** in lieu of the pyranopyran **3** reported previously.

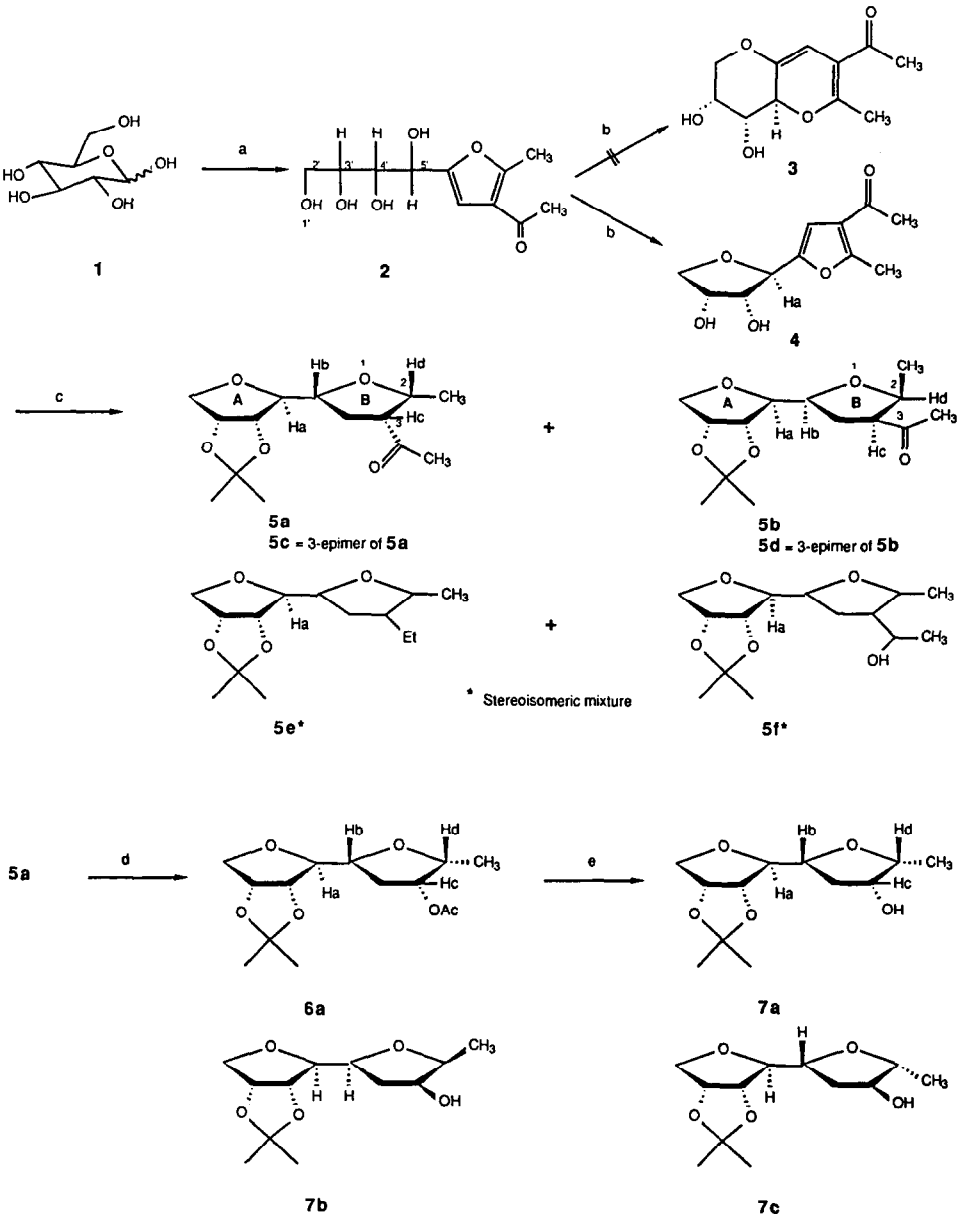
During efforts to devise an efficient means for gaining access to certain pyranopyrans, [1] our attention was drawn to a literature report published in 1945 which disclosed the preparation of the 1,5-dioxanaphthalene **3** by condensation of glucose with acetylacetone followed by acid catalyzed rearrangement of the initially formed furan **2**.[2,3]

On repeating this work, we were surprised to find that **3** was not formed when **2** was heated with 10% aqueous acetic acid. Instead, the tetrahydrofuranylfuran **4** was the sole product isolated (**1**→**2**→**4**, 31.3% yield). This structure was fully corroborated by a single crystal x-ray analysis of both **4** and its derivative the bi-tetrahydrofuran **7c** (vide infra). Thus it is clear that a ring closing reaction had occurred between the 1' oxygen atom and the 5' carbon atom of the tetraol **2** in lieu of the more extensive rearrangement process required to produce the pyranopyran structure **3**. Prolonged heating of **4** under acidic conditions failed to provide any further rearrangement products. Since the optical rotation and melting point reported for **3** are close to those found for **4**,[4] we must conclude that the original work[2] is in error and that **4** is the actual product formed by exposure of **2** to acid.

While the foregoing results certainly curtailed the intended application of this chemistry to pyranopyran synthesis, we decided to investigate the possible transformations of **4** to tetrahydrofuranyltetrahydrofurans. Since such bi-tetrahydrofurans constitute part structures of many naturally occurring antibiotic systems,[5] the additional effort appeared worthwhile.

Specifically, the behavior of **4** to a variety of hydrogenation conditions was examined. When Pd/C was employed as the catalyst, hydrogenation of **4** followed by acetonization gave rise to a mixture of products of

Scheme 1. Bi-Tetrahydrofuran Synthesis



Reaction conditions:

a. $CH_3COCH_2COCH_3$, CH_3OH, $ZnCl_2$; b. 10% HOAc - H_2O, 105 °C, 3 hr.;

c. 10% Pd / $BaSO_4$, C_2H_5OH, r.t., H_2; $(CH_3)_2C(OCH_3)_2$, CH_2Cl_2, cat. PPTS;

d. CF_3CO_3H, Na_2HPO_4, CH_2Cl_2; e. 5% KOH - CH_3OH

which **5e** was the major component. On the other hand, the use of 10% Pd/C on $BaSO_4$ as catalyst under 1 atm of hydrogen afforded after acetonization the bi-tetrahydrofuran **5a** as the major reaction product (30% isolated yield) in addition to **5b** - **5f**.[6,7] While attempts to carry out a Baeyer-Villiger reaction on **5a** failed using MCPBA[8] or 3,5-dinitroperoxybenzoic acid,[9] trifluoroperacetic acid buffered with Na_2HPO_4 afforded the acetate **6a** in 70% yield. Upon base hydrolysis, the acetate **6a** was converted to the alcohol **7a** which spectroscopically exhibited strong intramolecular hydrogen bonding.[7] Bi-tetrahydrofurans **7b** and **7c** were prepared in a similar fashion from **5b** and **5c**. The structure of alcohol **7c** was ensured through a single crystal x-ray analysis.

The structures of the minor compounds (**5b** - **5d** and **5f**) formed in the hydrogenation reaction were confirmed as follows. Since the ketones **5c** and **5d** were formed from **5a** and **5b**, respectively, by DBU/MeOH treatment, they must represent the C-3 epimers of the latter. Compound **5f**, on the other hand, can be oxidized with PCC in CH_2Cl_2 to a mixture of **5a** and **5b**. Thus **5f** must be the corresponding alcohol which is formed as a mixture of streoisomers.

The structure of **5b** is depicted as such for the following reasons: (a) the $J_{c,d}$ coupling constants (8.2 Hz) are identical for **5a** and **5b** suggesting the same cis relationship between the methyl and acetyl groups. The cis-stereochemistry is further supported by the ease of epimerization of the C-3 center of **5a** and **5b**, and the closeness of the $J_{c,d}$ coupling constants for the alcohol derivatives **7a** and **7b** (2.54 and 2.90 Hz, respectively), (b) since **5a** was formed from **4** by the delivery of hydrogen to a single face of the furan ring, it appears likely that the all-cis delivery of four hydrogen atoms to the other face of the furan ring should take place as well. The obtention of *cis*-2,5-disubstituted tetrahydrofurans from 2,5-disubstituted furans is, of course, well precedented.[10] Compound **5b** therefore has all three of its substituents on the same side of the B-ring, but these are all "up" rather than all "down" as in **5a**. The conformations of **7a** and **7b** are such that intramolecular hydrogen bonding is observed in the ^1H NMR spectra of each.

The present work thus provides a relatively novel approach to certain bi-tetrahydrofurans. Details regarding the biological activity of compounds **7a** and **7b** will be reported elsewhere.[11]

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4. **4:** mp 107.5-108.5°C (lit.[2] mp 102°C); $[\alpha]_D^{23}$ -118° [lit.[2] $[\alpha]_D^{20}$ -104°(c 0.4, CH_3OH)] (c 0.9.CH_3OH); ^1H NMR ($CDCl_3$) δ 6.60 (s, 1H), 4.64 -4.66 (d, 1 H, J = 6.4 Hz), 4.36-4.40, (m, 2H), 4.22-4.27 (dd, 1H, J = 10 and 4.7 Hz), 3.87-3.91 (dd, 1 H, J = 10 and 2.3 Hz), 3.35 (br s, 1 H, OH), 3.50 (br s 1 H, OH) 2.57 (s, 3H), 2.38 (s, 3H); exact mass calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0832. **2:** mp 151-151.5°C (lit.[2] mp 152°C; $[\alpha]_D^{23}$ -16° (c 1.9, H_2O) [lit.[2] $[\alpha]_D$ -18° (c 5.0, H_2O)].

5. See, for example Mizutani, T.; Yamagishi, M.; Hara, H.; Omura, S.; Ozeki, M.; Mizoue, K.; Seto, H.; Otake, N. *J. Antibiot.*, **1980**, *33*, 1224; Jouany, J.P.; Bertin, G.; Thivend, P. *Reprod. Nutr., Dev.*, **1986**, *26* (1B), 295; David, L.; Ayala, H.L.; Tabet, J.C. *J. Antibiot.*, **1985**, *38*, 1655; Brown, M.A.; Rajan, S. *J. Agric. Food Chem.*, **1986**, *34*, 470; Ubukata, M.; Hamazaki, Y.; Isono, K. *Agric. Biol Chem.* **1986**, *50*, 1153; Isono, K.; Hamazaki, Y.; Ubukata, M. *Chem. Abstr.*, **1985**, *104*, 130219e; Penrose, A.B.; Ruddock, J.C.; Shibakawa, R.; Tone, J.*Chem. Abstr.*, **1982**, *97*, 196808q; Cane, D.E.; Liang, T.C.; Hasler, H. *J. Am. Chem. Soc* **1982**, *104*, 7274; Smith, G.D.; Strong, P.D.; Duax, W. L. *Acta Crystallogr.*, Sec. B, **1978**, B34, 3436; Occolowitz, J.L.; Dorman, D.E.; Hamill, R.L. *J. Chem. Soc., Chem. Commun.*, **1978**, 683; Celmer, W.D.; Cullen, W.P.; Jefferson, M.T.; Moppett, C.E.; Routien, J.B.; Sciavolino, F.C. *Chem. Abstr.* **1978**, *90*, 150295x.

6. The ratio of hydrogenation products is 3:1:1:1:0.5 for **5a**:**5b**:**5c+5d**:**5e**:**5f**. The R_f values on E. Merck 60, F-254 glass TLC plates using ethyl acetate as the developing solvent are 0.51, 0.56, 0.70, 0.70, 0.88 and 0.30 for **5a-5f**, respectively.

7. The spectral and physical data for **5a**, **5b**, **7a**, **7b** and **7c** are:

5a: $[\alpha]_D^{23}$ -36.5° (c 2.2, CH_3OH); IR (thin film) 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.81-4.85 (ddd, 1H, J = 6.3, 4.4. 1.5 Hz), 4.69-4.72 (dd, 1 H, (J = 6.3, 1.8 Hz), 4.26-4.31 (m, 1 H), 3.88-4.09 (m, 4 H), 3.24-3.33 (m, 1 H, $J_{c,d}$ = 8.2 Hz) 2.29-2.39 (m, 1H), 2.18 (s, 3H), 1.90-1.98 (m, 1 H), 1.52 (s, 3H), 1.35 (s, 3 H), 1.10 and 1.13 (d 3 H, J = 6.5 Hz); exact mass calcd for $C_{13}H_{19}O_5$ 255.123729, found 255.123779.

5b: $[\alpha]_D^{23}$ -38.4° (c 1.5, CH_3OH), IR (thin film) 1707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.90-4.93 (dd, 1 H, J = 6.3, 1.2 Hz), 4.76-4.80 (ddd, 1 H, J = 6.3, 4.0, 1.8 Hz), 4.26-4.30 (m, 1 H), 4.06-4.08 (dd, 1 H, J = 4.5, 1.2 Hz) 3.87-4.00 (m, 3 H), 3.27-3.35 (m, 1 H, $J_{c,d}$ = 8.0 Hz), 2.19 (s, 3 H), 2.03-2.17 (m, 2 H),1.52 (s, 3 H), 1.37 (s, 3 H), 1.12 and 1.14 (d, 3 H, J = 6.4 Hz); exact mass calcd for $C_{14}H_{21}O_5$ 269.1388, found 269.139969.

7a: $[\alpha]_D^{23}$ -80.8° (c 0.5, CH_3OH); IR (thin film) 3387.4 cm^{-1} (sharp); ^1H NMR ($CDCl_3$) δ 4.83-4.91 (m, 2 H), 4.20-4.25 (m, 2 H), 3.99-4.02 (m, 2 H), 3.88-3.94 (m, 1 H), 3.78-3.83 (td, 1 H, $J_{c,d}$ = 2.5 Hz), 3.53 and 3.56 (d, OH, J = 10.6), 2.37-2.47 (m, 1 H), 1.91-1.97 (dd, 1 H, J = 14.2, 2.9 Hz), 1.52 (s. 3 H), 1.35 (s, 3 H), 1.23 and 1.25 (d, 3 H, J = 6.3 Hz), exact mass calcd for $C_{11}H_{17}O_5$ 229.10759, found 229.108490.

7b: $[\alpha]_D^{23}$ -7.8° (*c* 6.1, CH_3OH); IR (thin film) 3453 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.77-4.82 (m, 1 H), 4.58-4.62 (dd, 1H, J = 6.4, 3.8 Hz), 4.02-4.16 (m, 4 H), 3.92-3.97 (dd, 2 H, J = 10.2, 2.7 Hz), 3.77-3.81 (td, 1 H, $J_{c,d}$ = 2.9 Hz), 2.63-2.66 (d, OH, J = 8.5 Hz), 2.29-2.38 (m, 1 H), 1.72-1.78 (m, 1 H), 1.53 (s, 3 H), 1.35 (s, 3 H), 1.26 and 1.28 (d, 3 H, J = 6.3 Hz).

7c: $[\alpha]_D^{23}$ -41.6° (*c* 1.4, CH_3OH); IR (thin film) 3433 cm^{-1}; ^1H NMR ($DCDl_3$) δ 4.82-4.86 (m, 1 H), 4.76-4.78 (dd, 1 H, J = 6.3, 1.3 Hz), 4.17-4.24 (m, 1 H), 3.92-4.09 (m, 4 H),3.80-3.87 (td, 1 H, $J_{c,d}$ = 3.24), 2.15-2.25 (m, 1 H), 1.77-1.84 (m, 1 H), 1.51 (s, 3 H), 1.35 (s, 3 H), 1.19 and 1.21 (d, 3 H, J = 6.41 Hz); exact mass calcd for $C_{11}H_{17}O_5$ 229.10759, found 229.105499.

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