Carbanions in Carbohydrate Chemistry: a New Synthesis of C-Glycosyl Compounds

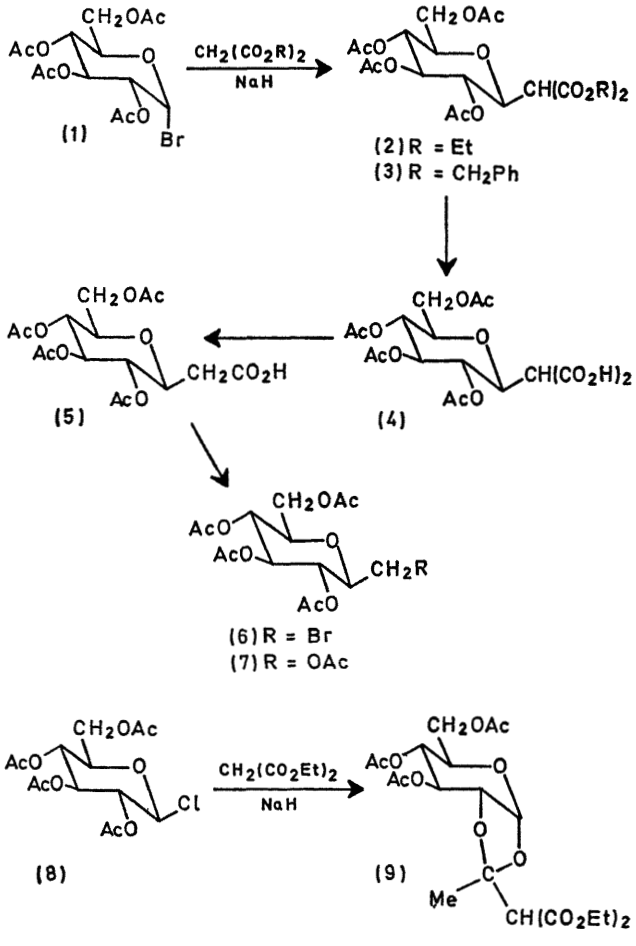
By S. HANESSIAN* and A. G. PERNET

(*Department of Chemistry, University of Montreal, Montreal* 101, *Quebec, Canada*)

Summary The reaction of substituted glycosyl halides with malonic esters leads to *C*-glycosyl compounds.

RELATIVELY few methods of general preparative significance are available for the formation of C-C bonds at the anomeric centre in cyclic carbohydrate derivatives. Yields are generally low, and in most cases the anomeric substituents have been alkyl or aryl groups,[1] which are chemically inert and of no functional utility. Glycosyl cyanides, which can be considered as potential *C*-glycosides, have been little studied[2] and with few exceptions,[2,3] are also formed in low yields.[4] These shortcomings, and the known importance of naturally occurring *C*-glycosyl compounds,[5] particularly *C*-nucleosides,[6] prompted us to report a new and general method for the synthesis of highly functionalized *C*-glycosyl compounds by the reaction of glycosyl halides with the carbanion derived from malonic esters. To the best of our knowledge, the reactions of cyclic α-halogeno-ethers with carbanions have few precedents.[7] The structural features of the newly introduced side-chain allow for a variety of chemical transformations leading eventually to the construction of heterocyclic systems such as *C*-nucleosides.

Treatment of (**1**) with sodio diethyl malonate in anhydrous 1,2-dimethoxyethane (room temp., 3h) afforded crystalline (**2**), m.p. 91·5—92°, (20%);† $[\alpha]_D$ −18·5° ($CHCl_3$); *m/e* 445 (*M* − OEt) 417 (*M* − OEt − CO), *etc.*; n.m.r. (220 MHz, $CDCl_3$) τ 8·714, 8·705 ($CO_2CH_2CH_3$, centres of two triplets), 6·384 (d, *J* 6·2 Hz), 6·283 (5-H, q, $J_{5,6}$ 2·5, $J_{5,6'}$ 5·0 Hz), *etc.* Condensation of (**1**) with sodio dibenzyl malonate in 1,2-dimethoxyethane (room temp., 2 d) gave (**3**) as a syrup (80%). Hydrogenolysis in the presence of 5% Pd–C in absolute ethanol gave the crystalline malonic acid derivative (**4**) (51%), m.p. 147°; $[\alpha]_D$ − 18·0° (EtOH). Treatment of (**4**) with triethyloxonium fluoroborate[8] afforded (**2**), thus establishing the configurational relationship between (**2**) and (**3**). Decarboxylation of (**4**) in acetic acid under



† All crystalline compounds gave correct analyses. Compounds reported herein had i.r. n.m.r., and mass spectra which were in accordance with their structures. M.p.s are uncorrected.

reflux (3 h) led to crystalline (**5**) (quant.), m.p. 104·5°—105·5°; $[\alpha]_D$ −4·31° ($CHCl_3$). The structures and stereochemistry of (**2**) and (**3**) were unequivocally established by transforming the acid (**5**) into the crystalline bromide (**6**) (87%), m.p. 119·5—120°; $[\alpha]_D$ −12.42° ($CHCl_3$), by application of the modified Hunsdiecker reaction,[9] and solvolysis of (**5**) in dimethylformamide containing anhydrous sodium acetate. The resulting product was identified as 1,3,4,5,7-penta-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*gulo*-heptitol, m.p. 93—94°; $[\alpha]_D$ 0° ± 1·0 ($CHCl_3$) reported,[4] m.p. 89°.

The stereoselective condensation reactions of carbanions with (**1**), prompted us to study the reaction of the β-chloride (**8**) with sodio diethyl malonate. In dimethylformamide (room temp., 4 h), an almost quantitative conversion of (**8**) into the syrupy mixed acetal (**9**) was observed. The structure of this product was evident from its n.m.r. and mass spectra and from chemical transformations. Sequential deacetylation (NaOEt, EtOH), methylation (MeI, Ag_2O), hydrolysis, and oxidation with bromine gave 3,4,6-tri-*O*-methyl-D-gluconolactone, characterized as its crystalline phenylhydrazide, m.p. 126°; reported, m.p. 126—127°.[10] In addition, acetolysis of (**9**) led to α-D-glucose pentaacetate.

These reactions provide a new method for the introduction of functionalized side-chains at the anomeric position, which because of their higher levels of oxidation, are subject to a variety of chemical transformations.

The financial assistance of the National Research Council of Canada and a France-Quebec fellowship for A.G.P. are acknowledged. The 220 MHz spectra were obtained by courtesy of the Ontario Research Foundation, Sheridan Park, Ontario, Canada.

(*Received, March 17th*, 1971; *Com.* 329.)

[1] W. A. Bonner, *Adv. Carbohydrate Chem.*, 1951, **6**, 251; *Methods Carbohydrate Chem.*, 1963, **2**, 465.
[2] See for example B. Helferich and W. Ost, *Chem. Ber.*, 1962, **95**, 2612; B. Coxon and H. G. Fletcher, jun., *J. Amer. Chem. Soc.*, 1964, **80**, 922; and references cited therein.
[3] B. Coxon, *Tetrahedron*, 1966, **22**, 2281; M. Bobek and J. Farkaš, *Coll. Czech. Chem. Comm.*, 1969, **34**, 247.
[4] B. Coxon and H. G. Fletcher, jun., *J. Amer. Chem. Soc.*, 1963, **85**, 2637.
[5] L. J. Haynes, *Adv. Carbohydrate Chem.*, 1963, **18**, 227; 1965, **20**, 357.
[6] S. Hanessian and T. H. Haskell, in "The Carbohydrates", 2nd. edn., vol. 2, Academic Press, New York, 1970, p. 139; R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley, Interscience, 1970.
[7] See for example, R. P. Zelinski, N. G. Peterson, and H. R. Wallner, *J. Amer. Chem. Soc.*, 1952, **74**, 1504; J. V. Koštíř and M. Queisnerová, *Chem. Listy*, 1949, **43**, 277; *Chem. Abs.*, 1951, **45**, 553.
[8] H. Meerwein, *Org. Synth.*, 1966, **46**, 113.
[9] S. J. Cristol and W. C. Firth, *J. Org. Chem.*, 1961, **26**, 280.
[10] W. N. Haworth, E. L. Hirst, and L. Panizzon, *J. Chem. Soc.*, 1934, 154.