$H_2NHCH_2CH_2OH$, 88303-65-5; $NH_2CH_2CH_2NHCH_2CH_2OH$, 111-41-1.

H. D. Hollis Showalter,* Judith L. Johnson
Leslie M. Werbel
Department of Chemistry

Wilbur R. Leopold, Robert C. Jackson
Edward F. Elslager
Department of Chemotherapy
Warner-Lambert/Parke-Davis Pharmaceutical Research
Ann Arbor, Michigan 48105
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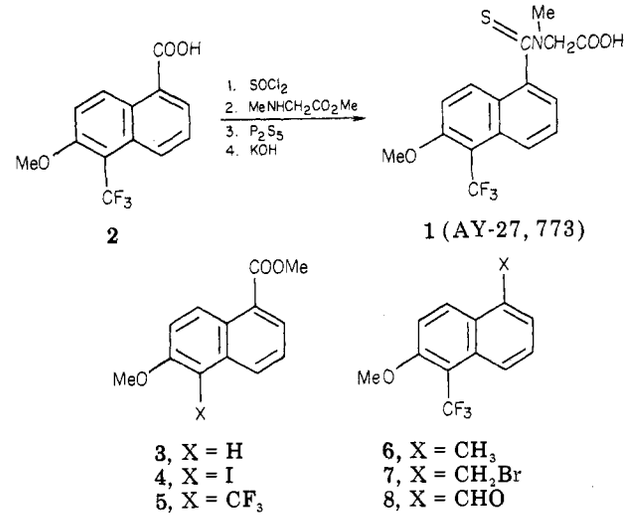
N-[[5-(Trifluoromethyl)-6-methoxy-1-naphthalenyl]thioxomethyl]-*N*-methylglycine (Tolrestat),[1] a Potent, Orally Active Aldose Reductase Inhibitor[2]

Sir:

Insulin therapy is effective for the primary control of glucose levels and has considerably reduced mortality from acute effects of diabetes. However, the complications of chronic diabetes, e.g., neuropathy, nephropathy, retinopathy, and cataracts, are, in practice, not controlled by insulin. The tissues involved (nerve, kidney, retina, and lens) do not require insulin for glucose uptake and, hence, are exposed to a high concentration of glucose, which enters the sorbitol pathway and is reduced by aldose reductase to sorbitol. The intracellular accumulation of sorbitol and its metabolite fructose can eventually result in a loss of osmotic integrity and cellular damage. These events have been linked to the development of some complications of chronic diabetes,[3] and, consequently, inhibition of the enzyme aldose reductase should provide a pharmacological approach to the treatment of these complications. Earlier work has appeared describing the biochemical, pharmacological, and clinical properties of alrestatin,[4-13] an aldose reductase inhibitor of relatively low potency developed in these laboratories. Efforts to develop a potent, orally active aldose reductase inhibitor have continued, and this report describes the chemistry, biochemistry, and pharmacology of *N*-[[5-(trifluoromethyl)-6-methoxy-1-naphthalenyl]thioxomethyl]-*N*-methylglycine (tolrestat,[1] 1).

Scheme I



2 — 1 (AY-27,773)

3, X = H
4, X = I
5, X = CF_3

6, X = CH_3
7, X = CH_2Br
8, X = CHO

Chemistry.[14] Tolrestat (1) was synthesized from 6-methoxy-5-(trifluoromethyl)naphthalene-1-carboxylic acid (**2**), mp 218–219 °C, by treatment of its acid chloride with methyl sarcosinate (Scheme I). The resulting carboxamide, mp 70–71 °C, was heated with phosphorus pentasulfide to afford 1 methyl ester, mp 109–110 °C, which on hydrolysis with KOH gave 1:[15] mp 164–165 °C; homogeneous by HPLC.[16]

The key intermediate **2**, as its methyl ester, was obtained in 87% yield via the iodination of methyl 6-methoxy-1-naphthalenecarboxylate (**3**)[17] with I_2/HIO_3 in an acetic acid–sulfuric acid mixture. The position of iodination was confirmed by the synthesis of **2** from authentic 2-methoxy-5-methyl-1-(trifluoromethyl)naphthalene (**6**)[18] (see below). The iodo derivative **4**, mp 98–99 °C, was reacted with trifluoromethyl iodide and copper powder in pyridine in an autoclave at 120 °C for 20 h to give **5**, mp 75–78 °C, in 93% yield. Hydrolysis of **5** afforded the key intermediate **2**, mp 221–222 °C. Alternatively, **2** was obtained directly from **6**[18] in 55% yield by potassium permanganate oxidation. Compound **6** was also brominated with NBS to afford **7**, mp 97–99 °C, which was converted to aldehyde **8**, mp 98–100 °C, in high yield under the conditions of the Sommelet reaction. Oxidation of **8** with potassium permanganate gave **2**.

Biochemistry and Pharmacology. Biochemical and pharmacological properties of tolrestat (1) were investigated and compared with data obtained with alrestatin (vide supra) or sorbinil,[19] the two aldose reductase inhib-

(1) Nonproprietary name adopted by the USAN Council; also known by the Ayerst code number AY-27,773.
(2) The contents of this paper have been presented; see: "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, DC, Aug 28–Sept 2, 1983; American Chemical Society: Washington, DC, 1983, Abstr MEDI 009.
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itors that have been studied clinically.

Inhibition of bovine lens aldose reductase was determined following the method of Hayman and Kinoshita[20] with DL-glyceraldehyde as substrate. The following IC_{50}'s were found: tolrestat, 3.5×10^{-8} M; alrestatin, 2.7×10^{-6} M; sorbinil, 1.5×10^{-6} M.

The doses that decreased galactitol accumulation by 50% in the sciatic nerve in the galactosemic rat model[4] after administration for 4 days in the diet were as follows: tolrestat, 7.3 ± 2.3 mg/(kg day); alrestatin, ~900 mg/(kg day).

In rats rendered diabetic with streptozotocin,[21] the doses that decreased sorbitol accumulation in the sciatic nerve by 50% after 3 weeks administration in the diet were as follows: tolrestat, 4.8 ± 2.4 mg/(kg day); alrestatin, ~1000 mg/(kg day).

Aldose reductase is present in the red blood cell (RBC), and sorbitol has been shown to accumulate in the human RBC when incubated in a high glucose-containing medium. This accumulation is blocked by the presence of the aldose reductase inhibitor tetramethyleneglutaric acid.[21] It has been suggested[21] that RBC sorbitol may be a useful indicator of the tissue sorbitol levels that participate in the pathogenesis of diabetes-associated complications. In rats rendered diabetic with streptozotocin, RBC sorbitol levels were 126 nmol/g of Hb, markedly higher than that seen in normal rats ~50 nmol/g of Hb). Treatment of diabetic rats with tolrestat in the diet for 7 days at a dose of 1.8 mg/(kg day) caused a reversal to normal RBC sorbitol levels.

On the basis of these and other pharmacological data to be published separately, tolrestat has been selected for clinical development and is currently being examined for the treatment of diabetic neuropathy.

Registry No. 1, 82964-04-3; 1 (methyl ester), 84533-04-0; 2, 84532-72-9; 2 (carboxamide derivative), 84533-46-0; 3, 61109-48-6; 4, 84532-68-3; 6, 85674-78-8; 7, 88245-14-1; 8, 88245-15-2; methyl sarcosinate, 5473-12-1; trifluoromethyl iodide, 2314-97-8; aldose reductase, 9028-31-3.

Kazimir Sestanj, Francesco Bellini, Steven Fung Nedumparambil Abraham, Adi Treasurywala Leslie Humber*
Chemistry Department

Nicole Simard-Duquesne, Dushan Dvornik
Biochemistry Department
Ayerst Laboratories Research Inc.
CN 8000, Princeton, New Jersey
Received August 2, 1983

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Articles

Cardiac Glycosides. 1.[1] A Systematic Study of Digitoxigenin D-Glycosides

Dwight S. Fullerton,*[†] Masaru Kihara,[†] Tamboue Deffo,[†] Eitaro Kitatsuji,[†] Khalil Ahmed,[‡] Bruce Simat,[‡] Arthur H. L. From,[‡] and Douglas C. Rohrer[§]

School of Pharmacy, Oregon State University, Corvallis, Oregon 97331, Veterans Administration Medical Center and University of Minnesota, Minneapolis, Minnesota 55417, and Medical Foundation of Buffalo, Inc., Buffalo, New York 14203.
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A series of digitoxigenin glycosides was studied: five with β-D-sugars varying stepwise in sugar structure from β-D-digitoxose to β-D-galactose, including one β-D/α-D pair. I_{50} values for these glycosides and digitoxigenin were determined with hog kidney Na^+,K^+-ATPase. These data suggest a major and unexpected role for 4'-OH conformation in the sugar. All the glycosides with an equatorial 4'-OH were more active than the two with the 4'-OH axial [digitoxigenin β-D-galactoside (**6**) $I_{50} = 6.45 \times 10^{-8}$ M; digitoxigenin 2'-deoxy-α-D-*ribo*-hexopyranoside (α-**3a**) $I_{50} = 9.33 \times 10^{-8}$ M; digitoxigenin $I_{50} = 1.17 \times 10^{-7}$ M]. Stereochemistry of the 3'-OH had much less of an activity role than that of the 4'-OH, in contrast to existing models of "sugar-site" binding.

The biological roles of the sugars of natural and semisynthetic cardenolide glycosides have long been of considerable interest. In their classic reviews of 1962 and 1966, Zorbach and Reichstein[2] summarized the syntheses and LD50 data of a variety of sugar analogues of digitoxigenin (1) and strophanthidin. The extensive Na^+,K^+-ATPase studies by Yoda and Yoda[3] focused on a variety of naturally occurring monoglycosides (convallatoxin, helveticoside, ouabain, and deglucocheirotoxin), as well as on a variety of semisynthetic cardiac glycosides [digitoxigenin β-D-digitoxoside (**2**), digitoxigenin bisdigitoxoside, and digitoxin acetates]. Thomas, Brown, and co-workers[4] have reported the syntheses and guinea pig inotropic activities of digitoxigenin β-D-glucoside (**5**), digitoxigenin β-D-galactoside (**6**), digitoxigenin α-L-rhamnoside, and the glucoside and galactoside of digoxigenin.

[†] Oregon State University.
[‡] VA Medical Center and University of Minnesota.
[§] Medical Foundation of Buffalo.

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