Notes

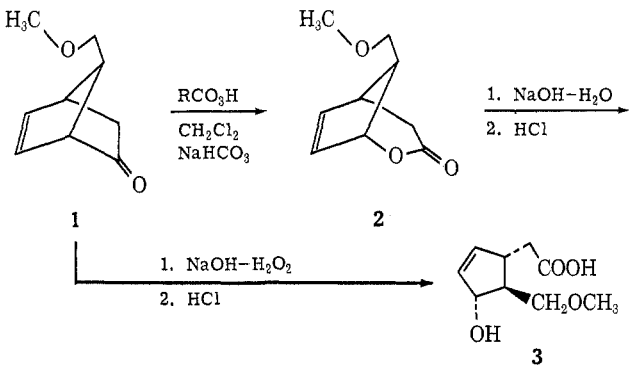
Basic Hydrogen Peroxide Cleavage of a Bicyclic Ketone. A New Procedure for a Prostaglandin Intermediate

NED M. WEINSHENKER* AND REBECCA STEPHENSON

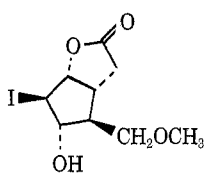
Alza Research, Palo Alto, California 94304

Received May 16, 1972

In work on improving the efficiency and simplicity of prostaglandin synthesis *via* the Corey method,[1] we questioned the need for isolating and then hydrolyzing the intermediate bicyclic lactone **2** in order to obtain hydroxy acid **3** for optical resolution.



Treatment of the ketone **1** (~85% pure) with 1.20 equiv of sodium hydroxide and 1.5 equiv of 30% hydrogen peroxide proceeded rapidly and exothermically to yield the desired product. This material could be isolated (quantitative) and resolved *via* *d*-ephedrine. Purification of this salt removed by-products formed from the oxidation of undesired isomers of the starting ketone. In addition, if *racemic* lactone **4** were desired,



4

direct iodolactonization of the resulting basic solution should be feasible according to the existing procedure.[2] This procedure greatly reduces the time and cost of reagents involved and is readily adaptable to scaling up.[3] Although this reaction is reported[4] to give poor to fair yields with unstrained ketones, it should work reasonably well with other strained bicyclic ketones.

(1) E. J. Corey, T. K. Schaaf, W. Huber, V. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

(2) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, **91**, 5675 (1969).

(3) The sequence has been carried out without difficulty on a 500-g scale.

(4) Several examples of basic hydrogen peroxide cleavage of ketones are given in J. G. Wallace, "Hydrogen Peroxide in Organic Chemistry," E. I. du Pont de Nemours and Co., Wilmington, Del., pp 35–37.

Experimental Section

(±)-3α-Carboxymethyl-4β-methoxymethyl-5α-hydroxycyclopentene (3).—The ketone **1** (45.1 g, 0.29€ mol, 85% pure by vpc analysis) was dissolved in 125 ml of ether and mixed with a solution of 14.1 g (0.353 mol) of sodium hydroxide in 120 ml of water. The two-phase system was cooled (ice bath) and rapidly stirred while 53 ml of 30% hydrogen peroxide solution was added over a period of 40 min. The internal reaction temperature was maintained at 10–25°. After the addition, vpc analysis indicated that the ether phase was devoid of starting ketone. The aqueous phase was separated, washed with 100 ml of ether, and then neutralized (pH 6–7) with concentrated hydrochloric acid. Solid sodium sulfite was added cautiously to destroy excess hydrogen peroxide. The ethyl acetate (100 ml) was added, the mixture was cooled in ice–water, and concentrated hydrochloric acid was added to pH 3–4. The aqueous phase was separated and extracted with ethyl acetate (4 × 50 ml and 2 × 100 ml). The combined organic phases were combined, dried ($MgSO_4$), and concentrated to yield 42.0 g (78%) of the hydroxy acid as a colorless, viscous oil. Further acidification of the aqueous phase (with cooling) to pH 1.5–2 and extraction with ethyl acetate yielded an additional 13.0 g of **3**, total yield 55.0 g (99%); tlc analysis (silica gel; benzene:dioxane:HOAc, 20:20:1) indicated material indentical with hydroxy acid prepared by the published procedure.[1]

Resolution[5] of the Hydroxy Acid 3.—The hydroxy acid (55.0 g) was dissolved in 655 ml of ethyl acetate and thoroughly mixed with 49.8 g of *d*-(+)-ephedrine (Fluka) dissolved in 1455 ml of benzene. The first crop of crystals (~35 g) was redissolved in 1400 ml of 30% ethyl acetate–benzene and yielded 27.3 g of resolved salt, $[\alpha]^{25}D$ 37.5° (*c* 1.0780, MeOH) [lit.[1] $[\alpha]^{23}D$ 37.2° (*c* 1.0, MeOH)]. The overall yield (61.5%) takes into consideration the actual amount of desired ketone in the starting material.

Registry No.—**3**, 35672-36-7; hydrogen peroxide, 7722-84-1.

(5) The solvent system for resolution of the hydroxy acid has been modified from the original procedure[2] and allows for a severalfold decrease in the volume of solvent with no compromise in optical purity or number of crystallizations. The solvent system was developed by Dr. Niels Andersen.

Disaccharide Nucleosides of Benzimidazole

DAVALURI R. RAO AND LEON M. LERNER*

Department of Biochemistry, State University of New York, Downstate Medical Center, Brooklyn, New York 11203

Received May 4, 1972

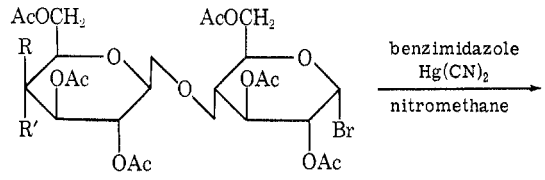
This laboratory has been engaged in exploring methods of synthesis of disaccharide nucleosides, and reports concerning the synthesis of 9-β-melibiosyladenine[1] and 9-(2-deoxycellobiosyl)adenine[2] have appeared. The method of preparation of these compounds was based upon the coupling procedure devised by Davoll and Lowy,[3] in which a blocked glycosyl halide was condensed with the mercuric chloride salt of a purine base in a neutral solvent such as xylene or toluene. Similar techniques were used by Wol-

(1) L. M. Lerner, *J. Org. Chem.*, **32**, 3663 (1967).

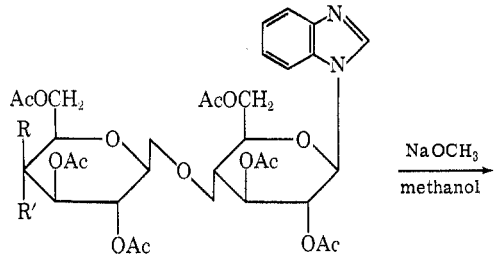
(2) L. M. Lerner, *J. Med. Chem.*, **11**, 912 (1968).

(3) J. Davoll and B. A. Lowy, *J. Amer. Chem. Soc.*, **73**, 1650 (1951).

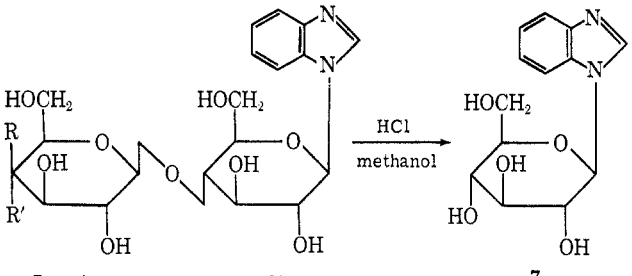
SCHEME I



2, R′ = OAc; R = H, cellobio-
3, R′ = H; R = OAc, lacto-



4, cellobio- or lacto-



5, R′ = OH; R = H, cellobio-
6, R′ = H; R = OH, lacto-

7

from and coworkers,[4] who prepared purine nucleosides derived from maltose, cellobiose, and lactose. In more recent work,[5] applications to nucleoside synthesis have been made of a procedure for glycoside synthesis first reported by Helferich and coworkers[6] in which glycosyl halides were treated with alcohols in nitromethane using mercuric cyanide as an acid acceptor. Thus, the disaccharide nucleoside, 2,6,8-trichloro-9-(hepta-*O*-acetyl-β-D-gentiobiosyl)purine (**1**), was prepared in 45% yield under quite similar conditions using hot nitroethane as the solvent and anhydrous calcium sulfate (Drierite) as an internal desiccant.[5] This same article also reported a good yield of 1-β-D-glucopyranosylbenzimidazole when the coupling reaction was performed in refluxing nitromethane. We now wish to report on what appears to be the first preparation of disaccharide nucleosides of benzimidazole.[7]

Taking note of the fact that Yamaoka, *et al.*,[5] had failed in their attempt to prepare **1** by using a heavy metal salt of the purine and of the failure of other coupling procedures tried in this laboratory to give significant yields of disaccharide nucleosides when attempted with a variety of nitrogen bases, the mercuric cyanide–nitromethane procedure[5,6] was applied toward the synthesis of 1-β-cellobiosylbenzimidazole (**5**) and 1-β-lactosylbenzimidazole (**6**) and successfully carried out (Scheme I). Hepta-*O*-acetyl-α-cellobiosyl bromide[8] (**2**) and hepta-*O*-acetyl-α-lactosyl bromide[9] (**3**) were each treated with benzimidazole in refluxing nitromethane. After work-up and deacetylation in methanolic sodium methoxide, the nucleosides were isolated free of sugar by-products and unreacted disaccharides by preparation of their crystalline picrates. Removal of the picrate ion with an anion exchange resin[10] followed by cellulose column chromatography gave **5** and **6**.

Proof of structure of these new compounds was based upon (1) elementary analyses, (2) ultraviolet spectra, which were similar to those reported earlier for benzimidazole nucleosides,[11] and (3) degradation of **5** and **6** to 9-β-D-glucopyranosylbenzimidazole (**7**), which was crystallized as the picrate.[12] The latter procedure was conducted in a manner similar to that which was applied to the structure proof of some pyrimidine disaccharide nucleosides,[13] namely by cleavage of the *O*-glycosidic bond of the disaccharide in a mixture of hydrogen chloride in methanol. This procedure, therefore, demonstrated that the configuration at the *N*-glucosyl bond was β.

Experimental Section[14]

1-β-Cellobiosylbenzimidazole (**5**).—A suspension of benzimidazole (1.2 g, 10 mmol) and mercuric cyanide (5 g) in 800 ml of nitromethane was dried by distillation of 150 ml of the solvent. The mixture was allowed to cool slightly and 5 g of molecular sieves 3A and 14.8 g (21 mmol) of hepta-*O*-acetylcellobiosyl bromide[8] (**2**) in 50 ml of dry nitromethane were added. The reaction mixture was heated at reflux for 18 hr (*hood!*) and filtered while hot, and the solvent was evaporated. The residue was extracted with hot chloroform (300 ml) and this extract, after cooling, was washed three times with 150-ml portions of 30% aqueous potassium iodide and once with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a foam containing the blocked nucleoside **4**, which was deacetylated by heating at reflux in methanolic sodium methoxide (*ca.* pH 11 with moist pH paper) for 45 min. The methanol was removed by evaporation, the residue was dissolved in 200 ml of water, and the pH was adjusted to 7 with a Dowex-50 (H^+) resin. The aqueous solution was washed well with chloroform and evaporated to a residue which was dissolved in a minimum amount of methanol and treated with 50 ml of 10% methanolic picric acid. After being chilled in the refrigerator for several days, a crystalline picrate was obtained which was recrystallized from water to afford 1.6 g (26%). An analytical sample was obtained by recrystallization from water, mp 150–151°.

Anal. Calcd for $C_{25}H_{29}N_5O_{17}$: C, 44.72; H, 4.35; N, 10.43. Found: C, 44.59; H, 4.34; N, 10.23.

The main portion of the picrate (1.35 g) was dissolved in 200 ml of warm water and treated with Bio-Rad AG1-X8 (CO_3^{2-}) anion exchange resin until the solution became colorless.[10] After an additional 1 hr of stirring, the resin was removed by filtration and the water was evaporated to give a foam which was chromatographed on a column (48 × 4.5 cm) of Whatman cellulose powder with 86:14 *n*-butyl alcohol–water. Fractions containing

(4) M. L. Wolfrom, P. McWain, and A. Thompson, *J. Amer. Chem. Soc.*, **82**, 4353 (1960); M. L. Wolfrom, P. McWain, F. Shafizadeh, and A. Thompson, *ibid.*, **81**, 6080 (1959).

(5) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965).

(6) B. Helferich and K. Weis, *Chem. Ber.*, **89**, 314 (1956); B. Helferich and R. Steinpreis, *ibid.*, **91**, 1794 (1958).

(7) For an excellent review of the subject of benzimidazole nucleosides, see L. B. Townsend and G. R. Revankav, *Chem. Rev.*, **70**, 389 (1970).

(8) K. Freudenberg and W. Nagai, *Justus Liebigs Ann. Chem.*, **494**, 63 (1932).

(9) E. Fischer and H. Fischer, *Ber.*, **43**, 2521 (1910).

(10) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

(11) G. R. Revankar and L. B. Townsend, *J. Heterocycl. Chem.*, **5**, 477 (1968); J. Davoll and G. B. Brown, *J. Amer. Chem. Soc.*, **73**, 5781 (1951).

(12) A. W. Johnson, G. W. Miller, J. A. Mills, and A. R. Todd, *J. Chem. Soc.*, 3061 (1953).

(13) C. L. Stevens and P. Blumbergs, *J. Org. Chem.*, **30**, 2723 (1965).

(14) Melting points were determined on a Kofler micro hot stage and are corrected values. Elementary analyses were performed by the Baron Consulting Co., Orange, Conn. Evaporations were carried out under reduced pressure on a rotary evaporator at a bath temperature of 40–45°.

10 ml each were collected and the major component was found in tubes 49–102. The fractions were combined, the solvents were evaporated, and the product was crystallized from aqueous ethanol to afford 0.8 g (86%) of colorless needles: mp 186–188°; $[\alpha]^{25}D$ 13.5° (*c* 0.4, 0.1 *N* HCl); uv max (0.01 *N* HCl) 253 mμ (ε 5300), 262 (5610), 268 (6580), and 274 (5560).

Anal. Calcd for $C_{19}H_{26}O_{10}N_2 \cdot H_2O$: C, 49.56; H, 6.13; N, 6.09. Found: C, 49.14; H, 6.24; N, 6.12.

1-β-Lactosylbenzimidazole (6).—The preparation of **6** followed the exact same procedure given above for the preparation of **5**. A picrate was obtained from cold methanol, the analytical sample of which had mp 219–222°.

Anal. Calcd for $C_{25}H_{29}N_5O_{17}$: C, 44.72; H, 4.35; N, 10.43. Found: C, 44.93; H, 4.59; N, 10.29.

Regeneration of the free nucleoside with an anion exchange resin as described above and chromatography on a cellulose column gave **6**, which resisted crystallization for many months. Therefore, it was lyophilized and dried further in a drying pistol (P_2O_5) under high vacuum at 40° for 48 hr and at 110° for 24 hr to afford 0.46 g of a fluffy, white powder which liquified slowly at temperatures above 170° to a viscous syrup: $[\alpha]^{25}D$ 4° (*c* 1.3, H_2O); uv max (0.01 *N* HCl) 253 mμ (ε 5095), 262 (5390), 268 (6230), and 275 (5325).

Anal. Calcd for $C_{19}H_{26}N_2O_{10} \cdot H_2O$: C, 49.56; H, 6.13; N, 6.09. Found: C, 49.77; H, 5.80; N, 6.00.

Picrate of 1-β-D-Glucopyranosylbenzimidazole (7). From 5.—A sample (0.2 g) of **5** was dissolved in 50 ml of methanol and the solution was saturated with dry hydrogen chloride gas at 0°, then kept at room temperature for 2 days in a pressure bottle. The solution was evaporated to dryness, the residue was dissolved in methanol, and the pH (moist pH paper) was adjusted to neutrality with a few drops of ammonium hydroxide. To this solution was added 1 ml of 10% methanolic picric acid and the flask was chilled in the refrigerator for several days. The crystals (mp 142–152°) were filtered off and recrystallized from water to give yellow needles, mp 146–149°, $[\alpha]^{25}D$ −19.4° (*c* 1, pyridine) [lit.[12] mp 145–148°, $[\alpha]^{15}D$ −18° (*c* 2, pyridine)].

From 6.—Application of the same procedure as above to **6** resulted in a product (mp 128–138°) which required two recrystallizations from water to give yellow needles whose melting point was not depressed upon admixture with the picrate of **7**.

Registry No.—**5**, 35672-33-4; **5** picrate, 35672-34-5; **6**, 35672-35-6; **6** picrate, 35737-07-6.

A Convenient Deuterium Exchange Technique

JAMES M. WATSON, ALAN R. TANNER, AND ROYSTON M. ROBERTS*

Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712

Received May 1, 1972

During the course of our investigations of the enolene rearrangement,[1-3] a convenient and mild deuterium exchange technique was developed which we believe to be superior to presently used procedures. Our technique capitalizes on the elegant procedure of Pasto and Meyer,[4] which makes ethanol-*O*-d_1 easily and economically available as a source of exchangeable deuterium and incorporates a novel method of isolating the desired deuterated product from the reaction mixture.

The compound to be deuterated is dissolved in an appropriate excess of ethanol-*O*-d_1 and a catalytic amount of sodium metal is added. The resulting solution is stirred at room temperature overnight, the ethanol is removed *in vacuo*, and a second portion of ethanol-*O*-d_1, is added. After exchange with two or three portions of ethanol-*O*-d_1 has been carried out in this way, an amount of acetyl chloride just sufficient to destroy the sodium ethoxide present is added. The resulting ethyl acetate is removed along with ethanol-*O*-d_1 by flash distillation, and the remaining material is distilled to effect isolation of the desired deuterated product.

This method has been shown to be generally applicable to ketones which boil considerably higher than ethanol and ethyl acetate and it should also be suitable for the deuteration of other compounds which possess acidic hydrogens. Among the compounds which were successfully deuterated in the α position by this technique are 4-pentenophenone; 4′-R-4-pentenophenone where R = CH_3, CH_3O, Cl; 2-R-4-pentenophenone where R = CH_3, CH_2CH_3, $(CH_2)_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, and C_6H_5; 2-allyl-1-indanone; 2-allyl-1-tetralone; 3-methyl-4-pentenophenone; 2,3-dimethyl-4-pentenophenone; 2-ethyl-3-methyl-4-pentenophenone; 3-methyl-2-*m*-propyl-4-pentenophenone; and 2-α-methylallyl-1-tetralone.

In all cases encountered in our work, the reaction substrate was soluble in ethanol; however, in instances where the material to be deuterated is not ethanol soluble, an inert cosolvent such as dioxane may be added to maintain homogeneity.

Experimental Section

The following examples are representative of the technique.

4-Pentenophenone-2-d_2.—4-Pentenophenone[2] (8.0 g, 0.05 mol) was stirred with 59 ml (1.0 mol) of ethanol-*O*-d_1 and *ca.* 0.2 g of sodium metal for 24 hr, after which time the ethanol-*O*-d_1 was removed by the application of aspirator vacuum and a second 59-ml portion of ethanol-*O*-d_1 was added. After 24 hr this process was again repeated and, after the final period of stirring, the solution was neutralized by the addition of *ca.* 1 ml of acetyl chloride. The resulting mixture was concentrated and distilled *in vacuo* to obtain product, bp 58–65° (0.05 mm), $n^{25}D$ 1.5282. The yield was 6.5 g. The nmr spectrum (CCl_4) was consistent with the structure of 4-pentenophenone-2-d_2: δ 2.45 (d, $-CH_2-$, 2 H), 5.0 (m, $=CH_2$, 2 H), 5.9 (m, $-CH=$, 1 H), 7.4 and 7.9 ppm (2 m, H_{arom}, 5 H). The ir spectrum contained strong absorptions at 1690, 975, and 910 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}D_2O$: C, 81.44; H + D, 8.69. Found: C, 81.27; H + D, 8.70.

4′-Chloro-4-pentenophenone-2-d_2.—The deutration procedure used was identical with that employed with 4-pentenophenone: 5.0 g (0.026 mol) of 4′-chloro-4-pentenophenone[5] was used and, after work-up, vacuum distillation gave water-clear distillate, bp 80–85° (0.06 mm). This product was further purified by column chromatography on silica gel [petroleum ether (bp 60–80°)–benzene] followed by micro vacuum distillation. The product thus obtained was pure to glpc analysis and the nmr spectrum (neat) was consistent with the structure of 4′-chloro-4-pentenophenone wherein the α position was 96.5% deuterated: δ 2.1 (d, $-CH_2-$, 2 H), 2.5 (m, $-CH_2-$, 0.07 H), 4.7 (m, $=CH_2$, 2 H), 5.5 (m, $-CH=$, 1 H), 6.9 (d, H_{arom}, 2 H), and 7.4 ppm (d, H_{arom}, 2 H). The ir spectrum contained strong absorptions at 1680, 1000, and 915 cm^{-1}.

Anal. Calcd for $C_{11}H_9D_2OCl$: C, 67.17; H + D, 6.66. Found: C, 67.31; H + 6.64.

2-Methyl-4-pentenophenone-2-d.—The deuteration applied to 2-methyl-4-pentenophenone[6] was identical with that employed with 4-pentenophenone with the exception that reflux was

(1) R. M. Roberts and R. G. Landolt, *J. Amer. Chem. Soc.*, **87**, 2281 (1965).

(2) R. M. Roberts, R. G. Landolt, R. N. Greene, and E. W. Heyer, *ibid.*, **89**, 1404 (1967).

(3) R. M. Roberts and J. M. Watson, *J. Org. Chem.*, **34**, 4191 (1969).

(4) D. J. Pasto and G. R. Meyer, *ibid.*, **33**, 1257 (1968).

(5) J. M. Watson, Ph.D. Dissertation, University of Texas at Austin, 1969.

(6) A. R. Tanner, Ph.D. Dissertation, University of Texas at Austin, 1969.