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Note

Synthesis of (polyhydroxyalkyl)heterocycles: preparation of (dihydroxyethyl)tetrahydropyrimidines

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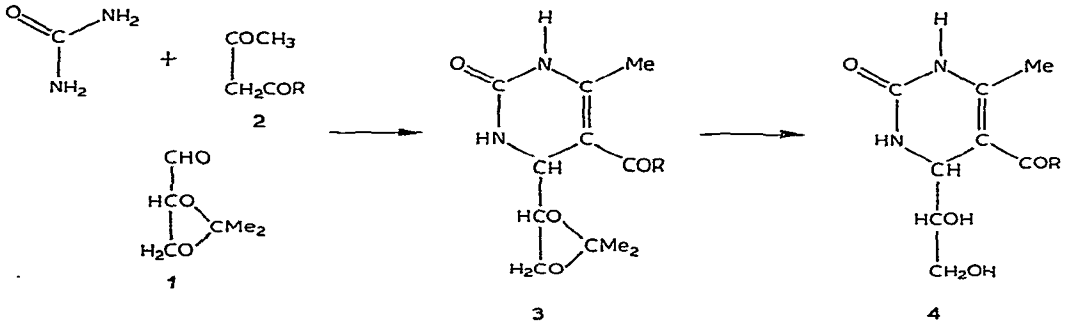
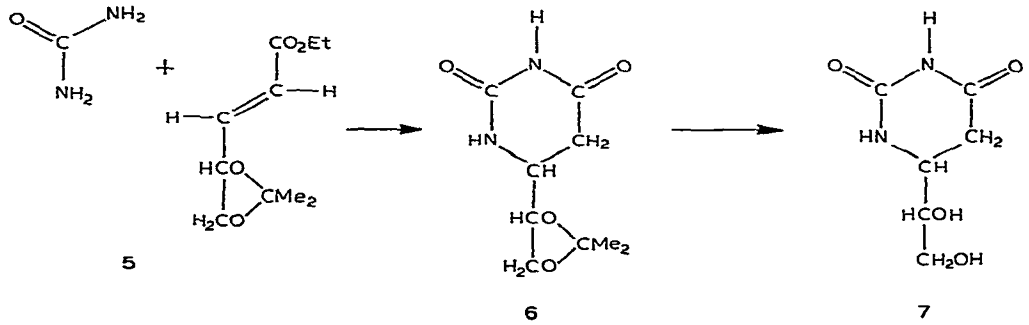
In studying (polyhydroxyalkyl)heterocycles[1], we have applied the Biguinelli reaction[2] to aldehydo derivatives of monosaccharides. 2,3-*O*-Isopropylidene-D-



a series, R = OEt
b series, R = OMe
c series, R = Me



glyceraldehyde (**1**) reacts with active methylene compounds (**2**) and urea, yielding the corresponding tetrahydropyrimidines. Thus, methyl and ethyl acetoacetate yielded 4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-methoxycarbonyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (**3b**) and the 5-ethoxycarbonyl derivative (**3a**), respectively.

The yields of these pyrimidine derivatives were low (16–25%); when the reaction was applied to pentane-2,4-dione (**2c**), no product was obtained. Since the Biguinelli reaction is acid catalysed, reactions of **2c** were performed in the presence of hydrochloric acid, and a low yield of 5-acetyl-4-[(*S*)-1,2-dihydroxyethyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (**4c**) was obtained. Hydrolysis of the isopropylidene group under the acid conditions would yield D-glyceraldehyde, thus creating other possibilities for reaction such as the formation of furan derivatives[5] and the Knoevenagel reaction[6]. The other products formed from the reaction of **2c** were not identified.

Acid hydrolysis of **3a** and **3b** gave the respective dihydroxyethyl derivatives **4a** and **4b**, which consumed the expected amount of periodate, as did **4c**.

The aldehydic products of these reactions could not be isolated pure. When the periodate oxidation of **4b** was monitored by p.m.r. spectroscopy, the appearance of signals corresponding to the hydrate of the expected aldehyde, 4-formyl-6-methoxycarbonyl-5-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine, was detected.

C-(Polyhydroxyalkyl)tetrahydropyrimidines may also be synthesised by the Phillippe and Spenner reaction[3]. Thus, the reaction of urea with ethyl (*S*)-4,5-isopropylidenedioxy-*trans*-2-pentenoate[4] (**5**) in a sealed tube at 140° gave the expected 4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,6-dioxohexahydropyrimidine (**6**), which yielded the glycol **7** on acid hydrolysis.

EXPERIMENTAL

General methods. — Melting points are uncorrected. I.r. spectra were recorded for KBr discs with a Beckman Aculab IV spectrometer, and ^{1}H-n.m.r. spectra with a Perkin–Elmer–Hitachi R-20B or Perkin–Elmer R-24B spectrometer.

Solvents were evaporated under diminished pressure at <40° using a rotary evaporator.

4-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5-ethoxycarbonyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (**3a**). — Urea (6 g, 0.1 mol), **1** (13 g, 0.1 mol), and ethyl acetoacetate (26 g, 0.2 mol) were successively dissolved in ethanol (40 ml). After being heated under reflux for 5 h, the mixture was kept at ~5° to give **3a** (7.6 g). Recrystallisation from ethanol gave material (5.2 g) having m.p. 208–210°, $[\alpha]_D^{20}$ $-113°$ (*c* 1.7, chloroform); ν_{max} 3360, 3230, 3110, 2980, 1920, 1720, 1690, 1640, 1370, 1220, and 1090 cm^{-1}. N.m.r. data (CDCl$_3$, internal Me$_4$Si): δ 8.50–8.90 (bs, 1 H, NH-1, exchangeable with D$_2$O), 5.9–6.5 (bs, 1 H, NH-3, exchangeable with D$_2$O), 3.7–4.4 (m, 4 H, H-1′,2′a,2′b,6), 4.16 (q, 2 H, *J* 7 Hz, H-1″), 2.3, 1.4, 1.3 (3 s, 9 H, 3 Me), and 1.33 (t, 3 H, *J* 7 Hz, H-2″).

Anal. Calc. for $C_{13}H_{20}N_2O_5$: C, 54.98; H, 6.89; N, 9.70. Found: C, 54.92; H, 7.09; N, 9.81.

4-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5-methoxycarbonyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (**3b**). — Use of the foregoing procedure with methyl acetoacetate gave **3b** (12%), m.p. 211–213°, $[\alpha]_D^{20}$ −123° (*c* 2, chloroform). With 1:1:1 ratios of reactants, the yield was 16%. The product had ν_{max} 3290, 2970, 2870, 1690, 1630, 1430, 1230, and 1100 cm^{-1}. N.m.r. data: δ 8.82 (bs, 1 H, NH, exchangeable with D_2O), 6.48 (bs, 1 H, NH, exchangeable with D_2O), 3.71–3.40 (m, 4 H, H-1',2'a,2'b,6), 3.70 (s, 3 H, OMe), 2.28 (s, 3 H, Me), 1.4 and 1.3 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.16; H, 6.73; N, 10.24.

Acid hydrolyses. — (*a*) A solution of **3a** (1.2 g) in acetic acid–water (10 ml, 1:1) was heated under reflux for 1 h and then concentrated, and traces of acetic acid were removed by evaporation of water (5 ml) from the residue. Recrystallisation of the residue from ethyl acetate and then from acetone gave 4-[(*S*)-1,2-dihydroxyethyl)-5-ethoxycarbonyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (**4a**, 1 g), m.p. 203–205°, $[\alpha]_D^{20}$ −188° (*c* 1, pyridine); ν_{max} 3250, 3110, 2900, 1720, and 1670 cm^{-1}. N.m.r. data (D_2O, internal DSS): δ 3.6–5.0 (m, 4 H, H-1',2'a,2'b,6), 4.2 (q, 2 H, *J* 8 Hz, H-1"), 2.28 (s, 3 H, Me), and 1.28 (t, 3 H, *J* 8 Hz, H-2").

Anal. Calc. for $C_{10}H_{16}N_2O_5$: C, 49.17; H, 6.59. Found: C, 49.02; H, 6.47.

(*b*) Hydrolysis of **3b**, as described for **3a**, gave 4-[(*S*)-1,2-dihydroxyethyl]-5-methoxycarbonyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (**4b**, 0.9 g), m.p. 218–219°, $[\alpha]_D^{20}$ −224° (*c* 0.5, pyridine); ν_{max} 3400, 3350, 3280, 3220, 3150, 2980, 2900, 1710, 1650, 1250, and 1090 cm^{-1}. N.m.r. data (Me_2SO-d_6, internal Me_4Si): δ 8.74 (bs, 1 H, NH), 6.72 (bs, 1 H, NH), 4.0–4.7 (m, 4 H, H-1',2'a,2'b,6), 3.75 (s, 3 H, OMe), 2.17 (s, 3 H, Me), and 3.3 (s, 2 H, OH).

Anal. Calc. for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.12; N, 12.16. Found: C, 46.97; H, 6.21; N, 12.05.

5-Acetyl-4-[(S)-1,2-dihydroxyethyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (**4c**). — To a solution of urea (7.3 g) and **1** (16 g) in ethanol (75 ml) was slowly added, under reflux during 1 h, a solution of pentane-2,4-dione (12.3 g) and conc. hydrochloric acid (3 drops) in ethanol (25 ml). Heating was then continued for 1.5 h. The volume of the resulting, red solution was decreased to half. Addition of ethyl acetate then gave a white solid (100 mg). Recrystallisation from ethanol gave **4c**, (m.p. 180–181°; ν_{max} 3300, 2900, 1720, 1620, 1590, and 1260 cm^{-1}.

Anal. Calc. for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.58; N, 13.07. Found: C, 50.12; H, 6.59; N, 12.67.

6-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5,6-dihydrouracil (**6**). — A mixture of urea (6 g) and ethyl (*S*)-4,5-isopropylidenedioxy-*trans*-2-pentenoate (**5**, 10 g) in ethanol (10 ml) was heated for 18 h at 140° in a sealed tube. Upon cooling, **6** (2.3 g) crystallised. Recrystallisation from ethanol gave material having m.p. 266–268° (dec.), $[\alpha]_D^{20}$ −68° (*c* 0.9, pyridine); ν_{max} 3230, 3080, 2980, 2890, 1700, 1240, 1200, and 1075 cm^{-1}. N.m.r. data (Me_2SO-d_6, internal Me_4Si): δ 7.97 (bs, 1 H, NH), 7.4 (bs, 1 H, NH), 3.7–4.0 (m, 4 H, H-1′,2′a,2′b,6), 2.3–3.1 (m, 2 H, H-5), 1.26 and 1.22 (2s, 3 H, 2 Me).

Anal. Calc. for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.58. Found: C, 50.37; H, 6.50%.

Acid hydrolysis of **6**. — The ketal **6** (1.4 g) was hydrolysed by acetic acid–water (10 ml, 1:1) for 30 min at 95°. The solvent was removed, water was added and distilled to remove traces of acid, and the residue was recrystallised from ethanol to give 6-[(*S*)-1,2-dihydroxyethyl]-5,6-dihydrouracil (**7**, 0.55 g), m.p. 173–175°, $[\alpha]_D^{20}$ −48° (*c* 0.9, pyridine); ν_{max} 3350, 3270, 3180, 3100, 2900, 1710, 1660, and 1190 cm^{-1}. N.m.r. data (D_2O, internal DSS): δ 3.5–4.0 (m, 4 H, H-1′,2′a,2′b,6) and 2.73 (m, 2 H, H-5).

Anal. Calc. for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.79. Found: C, 41.30; H, 5.78%.

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