## Synthesis and Antifertility Activity of 5-(Phenoxymethyl)-2-oxazolidinethiones

GILBERT A. YOUNGDALE, GORDON W. DUNCAN, D. EDWARD EMMERT, AND DANIEL LEDNICER

*Research Laboratories, The Upjohn Company, Kalamazoo, Michigan*

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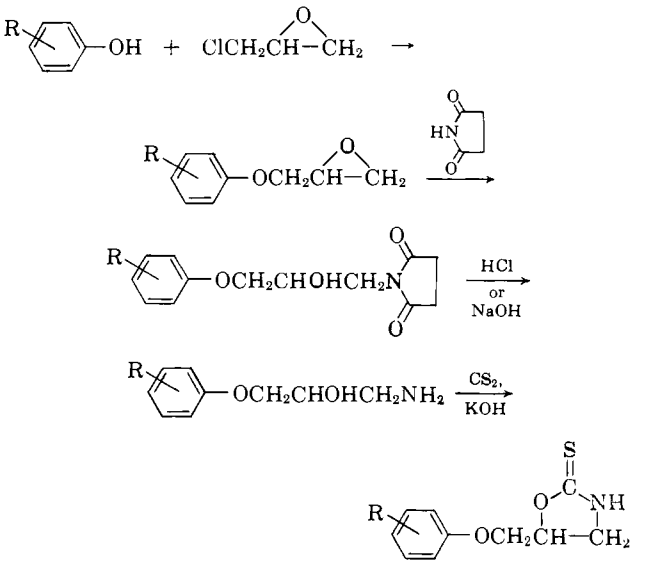
As part of a program toward the preparation of potential muscle relaxants, 5-($\alpha,\alpha,\alpha$-trifluoro-*m*-tolyloxymethyl)-2-oxazolidinethione (**38**) was synthesized. Though the compound was found to have only minimal activity on the loss of righting reflex,[1] additional testing uncovered the fact that it was active as an antifertility agent[2] in the female rat. In an effort to determine the structural features required for activity, a number of analogs were prepared.

The 5-phenoxymethyl-2-oxazolidinethiones (Table I) were prepared by reaction of 1-amino-3-phenoxy-2-propanols with carbon disulfide in ethanolic potassium hydroxide.[3] The majority of the amino alcohols (Table II) were prepared by the method of Petrow and Stephenson[4] which consists of the addition of succinimide to a 1-phenoxy-2,3-epoxypropane followed by the acid or basic (Table II) hydrolysis of the resulting succinimide (Table III). 1-Amino-3-(*m*-methoxyphenoxy)-2-propanol was prepared by addition of ammonia to 1-(*m*-methoxyphenoxy)-2,3-epoxypropane. The required 1-phenoxy-2,3-epoxypropanes (Table IV) were obtained from commercial sources or were prepared by literature procedures or by addition of a phenol to epichlorohydrin.

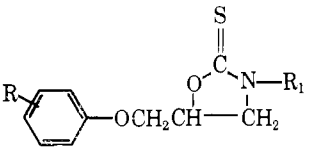


The preparation of 3-methyl-5-[($\alpha,\alpha,\alpha$-trifluoro-*m*-tolyloxy)methyl]-2-oxazolidinethione (**39**) required a different procedure. 1-Methylamino-3-($\alpha,\alpha,\alpha$-trifluoro-*m*-tolyloxy)-2-propanol was made by addition of methylbenzylamine to 1-($\alpha,\alpha,\alpha$-trifluoro-*m*-tolyloxy)-2,3-epoxypropane[5] followed by hydrogenolysis of the benzyl group. Preparation of **39** from the amino alcohol was not successful using carbon disulfide and potassium hydroxide[3] or by using carbon disulfide, potassium hydroxide, and lead nitrate.[6] However, reaction with N,N'-thiocarbonylimidazole[7] produced **39** in good yield.

The lack of antifertility activity (Table I) at the screening dose of the bulk of the compounds reported

TABLE I

5-(PHENOXYMETHYL)-2-OXAZOLIDINETHIONES



| Compd. | R | $R_1$ | Yield, % | Recrystn. solvent[a] | M.p., °C. | Formula | Calcd., % C | H | S | Found, % C | H | S | Antifertility $MED_{100}$,[b] mg./rat/day |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 28 | H | H | 51 | A–S | 105–106 | $C_{10}H_{11}NO_2S$ | 57.38 | 5.30 | 15.32 | 57.42 | 4.90 | 15.48 | >10[c] |
| 29 | *p*-Cl | H | 43 | A–S | 130–131 | $C_{10}H_{10}ClNO_2S$ | 49.28 | 4.14 | 13.15 | 49.27 | 3.95 | 13.29 | >10[d] |
| 30 | *m*-Cl | H | 69 | M–W | 99–102.5 | $C_{10}H_{10}ClNO_2S$ | 49.28 | 4.14 | 13.15 | 49.29 | 3.85 | 13.37 | >10 |
| 31 | *m*-Br | H | 65 | M–W | 123–126.5 | $C_{10}H_{10}BrNO_2S$ | 41.68 | 3.50 | 11.13 | 41.92 | 3.27 | 10.72 | >10 |
| 32 | *m*-F | H | 62 | M–W | 113–116 | $C_{10}H_{10}FNO_2S$ | 52.85 | 4.44 | 14.11 | 52.99 | 4.45 | 14.14 | >10 |
| 33 | *m*-$CH_3$ | H | 51 | A–S | 110–111 | $C_{11}H_{13}NO_2S$ | 59.15 | 5.87 | 14.36 | 59.10 | 6.07 | 14.32 | >10 |
| 34 | *m*-$(CH_3)_3C$ | H | 45 | M–W | 129–130.5 | $C_{14}H_{19}NO_2S$ | 63.36 | 7.22 | 12.08 | 63.41 | 6.87 | 12.45 | 10 |
| 35 | *p*-$OCH_3$ | H | 64 | A–S | 153–154 | $C_{11}H_{13}NO_3S$ | 55.20 | 5.47 | 13.40 | 55.36 | 5.30 | 13.54 | >10 |
| 36 | *m*-$OCH_3$ | H | 46 | A–S | 128–130 | $C_{11}H_{13}NO_3S$ | 55.20 | 5.47 | 13.40 | 55.22 | 5.27 | 13.46 | >10 |
| 37 | *o*-$CF_3$ | H | 67 | A–S | 101–102 | $C_{11}H_{10}F_3NO_2S$ | 47.63 | 3.64 | 11.56 | 48.09 | 3.37 | 11.70 | >10 |
| 38 | *m*-$CF_3$ | H | 53 | Et–S | 90–92 | $C_{11}H_{10}F_3NO_2S$ | 47.63 | 3.64 | 11.56 | 47.76 | 3.23 | 11.81 | 2.5 |
| 39 | *m*-$CF_3$ | $CH_3$ | 87 | Et–S | 81–82 | $C_{12}H_{12}F_3NO_2S$ | 49.48 | 4.15 | 11.01 | 49.62 | 4.55 | 11.59 | >10 |
| 40 | *p*-$C_6H_5$ | H | 57 | THF | 192–194 | $C_{16}H_{15}NO_2S$ | 67.34 | 5.30 | 11.24 | 67.14 | 5.32 | 11.30 | >10 |
| 41 | *p*-$C_6H_5CH{=}CH$ | H | 17[e] | W–THF | 225–226.5 | $C_{18}H_{17}NO_2S$ | 69.42 | 5.80 | 10.30 | 69.15 | 5.70 | 10.41 | >10 |

[a] A, acetone; Et, ether; M, methanol; S, Skellysolve B (a saturated hydrocarbon fraction, b.p. 60–71°); THF, tetrahydrofuran; and W, water. [b] Minimal effective dose for 100% inhibition of pregnancy, subcutaneous administration. [c] At 10 mg., 50% inhibition of pregnancy. [d] At 10 mg., 67% inhibition of pregnancy. [e] Yield based on crude amino alcohol.

(1) An $LRRD_{50}$ was determined from the dose which, injected intraperitoneally, causes 50% of the mice to fail to right themselves within 1 min. after being placed on their backs.

(2) For a description of the testing method, see G. W. Duncan, J. C. Babcock, S. C. Lyster, and D. Lednicer, *Proc. Soc. Exptl. Biol. Med.*, **109**, 163 (1962).

(3) Modeled after the procedure of H. A. Bruson and J. W. Eastes, *J. Am. Chem. Soc.*, **59**, 2011 (1937).

(4) V. Petrow and O. Stephenson, *J. Pharm. Pharmacol.*, **5**, 359 (1953).

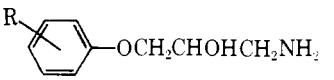
(5) M. S. Newman, W. Fones, and M. Renoll, *J. Am. Chem. Soc.*, **69**, 723 (1947).

(6) M. G. Ettlinger, *ibid.*, **72**, 4792 (1950).

(7) H. A. Staab, *Angew. Chem., Intern. Ed. Engl.*, **1**, 351 (1962).

TABLE II

1-AMINO-3-PHENOXY-2-PROPANOLS

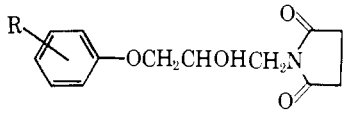


| Compd. | R | Yield, % | Recrystn. solvent[a] | M.p., °C. | Formula | Calcd., % C | H | N | Found, % C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 18[b] | *m*-Cl | 52 | E | 187–190 | $C_{15}H_{15}ClN_4O_9$[c] | 41.82 | 3.51 | 13.01 | 42.02 | 3.33 | 13.17 |
| 19[b] | *m*-Br | 84 | E | 189–191.5 | $C_{15}H_{15}BrN_4O_9$[c] | 37.91 | 3.18 | 11.79 | 38.11 | 3.24 | 11.75 |
| 20[b] | *m*-F | 76 | S | 80–82 | $C_9H_{12}FNO_2$ | 58.36 | 6.53 | 7.56 | 59.06 | 6.57 | 7.69 |
| 21[d] | *m*-$CH_3$ | 40 | THF–S | 78–79 | $C_{10}H_{15}NO_2$ | 66.27 | 8.34 | 7.73 | 66.40 | 8.52 | 7.92 |
| 22[b] | *m*-$(CH_3)_3C$ | 88 | S | 66–69 | $C_{13}H_{21}NO_2$ | 69.92 | 9.48 | | 69.95 | 9.40 | |
| 23[d] | *p*-$OCH_3$ | 8 | THF–S | 98–99 | $C_{10}H_{15}NO_3$ | 60.89 | 7.67 | 7.10 | 60.97 | 7.88 | 7.12 |
| 24[d] | *o*-$CF_3$ | 50 | Et–S | 89–90.5 | $C_{10}H_{12}F_3NO_2$ | 51.05 | 5.14 | 5.96 | 50.78 | 5.30 | 5.76 |
| 25[d] | *m*-$CF_3$ | 66 | Et–S | 66–67 | $C_{10}H_{12}F_3NO_2$ | 51.05 | 5.14 | 5.96 | 50.70 | 5.07 | 5.95 |
| 26[b] | *p*-$C_6H_5$ | 74 | M | 170.5–173 | $C_{15}H_{17}NO_2$ | 74.05 | 7.04 | 5.76 | 73.66 | 7.17 | 5.70 |
| 27[b] | *p*-$C_6H_5CH{=}CH$ | | | [e] | | | | | | | |

[a] E, ethanol; Et, ether; M, methanol; S, Skellysolve B (a saturated hydrocarbon fraction, b.p. 60–71°); and THF, tetrahydrofuran. [b] Prepared by basic hydrolysis. [c] Picrate. [d] Prepared by acid hydrolysis. [e] Very high melting solid, could not be crystallized.

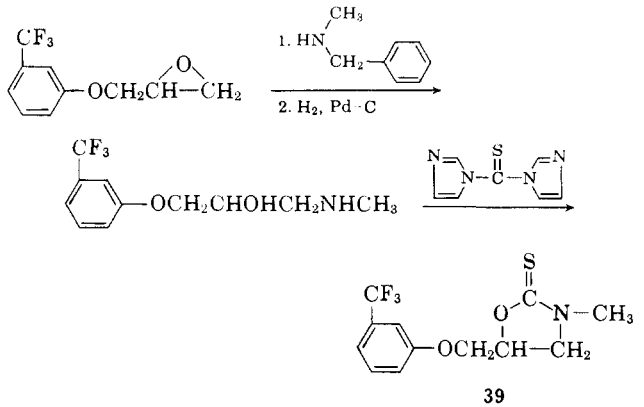
TABLE III

N-(3-PHENOXY-2-HYDROXYPROPYL)SUCCINIMIDES



| Compd. | R | Yield, % | Recrystn. solvent[a] | M.p., °C. | Formula | Calcd., % C | H | Found, % C | H |
|---|---|---|---|---|---|---|---|---|---|
| 8 | *m*-Cl | 71 | B | 101–104 | $C_{13}H_{14}ClNO_4$ | 55.03 | 4.97 | 55.12 | 5.04 |
| 9 | *m*-Br | 65 | E | 102.5–105 | $C_{13}H_{14}BrNO_4$ | 47.58 | 4.30 | 47.84 | 4.03 |
| 10 | *m*-F | 86 | M–W | 117–120 | $C_{14}H_{14}FNO_4$ | 58.42 | 5.28 | 58.43 | 5.13 |
| 11 | *m*-$CH_3$ | 58 | A–S | 104.5–105.5 | $C_{14}H_{17}NO_4$ | 63.86 | 6.51 | 64.05 | 6.50 |
| 12 | *m*-$(CH_3)_3C$ | 75 | S | 85.5–91.5 | $C_{17}H_{23}NO_4$ | 66.86 | 7.59 | 66.68 | 7.72 |
| 13 | *p*-$OCH_3$ | 47 | A–S | 139.5–140.5 | $C_{14}H_{17}NO_5$ | 60.20 | 6.14 | 60.50 | 6.32 |
| 14 | *o*-$CF_3$ | 33 | A–S | 121–122.5 | $C_{14}H_{14}F_3NO_4$ | 52.99 | 4.45 | 53.07 | 4.54 |
| 15 | *m*-$CF_3$ | 62 | A–S | 82–83.5 | $C_{14}H_{14}F_3NO_4$ | 52.99 | 4.45 | 53.32 | 4.65 |
| 16 | *p*-$C_6H_5$ | 86 | A | 183–184 | $C_{19}H_{19}NO_4$ | 70.14 | 5.89 | 70.22 | 6.05 |
| 17 | *p*-$C_6H_5CH{=}CH$ | 70 | THF | 213–220.5 | $C_{21}H_{21}NO_4$ | 71.78 | 6.02 | 71.63 | 6.05 |

[a] A, acetone; B, benzene; E, ethanol; M, methanol; S, Skellysolve B (a saturated hydrocarbon fraction, b.p. 60–71°); THF, tetrahydrofuran; and W, water.



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here frustrated any attempts to derive meaningful structure–activity relationships. A detailed account of the antifertility activity of **38** will be reported elsewhere.

### Experimental Section[8]

**1-(α,α,α-Trifluoro-*o*-tolyloxy)-2,3-epoxypropane (5).**—A mixture of 98 g. (0.6 mole) of *o*-trifluoromethylphenol, 167 g. (1.8 moles) of epichlorohydrin, and 3 ml. of piperidine was stirred at 100° for 17 hr. The excess epichlorohydrin was distilled under reduced pressure. The residue was added to a solution of 80 g. (2 moles) of NaOH in 500 ml. of water. The mixture was stirred at room temperature for 23 hr. and extracted with two 800-ml. portions of ether. The combined extracts were washed with two 200-ml. portions of water. The ether was evaporated. The product was distilled at 2.25 mm.: I, 57.8 g., b.p. 124–128°, $n^{25}D$ 1.4698; II, 22 g., b.p. 128–140°, $n^{25}D$ 1.4698. A portion of fraction I was analyzed.

**1-[3-(α,α,α-Trifluoro-*m*-tolyloxy)-2-hydroxypropyl]succinimide (15).**—A mixture of 23.5 g. (0.11 mole) of 1-(α,α,α-trifluoro-*m*-tolyloxy)-2,3-epoxypropane,[5] 10.9 g. (0.11 mole) of succinimide, 100 ml. of ethanol, and 4 drops of pyridine was refluxed for 20 hr. The solution was poured into 500 ml. of water. An oil separated and slowly solidified. The solid was filtered, washed with water, and crystallized from aqueous methanol giving 26.8 g. of yellow crystals. Recrystallization from ether–Skellysolve B gave 21.2 g. of pale yellow plates, m.p. 81.5–83°.

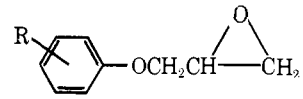
**1-(α,α,α-Trifluoro-*m*-tolyloxy)-3-amino-2-propanol (25).**—A mixture of 202.5 g. of 1-[3-(α,α,α-trifluoro-*m*-tolyloxy)-2-hydroxypropyl]succinimide and 1 l. of concentrated HCl was refluxed for 8 hr. The cooled mixture was diluted with 1 l. of water and extracted with 1 l. of ether. The aqueous layer was cooled in an ice bath and basified with 50% aqueous NaOH. The mixture was extracted with two 1500-ml. portions of ether. The combined ether extracts were washed twice with water. The ether was evaporated, and the residual oil was distilled giving 118.5 g. of yellow liquid, b.p. 153–156° (1.75 mm.), which solidified. The solid was crystallized from ether–Skellysolve B giving 100 g. of nearly colorless needles, m.p. 65.5–66.5°.

**1-Amino-3-(*m*-*t*-butylphenoxy)-2-propanol (22).**—A mixture of 37.5 g. of N-[3-(*m*-*t*-butylphenoxy)-2-hydroxypropyl]succinimide, 330 g. of NaOH, and 2 l. of ethanol was refluxed for 20 hr. Eth-

(8) Melting points were taken in open glass capillaries using a Thomas–Hoover Uni-Melt apparatus and are recorded as obtained. Intermediates not listed in the tables were obtained from commercial sources or by literature procedures.

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).

(3) M. Mugdan and D. P. Young, *J. Chem. Soc.*, 2988 (1949).

(4) F. Lautenschlaeger and G. T. Wright, *Can. J. Chem.*, **41**, 1972 (1963)