The Conversion of But-2-yne-1 : 4-diol into 2-Deoxyribose.

By M. M. Fraser and R. A. Raphael.

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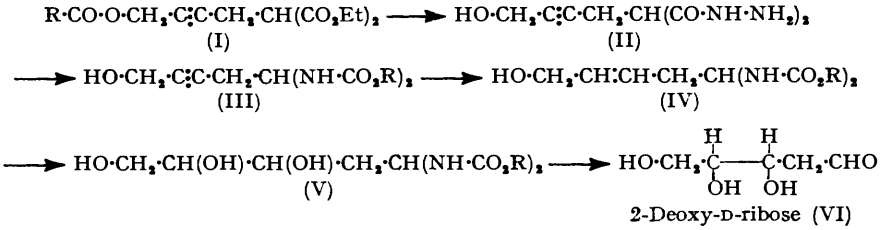
The preparation of monohydric derivatives of but-2-yne-1 : 4-diol is discussed. The condensation of 1-benzoyloxy-4-bromobut-2-yne with ethyl sodiomalonate followed by elaboration of the resulting ethyl 5-benzoyloxypent-3-yne-1 : 1-dicarboxylate (I; R = Ph) gives a small yield of 2-deoxy-DL-ribose isolated as its anilide.

The occurence of 2-deoxy-D-ribose (VI; written for brevity in the *aldehydo*-form) as a component of one of the nucleic acids has led to a need for a convenient method of preparation of this sugar (for a review see Overend and Stacey, *Adv. Carbohydrate Chem.*, 1953, **8**, 45). When this investigation began all the methods available were unsatisfactory and a total synthesis from non-carbohydrate precursors was therefore studied. Although preparative improvement was not attained the methods used possess intrinsic chemical interest.

The first necessity was a convenient method to transform but-2-yne-1 : 4-diol into a 4-halogenobut-2-yn-1-ol or a derivative thereof. This is achieved most directly by treating the diol with one mol. of thionyl chloride in pyridine whereby 4-chlorobut-2-yn-1-ol is produced (Fraser and Raphael, *J.*, 1952, 226; Colonge and Poilane, *Bull. Soc. chim. France*, 1955, 499, 502; Bailey and Fujiwara, *J. Amer. Chem. Soc.*, 1955, **77**, 165). This product, however, proved highly offensive; not only was the liquid a potent vesicant but even a trace of the vapour frequently provoked an intense dermatitic allergy. A less noxious derivative of this type was found in 1-benzoyloxy-4-bromobut-2-yne, which was readily prepared by the monobenzoylation of but-2-yne-1 : 4-diol and treatment of the resulting half-ester with phosphorus tribromide. Similarly, treatment of the diol with one mol.

of 2 : 3-dihydropyran and reaction of the product with phosphorus tribromide gave the non-toxic 4-bromo-1-(tetrahydro-2-pyranyloxy)but-2-yne in fair yield. A preparation of 1-acetoxy-4-chlorobut-2-yne by reaction of 1 : 4-dichlorobut-2-yne with one mole of potassium acetate gave poor yields of the required product.



Condensation of 1-benzoyloxy-4-bromobut-2-yne with ethyl sodiomalonate gave the expected ethyl 5-benzoyloxypent-3-yne-1 : 1-dicarboxylate (I; R = Ph) which was converted by hydrazine into the dihydrazide (II), the benzoyl group being removed as benzhydrazide. The product (II) was then subjected to a double Curtius degradation; reaction with nitrous acid, followed by treatment of the resulting diazide with methanol or ethanol, produced the acetylenic diurethane (III; R = Me or Et). Partial catalytic hydrogenation of this product gave the corresponding *cis*-ethylenic diurethane (IV). *cis*-Hydroxylation of this compound, using either dilute potassium permanganate or osmium tetroxide–hydrogen peroxide, yielded the *erythro*-triol (V) (Raphael, *J.*, 1949, S 44). Considerable difficulty was encountered in the hydrolysis of this product. Similarly constituted diamide derivatives of carbohydrates have usually been hydrolysed to the free sugar by hot mineral acid. Unfortunately 2-deoxyribose is very sensitive towards acidic reagents and much experimentation was needed before conditions could be established which enabled hydrolysis to take place with minimal destruction of the sugar. Even so, the yield of 2-deoxy-DL-ribose was very small; treatment of the crude product with aniline gave the crystalline anilide of the sugar identical with an authentic specimen.

In another approach to the *erythro*-triol (V) the acetylenic diurethane (III) was converted into the *trans*-ethylenic diurethane (IV) by reduction with sodium in liquid ammonia. The yield of the latter urethane was low, however, because of the formation of a by-product, *trans*-1 : 1-di(methoxycarbonylamino)pent-3-ene, obviously produced by reductive fission of the allylic hydroxyl group. This fission was, however, completely suppressed by carrying out the reduction on the sodium derivative from the diurethane (III), prepared *in situ* by the initial addition of sodamide. Treatment of the *trans*-ethylenic diurethane (IV) with perbenzoic acid gave the expected epoxide; however, attempts simultaneously to hydrate the epoxide ring and to hydrolyse the diurethane grouping failed.

Experimental

4-Benzoyloxybut-2-yn-1-ol.—The method is a modification of that used by Jones and Sondheimer (*J.*, 1949, 616) for the preparation of quinitol monobenzoate. But-2-yne-1 : 4-diol (95 g.), dissolved in a mixture of dry benzene (250 c.c.) and dry pyridine (110 c.c.), was cooled to 0° and benzoyl chloride (110 c.c.) in dry chloroform (200 c.c.) was added with stirring during 4 hr., the temperature being kept below 5°. Cooling was then stopped and the stirring continued for a further 4 hr. The solution was then washed with N-sulphuric acid (4 × 100 c.c.), followed by water (3 × 100 c.c.), and dried (Na_2SO_4); ethanol (150 c.c.) was then added and the solution kept at −16° overnight. The resulting crystalline dibenzoate (45 g., m. p. 75—76°) of but-2-yne-1 : 4-diol was filtered off. Evaporation of the solvent from the filtrate, followed by distillation, gave the *monobenzoate* (102 g., 61%) as an oil, b. p. 117°/8 × 10^{-5} mm., n_D^{19} 1·5510 (Found : C, 69·45; H, 5·25. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). The *phenylurethane* crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 120° (Found : N, 4·6. $C_{18}H_{15}O_4N$ requires N, 4·5%).

1-Benzoyloxy-4-bromobut-2-yne.—To a stirred solution of the above monobenzoate (70 g.) in benzene (1 l.) was added dropwise phosphorus tribromide (25 c.c.); stirring was continued at room temperature for 24 hr. Iced water was then added and the aqueous layer extracted with

ether. The combined organic layers were washed with sodium hydrogen carbonate solution and water and dried (Na_2SO_4), and the solvent evaporated off. Distillation gave 1-*benzoyloxy*-4-*bromobut*-2-*yne* (75 g., 81%) as a colourless liquid, becoming yellow at room temperature, b. p. 104—106°/8 × 10^{-5} mm., n_D^{18} 1·5744 (Found: C, 52·35; H, 3·8. $C_{11}H_9O_2Br$ requires C, 52·2; H, 3·6%). The compound has an irritant action on the skin.

4-(*Tetrahydro*-2-*pyranyloxy*)*but*-2-*yn*-1-*ol*.—But-2-yne-1 : 4-diol (35 g.) and six drops of concentrated hydrochloric acid were heated gently until the diol was molten. 2 : 3-Dihydropyran (34 g.) was then added during 1 hr. to the stirred diol, the heat of reaction serving to keep the mass fluid. After being set aside overnight the product was dissolved in ether and washed with sodium hydrogen carbonate solution and water. Drying (Na_2SO_4) and distillation gave the *alcohol*, m. p. 20—24°, b. p. 142—144°/14 mm., 109—111°/0·05 mm., n_D^{24} 1·4873 (Found: C, 63·5; H, 8·1. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%).

4-*Bromo*-1-(*tetrahydro*-2-*pyranyloxy*)*but*-2-*yne*.—A stirred solution of the above alcohol (8 g.) in dry ether (50 c.c.) and pyridine (10 c.c.) was treated slowly with phosphorus tribromide (2 c.c.) in ether (15 c.c.), and the solution left at room temperature overnight. It was then washed with dilute sulphuric acid, sodium hydrogen carbonate solution and water; drying, evaporation, and distillation gave the *bromo-ether* (4·1 g., 40%) as an oil which rapidly discolours at room temperature, b. p. 70°/0·05 mm., n_D^{24} 1·5246 (Found: C, 46·2; H, 5·5. $C_9H_{13}OBr$ requires C, 46·4; H, 5·6%).

Use of thionyl chloride and pyridine in the above reaction gave the corresponding *chloro-ether* (30%), b. p. 92—94°/13 mm., n_D^{20} 1·4912 (Found: C, 57·0; H, 7·0. $C_9H_{13}OCl$ requires C, 57·3; H, 7·0%).

1-*Acetoxy*-4-*chlorobut*-2-*yne*.—1 : 4-Dichlorobut-2-yne (16·5 g.; Johnson, *J.*, 1946, 1009), anhydrous potassium acetate (13·1 g., 1 mol.), and acetic acid (50 c.c.) were refluxed for 21 hr. The precipitated potassium chloride was filtered off and the bulk of the acetic acid removed by distillation. The residue was poured into water (50 c.c.), and the product isolated by ether. Drying, evaporation, and fractionation gave 1-*acetoxy*-4-*chlorobut*-2-*yne* (4·6 g., 23%), b. p. 98—100°/14 mm., n_D^{20} 1·4720 (Found: C, 49·25; H, 4·9. $C_6H_7O_2Cl$ requires C, 49·2; H, 4·8%).

Ethyl 5-*Benzoyloxypent*-3-*yne*-1 : 1-*dicarboxylate* (I; R = Ph).—Diethyl malonate (16 g.) was added dropwise to a stirred suspension of atomised sodium (2·3 g.) in toluene (250 c.c.) and the mixture heated for 4 hr. at 50°. 1-Benzoyloxy-4-bromobut-2-yne (25·3 g.) was then added during 30 min. at 50°, and the mixture heated at 100° for 16 hr. The cooled solution was washed with dilute sulphuric acid and water, and dried (Na_2SO_4) and the solvent removed under reduced pressure. Distillation gave the *ester* (22·5 g., 77%), b. p. 142—144°/8 × 10^{-5} mm., n_D^{20} 1·5056 (Found: C, 64·75; H, 5·8. $C_{18}H_{20}O_6$ requires C, 65·05; H, 6·05%).

An analogous reaction with 1-acetoxy-4-chlorobut-2-yne gave the corresponding *acetoxy-ester* (I; R = Me), b. p. 98—99°/10^{-4} mm., n_D^{22} 1·4549 (Found: C, 57·65; N, 6·65. $C_{13}H_{18}O_6$ requires C, 57·75; H, 6·7%).

5 : 5-*Di*(*hydrazinocarbonyl*)*pent*-2-*yn*-1-*ol* (II).—A mixture of the above benzoyl ester (21·2 g.) and an equal volume of hydrazine hydrate (100%) was heated in an oil-bath at 120° for 8 min. with vigorous shaking. Boiling ethanol (300 c.c.) was then added and the flask cooled to 0°. The precipitated *dihydrazide* was filtered off and crystallised from aqueous ethanol (90%) as needles (8·65 g., 68%), m. p. 145°. The compound is extremely water-soluble (Found: C, 42·2; H, 5·9. $C_7H_{12}O_3N_4$ requires C, 42·0; H, 6·0%).

5 : 5-*Di*(*methoxycarbonylamino*)*pent*-2-*yn*-1-*ol* (III; R = Me).—The above dihydrazide (10·7 g.) was dissolved in dilute sulphuric acid (concentrated acid, 5·7 c.c.; water, 50 c.c.), and a layer of ether (60 c.c.) added. The mixture was cooled to −8° and excess of sodium nitrite (15 g.) in water (30 c.c.) chilled to −8° was added during 15 min. with vigorous swirling, the temperature being kept below −4°. After 5 min. the green ether layer was decanted off and the semi-solid residue extracted as quickly as possible with ice-cold ether (5 × 50 c.c.). The combined extracts were washed with ice-water (50 c.c.) and dried (Na_2SO_4) at 0° for 30 min. To the filtered solution was added methanol (100 c.c.), and the ether removed by distillation; the resulting solution was refluxed for 4 hr. After removal of solvent the crude product (6·5 g.) was crystallised from ethyl acetate to give the *diurethane* (5·6 g., 84%) as needles, m. p. 116° (Found: C, 47·1; H, 5·9; N, 12·3. $C_9H_{14}O_5N_2$ requires C, 46·95; H, 6·1; N, 12·2%).

By employing ethanol in place of methanol the *diethyl analogue* (III; R = Et) was obtained, although in lower yield (37%). It crystallised from chloroform–carbon tetrachloride (1 : 4) in prisms, m. p. 138° (Found: C, 51·0; H, 7·05; N, 10·85. $C_{11}H_{18}O_5N_2$ requires C, 51·15; H, 7·0; N, 10·85%).

cis-5 : 5-*Di*(*ethoxycarbonylamino*)*pent*-2-*en*-1-*ol* (IV; R = Et).—The above ethyl diurethane

(7·37 g.) in ethyl acetate (150 c.c.) was shaken with hydrogen in the presence of 10% palladium–charcoal (400 mg.). The theoretical volume of hydrogen (803 c.c. at 21°/762 mm.) was absorbed in 30 min. The crude product, after removal of catalyst and solvent, was suspended in boiling light petroleum (b. p. 60—80°), and ethyl acetate added until solution was effected. The *cis-diurethane* (5·1 g.) crystallised as needles, m. p. 92° (Found : C, 50·75; H, 7·7. $C_{11}H_{20}O_5N_2$ requires C, 50·75; H, 7·7%).

erythro-5 : 5-*Di*(*ethoxycarbonylamino*)*pentane*-1 : 2 : 3-*triol* (V; R = Et).—(*a*) To a vigorously stirred solution of the above *cis*-diurethane (1·3 g.) in ice-water (30 c.c.), through which carbon dioxide was bubbling, was added aqueous potassium permanganate (2%; 30 c.c.) dropwise during 20 min. at 0—3°. The temperature was allowed to rise to 10° and a few drops of ethanol were added to destroy excess of permanganate. The precipitated manganese dioxide was filtered off and the filtrate passed through a column of cation-exchange resin (Amberlite IRC-50) to remove potassium. After extraction with chloroform the aqueous solution was taken to dryness under reduced pressure at room temperature. The residual glass was dissolved in dry ethanol, and the solution filtered and again taken to dryness under reduced pressure. The product was dried *in vacuo* over phosphoric oxide. The resulting *triol* was a glassy water-soluble solid which did not crystallise (Found : C, 44·3; H, 8·3; N, 9·1. $C_{11}H_{22}O_7N_2$ requires C, 44·9; H, 7·55; N, 9·5%).

(*b*) The *cis*-diurethane (0·5 g.) was dissolved in a 2·5M-solution (0·8 c.c.) of hydrogen peroxide in *tert.*-butyl alcohol and cooled to 0°. Two drops of a 0·5% solution of osmium tetroxide in *tert.*-butyl alcohol were added; an orange colour developed immediately. After 20 hr. at 0° the solvent was removed under reduced pressure to give the above triol.

2-*Deoxy*-DL-*ribose*.—A solution of the above triol (1·1 g.) in 0·1% sulphuric acid (30 c.c.) was kept in a boiling water-bath for 6 min. The solution was then rapidly cooled and passed through a column of anion-exchange resin (Amberlite IR-4B pre-saturated with carbon dioxide). Evaporation of the effluent to dryness under reduced pressure at room temperature gave a thick syrup which did not crystallise. It reduced Fehling's solution and gave an intense, stable blue colour with the Dische reagent (Deriaz, Stacey, Teece, and Wiggins, *J.*, 1949, 1222). Treatment of this product with ethanolic aniline by the usual procedure (Kent, Stacey, and Wiggins, *J.*, 1949, 1232) gave, after evaporation, a thick syrup. This was rendered more fluid by the addition of a few drops of dry ethanol and set aside at 0° for 2 days. Ice-cold ethanol was then added and the suspended solid rapidly centrifuged off. Crystallisation from a small volume of dry ethanol gave *N*-2-deoxy-DL-ribosylaniline (8 mg.), m. p. 154—156° (Kofler block) undepressed on admixture with an authentic sample prepared by mixing equal weights of the enantiomorphs. The *X*-ray powder photographs of the two samples were identical (we cordially thank Professor J. M. Robertson, F.R.S., for arranging these determinations).

trans-5 : 5-*Di*(*methoxycarbonylamino*)*pent*-2-*en*-1-*ol* (IV; R = Me).—To a stirred solution of 5 : 5-di(methylcarbonylamino)pent-2-yn-1-ol (III; R = Me) (5·06 g.) in liquid ammonia (600 c.c.) was added finely ground sodamide (0·85 g.). After 10 min. metallic sodium (2·02 g.) was added in small pieces. Stirring was continued for 8 hr., more sodium (total 1 g.) being added from time to time to keep the solution blue. Ammonium chloride (10 g.) was then introduced and the ammonia allowed to evaporate overnight. Extraction with hot ethyl acetate and crystallisation of the crude product from ethyl acetate–light petroleum (b. p. 60—80°) (1: 1) gave the trans-*diurethane* (3·03 g., 60%) as prisms, m. p. 101—102° (Found : C, 46·45: H, 6·7. $C_9H_{16}O_5N_2$ requires C, 46·55; H, 6·95%). Microhydrogenation disclosed 1 double bond.

When the sodamide was omitted from the preparation, the yield of the above compound dropped to 24%, the major constituent of the product being trans-1 : 1-*di*(*methoxycarbonylamino*)*pent*-3-*ene*, needles, m. p. 123—124° [from methanol–light petroleum (b. p. 60—80°) (4 : 1)] (Found : C, 50·2; H, 6·8; N, 13·3. $C_9H_{16}O_4N_2$ requires C, 50·0; H, 7·4; N, 13·0%). Microhydrogenation disclosed 0·95 double bond.

Treatment of the above hydroxy-diurethane (0·5 g.) in chloroform (4 c.c.) with chloroformic perbenzoic acid (4·45% w/v; 6·65 c.c.) at 0° gave the *epoxide*, crystallising from ethyl acetate in prisms, m. p. 122° (Found : C, 43·75; H, 6·5; N, 11·4. $C_9H_{16}O_6N_2$ requires C, 43·55; H, 6·5; N, 11·3%). Attempted hydrolyses of this compound gave no recognisable product.

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THE QUEEN'S UNIVERSITY, BELFAST.
THE UNIVERSITY, GLASGOW, W.2.

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