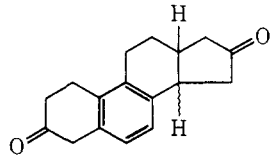

9, *trans*
10, *cis*

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

Experimental Section[9]

Methyl 2-Acetonyl-1,2,3,4-tetrahydro-7-methoxy-1-oxo-2-phenanthrenecarboxylate (1).—Hydration of **12** in AcOH, HCOOH, and H_2O catalyzed by Hg^{2+} [2] produced **1** in a yield of 95%, mp 160–162°. *Anal.* ($C_{20}H_{20}O_5$) C, H.

2-Acetonyl-3,4-dihydro-7-methoxy-2-methyl-1(2*H*)-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.* ($C_{19}H_{20}O_3$) C, H.

3-Methoxygona-1,3,5(10),6,8,14-hexaen-16-one (3).—A mixture of **1** (12.0 g), $Ba(OH)_2 \cdot 8H_2O$ (45.0 g) in 120 ml H_2O 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.* ($C_{18}H_{16}O_2$) 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 C_6H_6, a yield of 1.1 g (57%) of **4** was obtained, mp 178–180°. *Anal.* ($C_{20}H_{18}O_4$) 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 Csolution, using a Pd–C catalyst dried in refluxing PhMe produced a mixture of **6**(*cis* and *trans*) separated by fractional crystallization from Me_2CO 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.* ($C_{18}H_{18}O_2$) 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 (Me_2CO) 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.* ($C_{20}H_{20}O_4$) 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 $(CH_2OH)_2$ in C_6H_6 and Diglyme, with $MeSO_3H$ as catalyst, was refluxed using a Dean–Stark trap until evolution of H_2O ceased. The product was recovered and recrystallized from C_6H_6 to give 3.8 g (82%) of **13**, mp 99–101°. *Anal.* ($C_{22}H_{24}O_5$) 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.* ($C_{21}H_{24}O_4$) C, H.

C. 16,16-Ethylenedioxy-13-hydroxymethyl-3-methoxyestra-3,5(10),6,8-pentaene Methanesulfonate (15).—Treatment of **14** with $MeSO_2Cl$ in C_5H_5N produced **15** in 97% yields, mp 172–173°. *Anal.* ($C_{22}H_{26}O_6S$) 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 outlined[2] 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 (Me_2CO) to give **8**, mp 162–165° (169.5–171°)[4b] identical with that obtained from **16**. *Anal.* ($C_{19}H_{20}O_2$) 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 H_2O. Addition of H_2O followed by recrystallization of the crude product from Me_2CO gave a yield of 1.7 g (63%), mp 134–137°. *Anal.* ($C_{17}H_{18}O_2$) 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.* ($C_{17}H_{18}O_2$) C, H.

3,4-Dihydro-7-methoxy-2-methyl-1(2*H*)-phenanthrone (11).—3,4-Dihydro-7-methoxy-1(2*H*)-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(2*H*)-phenanthrone was converted into **12** by successive condensations with Me_2CO_3 and propargyl bromide in DMAC using NaH as catalyst, as previously outlined.[2] The overall yield of product was 88%, mp 115–118°. *Anal.* ($C_{20}H_{18}O_4$) 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.* ($C_{20}H_{22}O_3$) 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.* ($C_{20}H_{22}O_3$).

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

(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.

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 inhibitors[4] 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-

(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,[a] °C	$[\alpha]^{20}D$[b]	Crystn solvent	Formula	Analyses[c]
			N-Bromoacetyl			
1	D-Glucopyranosylamine	187–190	−13.5°	MeOH–Et_2O	$C_8H_{14}N_1O_6Br$	C,H,N
2	D-Galactopyranosylamine	192 dec	+13°	MeOH–Et_2O	$C_8H_{14}N_1O_6Br$	C,H,N
3	L-Fucosylamine	175	+ 2.8°	MeOH–Et_2O	$C_8H_{14}N_1O_5Br$	C,H,N
4	α-Lactosylamine	158	*e*	H_2O–Me_2CO	$C_{14}H_{24}N_1O_{11}Br$	C,H,N
			N-Vinylacetyl			
5	D-Glucopyranosylamine	175	*d*	MeOH–Et_2O	$C_{10}H_{17}N_1O_5$	C,H,N
6	D-Galactopyranosylamine	160	*d*	MeOH–Et_2O	$C_{10}H_{17}N_1O_6$	C,H,N
7	L-Fucopyranosylamine	175	*d*	MeOH–Et_2O	$C_{10}H_{17}N_1O_5$	C,H,N
			N-(4-Acetoxymercuri-3-methoxybutyryl)			
8	D-Glucopyranosylamine	160 dec	− 8°	MeOH–Et_2O	$C_{13}H_{23}N_1O_9Hg$	N[f]
9	D-Galactopyranosylamine	178–180	+12.1°	MeOH	$C_{13}H_{23}N_1O_9Hg$	N[f]
10	L-Fucopyranosylamine	195 dec	+ 3.4°	MeOH	$C_{13}H_{25}N_1O_8Hg$	N[f]

[a] Determined with a Büchi apparatus, and uncorrected. [b] C = 1, H_2O. [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 mercuration 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 Me_2CO–MeOH (10:1) as developing solvent; compounds were detected by spraying with concd H_2SO_4 and heating at 120°. The mercurials were examined by paper chromatography using *i*-PrOH–H_2O (4:1) as solvent, and detected with a 0.1% dithizone–$CHCl_3$ 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 glucoanalog. It was crystallized from H_2O–*i*-PrOH, and had mp 145–150° dec; $[\alpha]^{20}D$ + 3.5° (*c* = 2, H_2O). *Anal.* ($C_6H_{13}N_1O_4$) N.

Bromacetic and vinylacetic anhydrides were prepared by treating the appropriate acid (1 *M* equiv), in dry CCl_4, with DCI (0.5 *M* equiv). Dicyclohexyl urea was filtered off and the CCl_4 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 Et_2O was added, and the precipitated *N*-acyl derivative filtered and washed well with Et_2O. Compounds **1–7** were found homogenous by tlc, and were formed in almost quantitative yield.

Mercuration of 5–7.—The *N*-vinylacetylglycosylamine (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. Hg^{2+}, which gives a violet color with dithizone, was not detectable.

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(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. Isbell 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. Micheel, R. Frier, E. Plate, and A. Hiller, *Ber.*, **85**, 1092 (1952).

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

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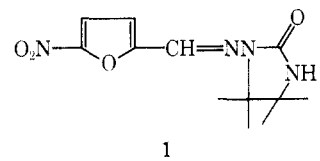
The activity of nifuradene[1] (**1**) led to an investigation of its use as a urinary tract antibacterial agent.[2] An intensive synthetic program was initiated to produce a series of compounds which were substituted on the imino nitrogen of **1**. This paper describes the synthesis and antibacterial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



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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* H_2SO_4. 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®, 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.