

9, *trans*
10, *cis*

ity. None of the compounds tested showed significant biological activity.

Experimental Section⁹

Methyl 2-Acetyl-1,2,3,4-tetrahydro-7-methoxy-1-oxo-2-phenanthrenecarboxylate (1).—Hydration of **12** in AcOH, HCOOH, and H₂O catalyzed by Hg²⁺ produced **1** in a yield of 95%, mp 160–162°. *Anal.* (C₂₀H₂₀O₆) C, H.

2-Acetyl-3,4-dihydro-7-methoxy-2-methyl-1(2H)-phenanthrone (2).—Alkylation of **11** (8.2 g) with propargyl bromide in Diglyme using NaH as catalyst, followed by hydration of the alkyne,² produced **13** (6.5 g, 66%), mp 79–81° (80–83°).^{4b} *Anal.* (C₁₉H₂₀O₃) C, H.

3-Methoxygona-1,3,5(10),6,8,14-hexaen-16-one (3).—A mixture of **1** (12.0 g), Ba(OH)₂·8H₂O (45.0 g) in 120 ml H₂O and 120 ml of methoxyethanol was refluxed for 4 hr. Recrystallization of the crude product from methoxyethanol gave 8.5 g (91%) of **3**, mp 177–179°. *Anal.* (C₁₈H₁₆O₂) C, H.

Methyl 3-Methoxy-16-oxoestra-1,3,5(10),6,8,14-hexaen-18-oate (4).—The annelation reaction was carried out in refluxing PhMe, containing a small amount of *N*-methylpyrrolidone, using NaH as the base.² Starting with **1** (2.0 g) and NaH (0.4 g) and recrystallizing the crude product from C₆H₆, a yield of 1.1 g (57%) of **4** was obtained, mp 178–180°. *Anal.* (C₂₀H₁₈O₄) C, H.

3-Methoxy-13-methylgona-1,3,5(10),6,8,14-hexaen-16-one (5).—Starting with **2** (6.4 g) and using the procedure outlined for **3**, a yield of 4.8 g (80%) of **5** was obtained, mp 203–206° (205–206°).^{2c}

3-Methoxy-14β-gona-1,3,5(10),6,8-pentaen-16-one (cis Isomer) and 3-Methoxygona-1,3,5(10),6,8-pentaen-16-one (trans Isomer) (6).—Hydrogenation of **3** in PhMe–DMA solution, using a Pd–C catalyst dried in refluxing PhMe produced a mixture of **6(cis)** and **6(trans)** separated by fractional crystallization from Me₂CO to produce **6(trans)**: mp 155–157°; λ_{max}^{alc} 231, 268 mμ; ν C=O 1739 cm⁻¹; **6(cis)**, mp 138–140°; λ_{max}^{alc} 229, 265 mμ; ν C=O 1734 cm⁻¹. *Anal.* (C₁₈H₁₈O₂) C, H.

cis- and trans-Methyl 3-Methoxy-16-oxoestra-1,3,5(10),6,8-pentaen-18-oate (7).—Hydrogenation of **4** by the method outlined for **3** produced a mixture of isomers containing about 90% of the *trans* and 10% of the *cis* isomer. Fractional crystallization (Me₂CO) produced **7(trans)**, mp 176–178°; λ_{max}^{alc} 233, 269 mμ; ν C=O (ketone) 1732 cm⁻¹, and **7(cis)**, mp 126–129°; λ_{max}^{alc} 231, 267 mμ; ν C=O (ketone) 1730 cm⁻¹. *Anal.* (C₂₀H₂₀O₄) C, H.

Conversion of 7(trans) into 8(trans). **A. trans-Methyl 16,16-ethylenedioxy-3-methoxyestra-1,3,5(10),6,8-pentaen-18-oate (13).**—A solution of **7** (6.3 g) and excess (CH₂OH)₂ in C₆H₆ and Diglyme, with MeSO₃H as catalyst, was refluxed using a Dean–Stark trap until evolution of H₂O ceased. The product was recovered and recrystallized from C₆H₆ to give 3.8 g (82%) of **13**, mp 99–101°. *Anal.* (C₂₂H₂₄O₆) C, H.

B. 16,16-Ethylenedioxy-13-hydroxymethyl-3-methoxygona-1,3,5(10),6,8-pentaene (14).—Reduction of **13** by LAH in THF produced **14** in 79% yields, mp 212° dec. *Anal.* (C₂₁H₂₄O₄) C, H.

C. 16,16-Ethylenedioxy-13-hydroxymethyl-3-methoxyestra-3,5(10),6,8-pentaene Methanesulfonate (15).—Treatment of **14** with MeSO₃Cl in C₂H₅N produced **15** in 97% yields, mp 172–173°. *Anal.* (C₂₂H₂₆O₅S) C, H.

D. 8(trans) from 15.—Refluxing **15** with KI in DMAC, followed by hydrolysis of the ketal and hydrogenolysis of the iodide

using the procedure previously outlined² converted **15** into **8(trans)** showing the original configuration of **7** was *trans*.

3-Methoxy-13-methylgona-1,3,5(10),6,8-pentaen-16-one (8).—Hydrogenation of **5** over Pd(C) followed by fractional crystallization of the crude product (Me₂CO) to give **8**, mp 162–165° (169.5–171°)^{4b} identical with that obtained from **16**. *Anal.* (C₁₉H₂₀O₂) C, H.

Gona-5(10),6,8-triene-3,16-dione (9).—A solution of **16** (3.3 g) in 45 ml of *n*-BuOH was refluxed with Na (2.5 g) until all Na had reacted. The mixture was then hydrolyzed and the crude product allowed to stand 60 min in a mixture of AcOH, 15 ml of HCOOH, and 5 ml of H₂O. Addition of H₂O followed by recrystallization of the crude product from Me₂CO gave a yield of 1.7 g (63%), mp 134–137°. *Anal.* (C₁₇H₁₈O₂) C, H.

14β-Gona-5(10),6,8-triene-3,16-dione (10).—The procedure used to prepare **9** was followed. Starting with **17** (3.7 g), a yield of 1.9 g (63%) of **10** was obtained, mp 126–131°. *Anal.* (C₁₇H₁₈O₂) C, H.

3,4-Dihydro-7-methoxy-2-methyl-1(2H)-phenanthrone (11).—3,4-Dihydro-7-methoxy-1(2H)-phenanthrone was converted into **11** using the procedure previously outlined for the benz[*e*]indene analogs.² The overall yield of product was 83%, mp 104–106° (108°).¹⁰

Methyl 1,2,3,4-Tetrahydro-7-methoxy-1-oxo-2-(2-propynyl)-2-phenanthrenecarboxylate (12).—3,4-Dihydro-7-methoxy-1(2H)-phenanthrone was converted into **12** by successive condensations with Me₂CO₃ and propargyl bromide in DMAC using NaH as catalyst, as previously outlined.² The overall yield of product was 88%, mp 115–118°. *Anal.* (C₂₀H₁₈O₄) C, H.

16,16-Ethylenedioxy-3-methoxygona-1,3,5(10),6,8-pentaene (16).—The procedure used to prepare **13** was followed, **16** being obtained in a yield of 90%, mp 130–132°. *Anal.* (C₂₀H₂₂O₃) C, H.

16,16-Ethylenedioxy-3-methoxy-14β-gona-1,3,5(10),6,8-pentaene (17).—The procedure used to prepare **13** was followed, **17** being obtained in a yield of 92%, mp 135–138°. *Anal.* (C₂₀H₂₂O₃).

(10) G. Haberland and E. Blanke, *Ber.*, **70**, 169 (1937).

Potential Specific Inhibitors of the Lactose Transport System of *Escherichia coli*

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The membrane component of the lactose transport system of *Escherichia coli*, known as lactose permease,² contains an SH group which is essential for its activity.³ Several galactosides protect this SH group from attack by SH reagents,³ implying a close spatial relationship between the galactoside binding site and the SH group. The galactosides described here were designed as specific and irreversible inhibitors⁴ of the permease—the D-galactose moiety enabling specific binding, while the *N*-bromoacetyl or *N*-(4-acetoxymercuri-3-methoxybutyryl) function could then react with the essential SH group. Analogs containing other carbohydrate moieties were prepared in order to test for specificity of inhibition. The unsubstituted gly-

(9) All melting points are corrected. Ir spectra were obtained on a Beckman IR7 spectrophotometer. Where analyses are indicated only by symbols of the element, analytical results obtained for those elements were within ±0.4% of the theoretical values. Nmr spectra were obtained on a Varian HA60 spectrophotometer. Spectral results agreed with the suggested structures routine.

(1) Present address: Department of Radiotherapeutics, Cambridge University, Cambridge, England.

(2) G. N. Cohen and J. Monod, *Bact. Rev.*, **21**, 169 (1957).

(3) C. F. Fox and E. P. Kennedy, *Proc. Nat. Acad. Sci. U. S.*, **60**, 725 (1968).

(4) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," John Wiley & Sons, New York, N. Y., 1967.

TABLE I

No.	Compd	Mp, ° C	$[\alpha]^{20}_D$ ^b	Crystalline solvent	Formula	Analyses ^c
<i>N</i> -Bromoacetyl						
1	D-Glucopyranosylamine	187-190	-13.5°	MeOH-Et ₂ O	C ₈ H ₁₄ N ₂ O ₆ Br	C, H, N
2	D-Galactopyranosylamine	192 dec	+13°	MeOH-Et ₂ O	C ₈ H ₁₄ N ₂ O ₆ Br	C, H, N
3	L-Fucosylamine	175	+2.8°	MeOH-Et ₂ O	C ₈ H ₁₄ N ₂ O ₆ Br	C, H, N
4	α-Lactosylamine	158	<i>c</i>	H ₂ O-Me ₂ CO	C ₁₄ H ₂₄ N ₂ O ₁₁ Br	C, H, N
<i>N</i> -Vinylacetyl						
5	D-Glucopyranosylamine	175	<i>d</i>	MeOH-Et ₂ O	C ₁₉ H ₁₇ N ₁ O ₅	C, H, N
6	D-Galactopyranosylamine	160	<i>d</i>	MeOH-Et ₂ O	C ₁₉ H ₁₇ N ₁ O ₅	C, H, N
7	L-Fucopyranosylamine	175	<i>d</i>	MeOH-Et ₂ O	C ₁₉ H ₁₇ N ₁ O ₅	C, H, N
<i>N</i> -(4-Acetoxymercuri-3-methoxybutyryl)						
8	D-Glucopyranosylamine	160 dec	-8°	MeOH-Et ₂ O	C ₁₅ H ₂₃ N ₁ O ₉ Hg	N ^f
9	D-Galactopyranosylamine	178-180	+12.1°	MeOH	C ₁₅ H ₂₃ N ₁ O ₉ Hg	N ^f
10	L-Fucopyranosylamine	195 dec	+3.4°	MeOH	C ₁₅ H ₂₃ N ₁ O ₉ Hg	N ^f

^a Determined with a Büchi apparatus, and uncorrected. ^b C = 1, H₂O. ^c Rotation very low. ^d Not determined. ^e Analytical values were all within 0.4% of theoretical. ^f Kjeldahl method.

cosylamines were used as starting materials, obviating the need for blocking groups.

Compounds **1-4** and **8-10** (Table I) were tested as irreversible inhibitors of lactose uptake as previously described.⁵ Both **1** and **2** were inactive at concentrations of up to 10⁻² M. However both **3** and **4** were inhibitors, **4** showing 100% inactivation of transport at 10⁻³ M. This finding demonstrates that a specific inactivation had occurred.⁶ On the other hand, compounds **8-10** all gave 100% inactivation at 10⁻⁴ M. This loss of specificity could be due to an extremely rapid mercuriation of the essential sulfhydryl by these compounds. Detailed studies of **3** and **4** are in progress.

Experimental Section

Tlc was carried out on silica gel G plates using Me₂CO-MeOH (10:1) as developing solvent; compounds were detected by spraying with concd H₂SO₄ and heating at 120°. The mercurials were examined by paper chromatography using *i*-PrOH-H₂O (4:1) as solvent, and detected with a 0.1% dithizone-CHCl₃ spray.

β-D-Glucopyranosylamine, β-D-galactopyranosylamine, and α-lactosylamine were prepared as described.⁷ L-Fucopyranosylamine (of unknown anomeric configuration) was prepared as described for the glucoanalogue. It was crystallized from H₂O-*i*-PrOH, and had mp 145-150° dec; $[\alpha]^{20}_D$ +3.5° (*c* = 2, H₂O). *Anal.* (C₆H₁₃N₁O₅) N.

Bromoacetic and vinylacetic anhydrides were prepared by treating the appropriate acid (1 M equiv), in dry CCl₄, with DCI (0.5 M equiv). Dicyclohexyl urea was filtered off and the CCl₄ removed *in vacuo*.

Acylation.—The glycosylamine (2 mmol) suspended in DMF (2 ml) was treated with the appropriate anhydride (2.5 mmol). After 3 hr at 25°, excess Et₂O was added, and the precipitated *N*-acyl derivative filtered and washed well with Et₂O. Compounds **1-7** were found homogenous by tlc, and were formed in almost quantitative yield.

Mercuriation of 5-7.—The *N*-vinylacetyl glycosylamine (1 mmol) was refluxed with a solution of Hg(OAc)₂ (1.1 mmol) in MeOH (10 ml) for 60 min. After removal of solvent and ACOH *in vacuo*, the residue was crystallized from MeOH. Paper chromatography showed compounds **8-10** to be homogenous, giving single orange spots with dithizone at *R_f* approximately 0.5. Hg²⁺, which gives a violet color with dithizone, was not detectable.

(5) J. Yariv, A. J. Kalb, E. Katchalski, R. Goldman, and E. W. Thomas, *FEBS Letters*, **5**, 173 (1969).

(6) Both *N*-chloroacetyl analogs of **3** and **4** were inactive, showing that the biological activity of **3** and **4** lay in their alkylating capacity.

(7) H. S. Ishell and H. L. Frush, *J. Org. Chem.*, **23**, 1309 (1958); C. A. Lobry de Bruyn and F. H. van Leent, *Rec. Trav. Chim. Pays-Bas*, **14**, 134 (1895); F. Mischeel, R. Frier, E. Plate, and A. Hiller, *Ber.*, **85**, 1092 (1952).

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1-Substituted 3-[(5-Nitrofurfurylidene)amino]-2-imidazolidinones

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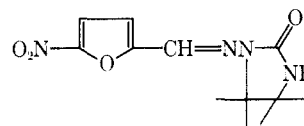
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The activity of nifuradene¹ (**1**) led to an investigation of its use as a urinary tract antibacterial agent.² An intensive synthetic program was initiated to produce a series of compounds which were substituted on the imino nitrogen of **1**. This paper describes the synthesis and antibacterial activity of these compounds.



1

Chemistry.—Several pathways were utilized in the preparation of the compounds. The first route started with an appropriately *N*-substituted ethylenediamine (**21**) which was heated with urea to form a 1-substituted 2-imidazolidinone (**2**) (see Scheme I). These ethyleneureas were nitrosated and then reduced with Zn dust in 2 N H₂SO₄. Condensation of the resulting 3-amino-1-substituted-2-imidazolidinones (**22**) with 5-nitro-2-furaldehyde (**3**) yielded **9-12**. The second route in-

(1) Renafur E, 1-[(5-nitrofurfurylidene)amino]-2-imidazolidinone.

(2) J. R. O'Connor, H. E. Russell, J. G. Michels, P. V. Newland, and W. F. Carey, IIIrd International Congress of Chemotherapy, July 22-27, 1963, Stuttgart, Germany, Paper C-52.