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Preliminary communication

A new method for the synthesis of aldityl derivatives of heterocyclic compounds*

HAJIME KOMURA, TERUO YOSHINO, and YOSHIHARU ISHIDO

Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, O okayama, Meguro-ku, Tokyo 152 (Japan)

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In a previous paper[1] of this series, condensation of ethylene carbonate (**1**) with a variety of phenols, catalyzed by tetraethylammonium halides was reported, the reaction was accompanied by evolution of carbon dioxide, and afforded the corresponding aryl 2-hydroxyethyl ethers in good yields. Moreover, such a condensation of **1** with heterocyclic species in the absence or presence of tetraethylammonium halides has recently been established[2], this reaction similarly afforded the corresponding 2-hydroxyethylated heterocyclic compounds in fairly good yields.

On the basis of these facts, we have examined the possibility of synthesizing some aldityl derivatives of heterocyclic compounds by means of a similar condensation reaction of 1,2,3,4-di-*O*-isopropylidene-D-mannitol 5,6-carbonate[3] (**2**) with theophylline (**3**), 6-(benzylamino)purine (**4**), 5,6-dimethylbenzimidazole (**5**), phthalimide (**6**), and succinimide (**7**), respectively, in the presence of tetraethylammonium bromide as the catalyst.

A mixture of **2** (2.9 g, 10 mmoles), tetraethylammonium bromide (0.5 g, 2.5 mmoles), and **3** (2.0 g, 11 mmoles) in *N,N*-dimethylformamide (DMF) (10 ml) was heated for 8.0 h at 50–160°, the mixture was then evaporated to dryness *in vacuo*, the residue was dissolved in chloroform, and the solution was successively washed with 1M aqueous sodium hydroxide solution and water, and evaporated to dryness. The resulting crude crystals were recrystallized from benzene–cyclohexane to afford 7-(1-deoxy-3,4,5,6-di-*O*-isopropylidene-D-mannitol-1-yl)theophylline[4,5] (**8**) (3.2 g, 75% yield), m.p. 160–161°, $[\alpha]_D^{20}$ +47.2° (*c* 1.0, chloroform), λ_{max}^{EtOH} 273 nm (ϵ_{mM} 9.40). Periodate oxidation of 7-(1-deoxy-D-mannitol-1-yl)theophylline[6] (**9**), which was obtained by boiling a solution of **8** in methanolic hydrogen chloride under reflux for ~10 h, proved that C-6 of **2** is first

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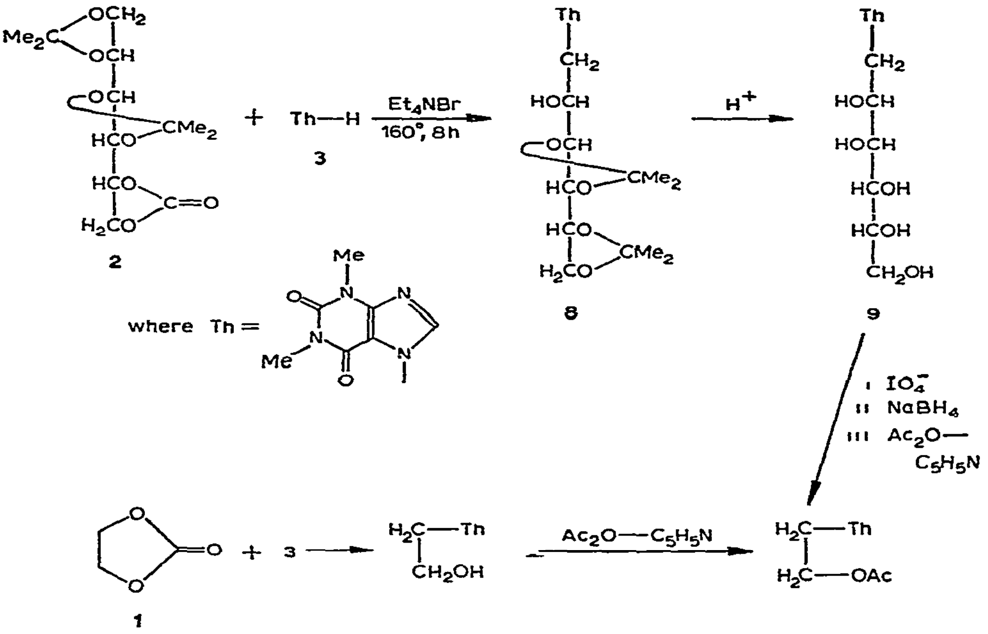
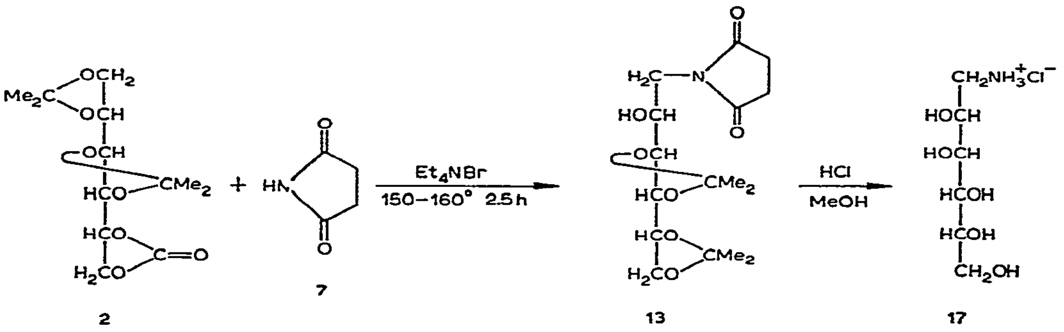
*Synthetic Studies by the Use of Carbonates. Part VII. For Part VI, see T. Yoshino, S. Inaba, H. Komura, and Y. Ishido, *Bull. Chem. Soc. Jap.*, in press.



substituted by the bromide ion of the ammonium salt, and the theophyllin-7-yl group is then introduced on C-6 of **2**, to give **8**.

In a similar way, compounds **4**, **5**, **6**, and **7** respectively afforded 6-(benzylamino)-7-(1-deoxy-3,4,5,6-di-*O*-isopropylidene-D-mannitol-1-yl)purine[4,7] (**10**) (45% yield), m p 220–221°, $[\alpha]_D^{20}$ +55° (*c* 1 1, DMF), $\lambda_{max}^{CHCl_3}$ 296 nm (ϵ_{mM} 18.90), 1-(1-deoxy-3,4,5,6-di-*O*-isopropylidene-D-mannitol-1-yl)-5,6-dimethylbenzimidazole[4] (**11**) (49% yield), m.p 212–213°, $[\alpha]_D^{20}$ −4° (*c* 1.0, chloroform), λ_{max}^{EtOH} 251 (ϵ_{mM} 8 30), 280 (ϵ_{mM} 6 90), and 289 nm (ϵ_{mM} 6 90), λ_{min}^{EtOH} 267 (ϵ_{mM} 4.70), and 286 nm (ϵ_{mM} 5 80), *N*-(1-deoxy-3,4,5,6-di-*O*-isopropylidene-D-mannitol-1-yl)phthalimide (**12**) (69% yield), and *N*-(1-deoxy-3,4,5,6-di-*O*-isopropylidene-D-mannitol-1-yl)succinimide[4] (**13**) (82% yield), m p 146–147°, $[\alpha]_D^{20}$ +10 7° (*c* 1.1, chloroform)

Treatment of **8**, **11**, **12**, and **13** with methanolic hydrogen chloride respectively afforded 7-(1-deoxy-D-mannitol-1-yl)theophylline[4] (**9**) (73% yield), m.p. 210° (dec), $[\alpha]_D^{20}$ +74° (*c* 1 0, H_2O), $\lambda_{max}^{H_2O}$ 273 nm (ϵ_{mM} 2 90), 1-(1-deoxy-D-mannitol-1-yl)-5,6-dimethylbenzimidazole hydrochloride[4] (**14**) (72% yield), m p 206–207° (dec), $[\alpha]_D^{20}$ +32° (*c* 1.1, H_2O), $\lambda_{max}^{H_2O}$ 277 (ϵ_{mM} 9 00) and 286 nm (ϵ_{mM} 8 60), $\lambda_{min}^{H_2O}$ 283 nm (ϵ_{mM} 7.60), $\lambda_{sh}^{H_2O}$ 257 (ϵ_{mM} 5 80) and 271 nm (ϵ_{mM} 7.30), *N*-(1-deoxy-D-mannitol-1-yl)phthalimide[4] (**16**) (96% yield), m p 231–233°, $[\alpha]_D^{20}$ +32° (*c* 1 0, DMF), $\lambda_{max}^{H_2O}$ 289 nm (ϵ_{mM} 2 70); and 1-amino-1-deoxy-D-mannitol hydrochloride[4,8] (**17**) (60% yield from **13**), m p 161 5–162 5°, $[\alpha]_D^{20}$ +3° (*c* 0 3, H_2O) Basification of **14**, and processing, gave 1-(1-deoxy-D-mannitol-1-yl)-5,6-dimethylbenzimidazole[4] (**15**) (43% yield from **14**), m.p 217–218°, $[\alpha]_D^{20}$ +72° (*c* 0 9, DMF), $\lambda_{max}^{H_2O}$ 241 (ϵ_{mM} 6.70), 246 (ϵ_{mM} 6 70), 269 (ϵ_{mM} 6 30), and 278 nm (ϵ_{mM} 5.80), $\lambda_{min}^{H_2O}$ 244 (ϵ_{mM} 6 60), 256 (ϵ_{mM} 4.60), and 275 nm (ϵ_{mM} 5 50)



REFERENCES

1 T Yoshino, S Inaba, and Y Ishido, *Bull Chem Soc Jap*, 46 (1973) 553

2 Unpublished data detailed results will be published elsewhere

3 H Komura, T. Yoshino, and Y. Ishido, *Bull. Chem. Soc Jap*, 46 (1973) 550

4 The elemental analysis data for these products were consistent with those calculated for the expected structures

5 When *p*-toluenesulfonamide was used as the activating agent [M Sekiya, T Yoshino, H Tanaka, and Y Ishido, *Bull Chem. Soc. Jap*, 46 (1973) 556], the yields were improved in the case of theophylline (80% yield) and 5,6-dimethylbenzimidazole (64% yield)

6 7-(2-Acetoxyethyl)theophylline was obtained by the periodate oxidation of 9 (1 mmole) in aqueous solution, treatment of the product with an excess of sodium borohydride, evaporation to dryness *in vacuo*, and acetylation with acetic anhydride in pyridine This product gave an n m r spectrum superposable on that of a specimen prepared by the reaction of theophylline with ethylene carbonate followed by acetylation

7 Compare, N Nakazaki, M Sekiya, T Yoshino, and Y Ishido, *Bull Chem. Soc Jap*, in press For the 6-(benzylamino)-D-ribofuranosylpurines, these authors found $\lambda_{max}^{H_2O}$ for the 7-isomer at 286 nm, and for the 9-isomer at 270 nm.

8 J. K N Jones, M B Perry, and J. C Turner [*Can. J Chem*, 40 (1962) 503] found m p 163–165°, $[\alpha]_D^{23 \pm 3}$ +5° (H$_2$O)