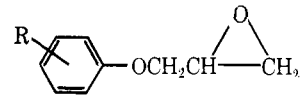
TABLE IV

1-PHENOXY-2,3-EPOXYPROPANES



Compd.	R	Yield, %	Recrystn. solvent[a]	B.p. (mm.) or m.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	*m*-Cl	27		109–110.5 (2)	$C_9H_9ClO_2$	58.70	4.81	58.55	4.84
2	*m*-Br	83		107.5–109.5 (0.9)	$C_9H_9BrO_2$	47.18	3.96	47.84	4.03
3	*m*-F	73		76–78 (0.9)	$C_9H_9FO_2$	64.28	5.39	64.63	5.94
4	*m*-$(CH_3)_3C$	83		97–102 (0.2)	$C_{13}H_{18}O_2$	75.69	9.54	74.83	8.89
5	*o*-CF_3	60		124–128 (2.25)	$C_{10}H_9F_3O_2$	55.02	4.16	54.98	4.20
6	*p*-C_6H_5	91	M–W	84–87.5[b]	$C_{15}H_{14}O_2$	79.62	6.24	79.44	6.05
7	*p*-$C_6H_5CH{=}CH$	85	A	135–136.5	$C_{17}H_{16}O_2$	80.92	6.39	80.91	6.54

[a] A, acetone; M, methanol; and W, water. [b] F. N. Alquist and H. R. Slagh, [U. S. Patent 2,181,085 (1939)] report b.p. 196–201° (2 mm.).

anol was distilled at reduced pressure, and 900 ml. of water was added to the residue. The mixture was then extracted repeatedly with ether. The ether extracts were combined, washed three times with 100-ml. portions of water and once with 100 ml. of saturated aqueous NaCl. The ether was evaporated, and the residue was recrystallized from petroleum ether (b.p. 60–71°) to give 24.0 g. of 1-amino-3-(*m*-*t*-butylphenoxy)-2-propanol.

1-Amino-3-(*m*-methoxyphenoxy)-2-propanol.—A mixture of 1-(*m*-methoxyphenoxy)-2,3-epoxypropane,[9] 800 ml. of ethanol, and 800 ml. of concentrated NH_4OH was stirred until a clear solution resulted which was left for 2 days. The alcohol was evaporated under reduced pressure on a hot-water bath. The remaining mixture was extracted with two 800-ml. portions of ether. The ether was evaporated. Vacuum distillation of the residual material gave 102.5 g. of a colorless liquid, b.p. 162–173° (0.35 mm.), which soon solidified. Crystallization from tetrahydrofuran–Skellysolve B gave 94 g. (32%) of colorless needles, m.p. 87.5–88.5°.

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.94; H, 7.73; N, 6.70.

5-(α,α,α-Trifluoro-*o*-tolyloxymethyl)-2-oxazolidinethione (37).—A cold solution of 5.6 g. (0.1 mole) of KOH in 15 ml. of water and 150 ml. of ethanol was added to a mixture of 12.2 g. (0.05 mole) of 1-(α,α,α-trifluoro-*o*-tolyloxy)-3-amino-2-propanol and 7.6 g. (0.1 mole) of CS_2. The mixture was refluxed for 4 hr. and the alcohol was evaporated under reduced pressure on a hot-water bath. The residual material was diluted with 300 ml. of water, cooled in an ice bath, and acidified with 6 *N* HCl. The solid which separated was filtered, washed with water, and crystallized from aqueous acetone giving 9.7 g. of buff solid, m.p. 100–101°.

1-(Benzylmethylamino)-3-(α,α,α-trifluoro-*m*-tolyloxy)-2-propanol Hydrochloride.—A mixture of 77.2 g. (0.35 mole) of 1-(α,α,α-trifluoro-*m*-tolyloxy)-2,3-epoxypropane[5] and 43.6 g. (0.36 mole) of methylbenzylamine was stirred and heated in an oil bath at 130° for 4 hr. Distillation of the reaction mixture gave the product as a yellow liquid: I, 53.5 g., b.p. 167–168° (0.35 mm.), $n^{25}D$ 1.5136; II, 46.9 g., b.p. 168–171° (0.35 mm.), $n^{25}D$ 1.5136. The total yield was 100 g. (84%). A 10.4-g. portion of fraction I dissolved in ether was treated with ethereal HCl. An oil separated and soon solidified. The solid was crystallized from ethanol–ether giving 11 g. of colorless crystals, m.p. 130–132°.

Anal. Calcd. for $C_{18}H_{20}F_3NO_2 \cdot HCl$: C, 57.52; H, 5.63; Cl, 9.44; N, 3.73. Found: C, 57.57; H, 5.86; Cl, 9.44; N, 3.73.

1-Methylamino-3-(α,α,α-trifluoro-*m*-tolyloxy)-2-propanol.—A mixture of 43.2 g. of 1-(benzylmethylamino)-3-(α,α,α-trifluoro-*m*-tolyloxy)-2-propanol, 2 g. of 5% palladium on charcoal, and 200 ml. of methanol was shaken on a Parr apparatus at an initial pressure of 3 atm. After 2 hr., 1 equiv. of hydrogen had been absorbed. The catalyst was removed by filtration. The solvent was evaporated under reduced pressure on a hot-water bath. The residual oil which solidified upon standing was combined with that obtained from a similar run on 46.9 g. of starting material and crystallized from ether–Skellysolve B giving 55.1 g. of colorless needles, m.p. 72.5–73.5°. Concentration of the filtrate gave 5 g. of pale yellow solid, m.p. 69–72°. The total yield was 60.1 g. (90%). An analytical sample was obtained by recrystallizing a portion of the first crop twice from ether–Skellysolve B affording colorless needles, m.p. 72.5–73.5°.

Anal. Calcd. for $C_{11}H_{14}F_3NO_2$: C, 53.00; H, 5.66; N, 5.62. Found: C, 53.00; H, 5.88; N, 5.49.

3-Methyl-5-[(α,α,α-trifluoro-*m*-tolyloxy)methyl]-2-oxazolidinethione (39).—A solution of 5.35 g. (0.03 mole) of N,N'-thiocarbonylimidazole[6] in 100 ml. of tetrahydrofuran was added dropwise during 45 min. to a stirred solution of 7.48 g. (0.03 mole) of 1-methylamino-3-(α,α,α-trifluoro-*m*-tolyloxy)-2-propanol in 100 ml. of tetrahydrofuran. The solution was refluxed for 23 hr. The solvent was evaporated under reduced pressure on a hot-water bath. The residue was dissolved in 300 ml. of ether. The ether solution was washed with two 100-ml. portions of 3 *N* HCl and 100 ml. of water and dried over anhydrous $MgSO_4$. The solution was concentrated, and Skellysolve B was added. Cooling gave 7.6 g. (87%) of ivory needles, m.p. 80–81°.

(9) A. Bell, U. S. Patent 2,805,170 (1957).

The Osmium Tetroxide Catalyzed Hydroxylation of 1,4-Dimethylenecyclohexanes

JAMES G. MURPHY

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

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It is well known that many tumors are characterized by excessive glucose utilization. The possibility of inhibiting this utilization in a reversible way and thereby also tumor growth is exemplified by 2-deoxy-D-glucose.[1] Such considerations led to the study here reported in which substances similar to glucose metabolites were synthesized. 1,2,4,5-Tetrahydroxycyclohexanedimethanol-1,4 (**6**), for example, replicates the functionality at positions 1, 2, 3, and 6 of D-fructofuranose, an intermediate in the catabolism of glucose.

The effectiveness of osmium tetroxide in catalyzing the addition of hydrogen peroxide to olefins was first shown for substantially anhydrous systems[2] and later[3] for aqueous ones. In this report the reagent is used with two diolefins permitting the simultaneous introduction of four hydroxyl groups.

1,4-Dimethylenecyclohexane (**2**)[4] was prepared by the exhaustive methylation of 1,4-cyclohexanebis-

(1) R. M. Hochster in "Metabolic Inhibitors," Vol. 1, R. M. Hochster and J. H. Quastel, Ed., Academic Press Inc., New York, N. Y., 1963, p. 141, and references therein.

(2) N. A. Milas and S. Sussmann, *J. Am. Chem. Soc.*, **58**, 1302 (1936).

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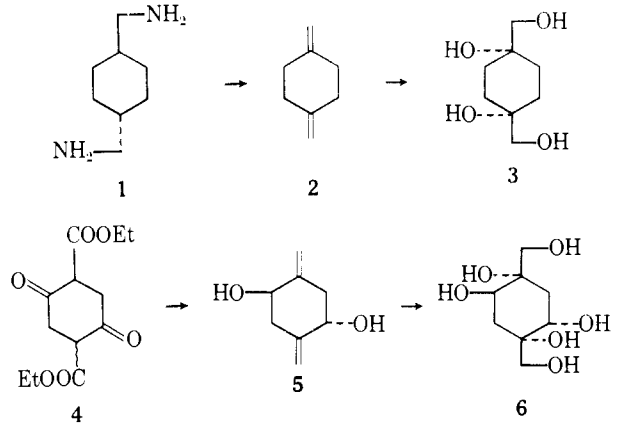
CHART I



(methylamine) (**1**) followed by Hofmann elimination (see Chart I). The utility of dimethyl sulfoxide for certain elimination reactions has been pointed out[5] and in this instance the use of potassium[5] *t*-butoxide in this solvent permitted a higher yield and purer product as well as a more direct preparation than the customary pyrolysis of the quaternary ammonium hydroxide.

The use of the OsO_4–H_2O_2 reagent on **2** required considerable experimentation in order to select conditions which would give a good yield. The use of lower temperature and brief reaction time permitted a 46% yield of **3**. This tetrol was homogeneous by thin layer chromatography (R_f 0.28 on silica gel using ethyl acetate–dioxane–water, 30:28.8:10). Despite examination of the mother liquors of **3** by preparative thin layer chromatography, no other isomer was isolated although overoxidation products were detected. The tetrol is given the *cis* configuration on the basis of its n.m.r. spectrum as a 10 mole % solution in dimethyl sulfoxide.[6] Nonequivalent tertiary alcohol groups were indicated by separate singlets at δ = 3.64 and 3.88 p.p.m. and nonequivalent primary alcohol groups gave triplets at δ = 4.31 (6-c.p.s. splitting) and 4.36 (6-c.p.s. splitting) p.p.m. These peaks were removed on exchange with deuterium oxide and the pattern is compatible with the chair form of *cis*-1,4-dihydroxycyclohexanedimethanol-1,4 (**3**).

Earlier work[7] had indicated that the lithium aluminum hydride reduction of **4** was anomalous. It has now been found that the use of excess $LiAlH_4$ in refluxing tetrahydrofuran on **4** gives a 38% yield of *trans*-2,5-dihydroxy-1,4-dimethylenecyclohexane (**5**). This result is analogous to that obtained from other β-keto ester systems.[8] The product rapidly absorbs 2 molar equiv. of hydrogen (platinum black, methanol) and shows olefin adsorption in the infrared (6.0 μ) and an ABX n.m.r. pattern (in deuteriopyridine) for the paraffin protons definitive for this structure.[9] When the n.m.r. spectrum was obtained as a 10 mole % solution in dimethyl sulfoxide, a single doublet for the equivalent secondary hydroxyl groups at δ = 4.99 p.p.m. (5 c.p.s. splitting) was obtained which was removed on equilibration with D_2O.

The application of the OsO_4–H_2O_2 reagent to **5** again required exploration of experimental conditions. Thus, comparative experiments demonstrated the need for dilute sulfuric acid and the superiority of operating at −15° rather than at 0° in order to get practical yields. The attained yield of 52% appears attractive in view of the multiplicity of products obtainable by overoxidation processes. The 1,2,4,5-tetrahydroxycyclohexanedimethanol-1,4 (**6**), obtained when observed as a 5 mole % solution in dimethyl sulfoxide, showed a single doublet at δ = 4.90 p.p.m. (4-c.p.s. splitting) for the secondary hydroxyl groups, two singlets at δ = 4.85 and 5.04 p.p.m. for the two tertiary hydroxyl groups, and an incompletely resolved triplet at δ = 4.25 p.p.m. (*ca.* 6-c.p.s. splitting) for the two primary alcohol groups, all of which bands were removed on exchange with deuterium oxide. These observations are compatible with a *cis* orientation of the tertiary hydroxyl groups and a *trans* orientation of the secondary hydroxyl groups in a chair conformation leading to the configuration designated in structural formula **6**.

The evidence for *cis* orientation at positions 1 and 4 in the tetrol, **3**, and the hexol, **6**, is suggestive that this reaction proceeded through an osmium transition state complex with transannular bonding. *cis*-1,4-Dihydroxycyclohexanedimethanol-1,4 (**3**) was found to be nontoxic and inactive when tested against Adenocarcinoma 755 and lymphoid leukemia L1210 at levels of 200 mg./kg. and also against Sarcoma 180 at 250 mg./kg. 1,2,4,5-Tetrahydroxycyclohexanedimethanol-1,4 (**6**) was nontoxic and inactive at 200 mg./kg. against lymphoid leukemia L1210 and P1798 lymphosarcoma and also against Dunning ascites leukemia at 100 mg./kg. Both substances were inactive in KB cell culture in which their ED_{50} was greater than 100 μg./ml.

Experimental Section[10]

1,4-Dimethylenecyclohexane (1).—With magnetic stirring and ice-bath cooling so that the temperature did not exceed 25°, 30.2 ml. of 1,4-cyclohexanebis(methylamine)[11] (0.20 mole) was added dropwise to a mixture of 74.8 ml. of methyl iodide (1.2 moles) and 20 ml. of water. This was followed by the dropwise addition at 25° of 160 ml. of 5 *N* NaOH. The high-melting (>300°) crude bismethiodide, after filtration, washing with ethanol, and air drying weighed 77.8 g.

The bismethiodide (24.1 g., 0.05 mole) was mixed with an equal weight of potassium *t*-butoxide and 150 ml. of dimethyl sulfoxide (dried over calcium hydride). This mixture was heated under nitrogen with stirring in an 85° bath for 30 min. during which time it became nearly transparent. It was then cooled, diluted with 150 ml. of water, and extracted with ether. The ether extract was successively washed with water, 1 *N* H_2SO_4, 1 *M* Na_2CO_3, and water, and then dried (Na_2SO_4, CaH_2). After distillation, there was obtained 2.06 g. of mobile liquid, b.p. 124–126°, yield 38%. The analytical sample had b.p. 125.5–126°.

Anal. Calcd. for C_8H_{12}: C, 88.81; H, 11.19. Found: C, 88.51; H, 11.34.

***cis*-1,4-Dihydroxycyclohexanedimethanol-1,4 (3).**—To a stirred solution of 13.3 ml. of catalyst (0.005 g. of OsO_4/ml. of *t*-butyl

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(6) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

(7) J. G. Murphy, *J. Med. Chem.*, **8**, 267 (1965).

(8) W. J. Bailey, M. E. Hermes, and W. A. Klein, *J. Org. Chem.*, **28**, 1724 (1963).

(9) The author is indebted to Dr. Edwin D. Becker for obtaining and analyzing this spectrum.

(10) Melting points were taken in capillaries using a Hershberg apparatus and are corrected. N.m.r. spectra were determined by Mrs. Josephine Goodwin on a Varian A-60 instrument using tetramethylsilane as internal reference. Microanalyses were performed by the staff of the Microanalytical Services Laboratory of this Institute under the direction of Dr. William C. Alford.

(11) A gift from Eastman Chemical Products, Inc., Kingsport, Tenn., and is a mixture of approximately 60% *trans* and 40% *cis* isomers.

alcohol), 10 ml. of *t*-butyl alcohol, 2.65 ml. of 1 *N* H_2SO_4, and 5.30 ml. of 30% H_2O_2 cooled in an ice–salt bath, a solution of 1.96 ml. of **2** in 10 ml. of *t*-butyl alcohol was added (the solution acquired a deep red-brown color). The temperature was maintained between 0 and −5°, and at the end of 2 hr., 10 ml. of water and 1.74 ml. of 5 *N* NaOH was added to neutralize the solution (phenolphthalein). Sodium metabisulfite (0.11 g.) was added and the mixture was stirred at reflux for 1 hr. After stripping off solvents, the residue was evaporatively distilled at 205° (20 μ). The 1.70-g. distillate on crystallization from *t*-butyl alcohol and acetone afforded 1.19 g. of white solid, m.p. 159–162° (46% yield). The analytical sample, recrystallized from methanol and dried at 100° (50 μ) had m.p. 166.5–167°.

Anal. Calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.25; H, 9.02.

***trans*-2,5-Dihydroxy-1,4-dimethylenecyclohexane (5).**—To 7.6 g. (0.20 mole) of $LiAlH_4$ in 150 ml. of tetrahydrofuran at reflux, there was added gradually with stirring a solution of 10.3 g. (0.04 mole) of **4** in 100 ml. of warm tetrahydrofuran over an 11-min. period. After refluxing for 1 hr. 39 ml. of ethyl acetate was added dropwise followed by 15 ml. of water. Carbon dioxide was passed into the mixture from which, after filtration, evaporation of the filtrate, and crystallization from chloroform, there was obtained 2.09 g. of **5**, a white solid, m.p. 160–161°. The analytical sample, from chloroform, had m.p. 162.5–163°.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.80; H, 8.86; O, 22.87.

1,2,4,5-Tetrahydroxycyclohexanedimethanol-1,4 (6).—To a solution of 25 ml. of catalyst (0.005 g. of OsO_4/ml. of *t*-butyl alcohol), 40 ml. of *t* butyl alcohol, 20 ml. of acetone, 5 ml. of 1 *N* H_2SO_4, and 10 ml. of 30% H_2O_2 prechilled to −15°, there was added 3.85 g. of **5**. The mixture was stirred overnight at −15° (ice–salt bath) and filtered. The white solid obtained, after washing with acetone and air drying, weighed 3.00 g., m.p. 225.5–226.5° dec. (52% yield). The analytical sample, crystallized from water and dried at 100° *in vacuo*, m.p. 238.5–239.5° dec.

Anal. Calcd. for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.40; H, 7.63.

Acknowledgment.—The author thanks Drs. Howard W. Bond and Harry B. Wood, Jr., of the Cancer Chemotherapy National Screening Center for arranging the biological testing.

New Compounds

Synthesis of β-5-Fluoro-2′-deoxyuridylyl-(5′→5′)-β-5-fluoro-2′-deoxyuridine[1]

DAVID G. PARSONS AND CHARLES HEIDELBERGER[2]

McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, Wisconsin 53706

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It is well known that nucleotides cannot penetrate Ehrlich ascites cells without degradation,[3] presumably because of their high negative charge. Since 5-fluoro-2′-deoxyuridine 5′-monophosphate (FUDRP) is the active intracellular form of 5-fluorouracil and 5-fluoro-2′-deoxyuridine (FUDR),[4] a number of derivatives were synthesized in which the phosphate group was altered in various ways.[5] However, none of these was more effective than the simple nucleotide at inhibiting the incorporation of labeled formate into DNA thymine in suspensions of Ehrlich ascites cells.[6] Hence, the report of Montgomery, *et al.*,[7] indicating that the 5′,5′-dinucleoside monophosphate of 6-mercaptopurine entered cells resistant to 6-mercaptopurine, stimulated us to synthesize the corresponding derivative of FUDRP, which is described below. This compound was less effective than FUDRP at inhibiting the above system and did not inhibit cells resistant to FUDR.[8] Consequently it does not enter these cells intact.

Experimental Section

Preparation of 3′-Acetyl-FUDRP.—5-Fluoro-2′-deoxyuridine 5-monophosphate diammonium salt[5] (100 mg.) was dissolved in 2 ml. of freshly distilled pyridine, and 1.0 ml. of distilled acetic anhydride was added. The mixture was stoppered, shaken vigorously, and allowed to remain at room temperature for 24 hr. The excess acetic anhydride was destroyed with 2 ml. of water, and the solution was evaporated *in vacuo* at 30°. When most of the pyridine and acetic acid had been removed, 5 ml. of water was added and evaporated to an oil; this process was repeated three times until all of the acetic acid had been removed. The residue was then evaporated *in vacuo* twice with dry pyridine to remove traces of water and was used for the next reaction without purification.

Condensation with 3′-Acetyl-FUDR.—The 3′-acetyl-FUDRP thus obtained (115 mg.) was dissolved in 2 ml. of dry pyridine, and 90 mg. of 3′-acetyl-FUDR[5] was added. A 4 molar excess (250 mg.) of dry dicyclohexylcarbodiimide was added, and the reaction was shaken at room temperature for 60 hr. The dicyclohexylurea was filtered and washed with a few drops of pyridine. Water (10 ml.) was added to the filtrate, and the aqueous solution was extracted three times with 10 ml. of heptane. The aqueous phase was evaporated to dryness *in vacuo*, and the residue was coevaporated three times water water to remove the pyridine. The residue was then shaken with 50 ml. of warm water, the insoluble material was filtered, and the filtrate was evaporated to 10 ml. This solution, containing the protected dinucleoside monophosphate was mixed with 10 ml. of 1 *N* NaOH and heated under reflux for 1 hr. The solution was cooled and Dowex 50 (H^+) was added to remove sodium ions. After filtration, the neutral, pale yellow solution was concentrated *in vacuo* to 5 ml.

A Dowex-1 formate column (2 × 25 cm.) was prepared, and the above product was added. The column was washed with water, and a peak of FUDR was eluted The column was then eluted with 0.5 *M* formic acid, and two small unidentified peaks were removed. A large peak was obtained on elution with 2 *M* formic acid, which contained the desired product. The fractions comprising this peak were combined (volume 1 l.) and evaporated in *vacuo* to 200 ml. Water was added and evaporated several times to remove formic acid. When the volume was reduced to 0.5 ml., ethanol was coevaporated twice, and excess ammonia was added. The ammonia was evaporated, and the residue was extracted with 90% ethanol. A small amount of insoluble, reddish brown material was removed and discarded, and the alcoholic solution was evaporated to a small volume. The ammonium salt was precipitated by the addition of ether, and the product was collected by centrifugation, washed with ether, and dried over P_2O_5 to give 59.2 mg. of **β-5-fluoro-2′-deoxyuridylyl-(5′→5′)-β-5-fluoro-2′-deoxyuridine ammonium salt**. This material gave a single spot on paper chromatography in isopropyl alcohol–ammonia–water (7:1:2, v./v.) (R_f 0.28). In this system FUDR has an R_f of 0.62 and FUDRP 0.14. The ultraviolet spectrum had a maximum at 269 mμ, which did not shift in alkali; the optical density was 21.0/mg. (molar extinction 15,700/g.-atom of phosphorus).

(1) This work was supported in part by Grant C-2832, from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) American Cancer Society Professor of Oncology.

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