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# Dehydrative Metabolites of 1-(3-Chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)ethanol as Potential Hypocholesteremic Agents

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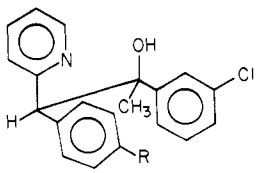
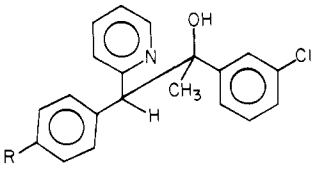
The *E* and *Z* isomers of 2-[2-(3-chlorophenyl)-1-phenyl-1-propenyl]pyridine (**2a,b**) and 2-[2-(3-chlorophenyl)-1-(4-hydroxyphenyl)-1-propenyl]pyridine (**4a,b**) were synthesized and separated as possible metabolites of 1-(3-chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)ethanol (**1a**). Following administration of **1a** to rats, a HPLC system was used to examine urine and serum specimens for the less polar metabolites of **1a**. Isomers **2a** and **2b** were not detected but their hydroxylated derivatives **4a** and **4b** were observed as minor metabolites. Compounds **2a,b** and **4a,b** exhibited hypocholesteremic activity in rats; compounds **4a** and **4b** are of special interest because they possessed relatively low estrogenicity.

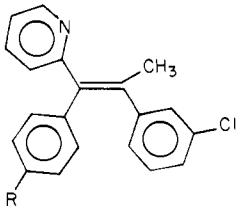
The compound 1-(3-chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)ethanol (**1a**) has shown promising hypocholesteremic activity in rats but not in rhesus monkeys or humans.[1] Studies are in progress in these laboratories to determine if species differences in the metabolic disposition of **1a** could be responsible for the species-specific hypocholesteremic activity. It has been reported that the 2-(4-hydroxyphenyl) derivative **3a** is a pharmacologically active metabolite of **1a**[2] in rats, and previous chemical studies indicated that dehydration of **1a** yielded the unsaturated isomers **2a** and **2b**.[3] Therefore, it was postulated that isomers **2a** and **2b** and their hydroxylated derivatives **4a** and **4b** could be metabolites of **1a** and might be involved in the species-specific activity of **1a**.



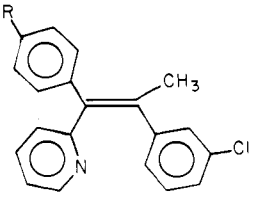
**1a**, R = H
**3a**, R = OH



**1b**, R = H
**3b**, R = OH



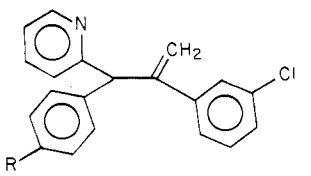
**2a**, R = H
**4a**, R = OH



**2b**, R = H
**4b**, R = OH

This paper reports the synthesis of compounds **2a,b**, **4a,b**, **5**, and **8** together with the determination of their hypocholesteremic and estrogenetic activities. Their importance as metabolites of compound **1a** in rats also has been evaluated.

**Chemistry.** As previously reported, dehydration of the higher melting racemate **1a** with 85% $H_3PO_4$ at 110 °C first yields the terminal olefin **5** which was followed by a slow conversion to the more thermodynamically stable conjugated *E* and *Z* isomers **2a** and **2b**.[3] However, dehydration of the lower melting diastereomer **1b** led largely



**5**, R = H
**8**, R = OH

to decomposition to 2-benzylpyridine (**6**) and 3-chloroacetophenone (**7**).

In the present investigation it was found that **1b**, produced in amounts equivalent to that of **1a** in its synthesis, but which was less hypocholesteremic, could be used as a source for **2a** and **2b** or **5** in a modified procedure. Dehydration of **1b** to the *E* and *Z* mixture **2a,b** was accomplished in 65% yield by limiting the temperature to 75–80 °C for 72 h to give primarily **5** and then heating at 110 °C to obtain the isomerized products **2a** and **2b**. Similarly, dehydration of **3b** gave a 91% yield of (*E*)- and (*Z*)-hydroxyphenyl compounds **4a** and **4b**. The terminal olefin compounds **5** and **8** could be isolated if the respective dehydration reactions were limited to 75–80 °C.

The presence of two singlets in the NMR for methyl groups at $\delta$ 2.19 and 2.23 ($CDCl_3$) for the mixture of compounds **2a,b** and at $\delta$ 2.08 and 2.20 ($Me_2SO$-$d_6$) for the mixture of compounds **4a,b** was the initial indication of the presence of *E* and *Z* mixtures. Both mixtures could be separated by TLC on 15% $AgNO_3$ impregnated silica gel with ethyl acetate–acetic acid as developing solvent. Preparative separation was by column chromatography with 20% $AgNO_3$ on silica gel and with ethyl acetate–acetic acid (9:1) as eluting solvent. The *E* and *Z* isomers of **4** could also be conveniently separated by trituration of the mixture in acetone at room temperature, as **4b** was the more soluble isomer.

The assignment of *E* and *Z* stereochemistry was on the basis of NMR comparisons to triprolidine hydrochloride (**9**) for which the effective antihistamine has been established as the *E* isomer while the less active isomer (**10**) is its *Z* isomer.[4] Of interest was a comparison of the NMR chemical shifts for the methylene and vinyl protons for compounds **9** and **10**. For triprolidine hydrochloride (**9**), which has the 2-pyridyl system (and thus the unshared pair

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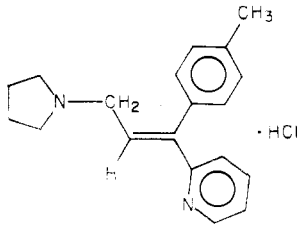
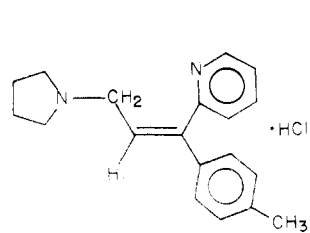


9



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of electrons for the pyridine nitrogen) trans to the methylene group but cis to the vinyl proton, the methylene protons have a chemical shift ($CDCl_3$) of $\delta$ 3.80 (d, $J$ = 7.5 Hz), while the vinyl proton is deshielded into the aromatic region. The $Z$ isomer **10**, on the other hand, with the pyridyl group cis to the methylene group and trans to the vinyl proton, now has a chemical shift for the methylene protons of $\delta$ 3.96 (d, $J$ = 7.5 Hz) and the vinyl proton with a chemical shift of $\delta$ 6.40 (t, $J$ = 7.5 Hz). There is clearly an anisotropic deshielding effect caused by the pyridine nitrogen. Comparable results have been reported by Ison and Casy.[5]

A similar effect is observed for the alkenylpyridines **2a,b** and **4a,b**, and thus the stereochemistry about the double bonds was assigned in an analogous manner. The chemical shift for the methyl group of **2a** is $\delta$ 2.23 and of **2b** $\delta$ 2.19. Therefore, **2a** was assigned the $E$ stereochemistry while **2b** was assigned the $Z$ stereochemistry. For the hydroxy derivatives **4a,b** the chemical shift differences were even more dramatic: $\delta$ 2.20 (**4a**) and $\delta$ 2.08 (**4b**) and thus **4a** analogously was designated as the $E$ isomer and **4b** the $Z$ isomer.

**Metabolic Studies.** The previous study[2] utilized TLC separation and comparison as well as isotope dilution techniques for the identification of **3a** and 2-(4-hydroxybenzyl)pyridine (**11**) as metabolites of $^3$H-labeled **1a**[6] in rats. The TLC systems developed for that study do not adaquately separate **2a** and **2b** from **1a** or **4a** and **4b** from **3**. Therefore, a HPLC system with a C-18 reverse-phase column eluted with methanol–water (65:35) was developed to identify these compounds in the present metabolism studies. Metabolite samples were injected with these reference samples for a comparison of radioactivity to UV absorption. Results of these HPLC studies are shown in Table I. Except where designated it was not possible to identify **11** and **3a** in the large (generally ±95% of the total radioactivity) quantity of polar metabolites and these are thus included with the polar metabolites.

Neither metabolite **2a** nor **2b** was present at the limits of observation (0.1–1.0% of the total radioactivity) in the pentane extracts of serum, urine, or urine and feces. The hydroxylated counterparts **4a,b** were present in small amounts in the unhydrolyzed fractions and analysis of the 72-h serum fraction after hydrolysis showed little increase in these compounds. The serum levels for compounds **4a** and **4b** were estimated to be less than 0.01% of the original dose. The presence of these compounds in urine and feces samples examined was found to represent less than 1% of the original dose.

**Biological Evaluations.** The unsaturated compounds **2a,b** and **4a,b** together with their intermediates **5** and **8** were tested for hypocholesteremic effects. Serum cholesterol values were measured by the method of Block et al.[7] after administration of the compounds to male rats as previously described for compound **1a**.[2] Compounds were administered starting at 1 p.m. and sera were obtained 24 h after the final dose. The results of these tests are summarized in Table II (with compound **1a** included for comparison purposes). Those compounds, showing statistically significant differences in cholesterol levels compared to control animals, were also tested for estrogenicity by a modification of an estrogen assay described by Dorfman and Dorfman.[8] These results are also included in Table II.

Table I. Metabolism of 1-(3-Chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)ethanol in Rats as Determined by $^3$H Eluents of C-18 Reverse-Phase HPLC[a]

| Fraction | 1a | 4a | 4b | 6 | Polar |
|---|---|---|---|---|---|
| Serum: 2 h[b] | 22.0 | | | 4.7 | 71.0 |
| 10 h | 0.9 | 0.9 | 0.3 | 2.4 | 95.0 |
| 72 h | 1.2 | 1.1 | 0.2 | 2.2 | 95.0 |
| 72 h hydrolyzed | 1.2 | 0.4 | 0.3 | 1.2 | 96.7 |
| Urine: Pentane extract | 1.6 | 2.1 | 1.0 | 8.6 | 86.8[c] |
| Fraction III[d] | <0.1 | 3.3 | 0.4 | 0.2 | 96.1 |
| Fraction V[d] | | | | | 100 |
| Feces: Pentane extract | | 7.2 | 3.2 | 69.0 | 9.1[e] |

[a] Percent of the total recovered HPLC radioactivity. [b] Time of serum sample after administration of compound 1a. [c] 81% 11 and 5.8% 3a. [d] Fractions from Sephedex G-10 chromatography of urine. [e] All radioactivity cochromatographed with compound 11.

Compounds **2a,b** and **4a,b** exhibited a significant hypocholesteremic effect in rats. However, they did not appear to add appreciably to the in vivo hypocholesteremic effect of the original compound **1a** since they were absent or only present in low metabolic levels in rat serum and urine specimens. Compounds **4a** and **4b** are of particular interest because of their relatively low estrogenicity.

## Experimental Section

Melting points were determined with a Mel-Temp apparatus and were uncorrected. NMR spectra were determined on a Varian A-60A spectrophotometer with $CDCl_3$ or $Me_2SO$-$d_6$ as solvents and $Me_4Si$ as internal standard; IR spectra were recorded on a Perkin-Elmer Model 281 spectrophotometer as KBr pellets; UV spectra in methanol were recorded on a Beckman DK-2A spectrophotometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. Column chromatography utilized 20% $AgNO_3$ impregnated silica gel (Applied Science Laboratories, Inc., Hi-Flostil-Ag, 60–200 mesh) with support to charge ratios of 200:1, with ethyl acetate–acetic acid (9:1) as eluting solvents. The following TLC system was used: Analtech Uniplate 15% $AgNO_3$ impregnated silica-gel plates (250 $\mu$, 20 × 20 cm), ethyl acetate–acetic acid (9:1).

**2-[2-(3-Chlorophenyl)-1-phenyl-2-propenyl]pyridine (5).** A solution of **1b** (3.24 g, 0.01 mol) in 85% $H_3PO_4$ (10 mL) was stirred at 75–80 °C for 72 h. The progress of the reaction was followed by removing a drop of solution, adding it to 10% $NH_4OH$ (1.0 mL), and extracting with ether (1.0 mL) and the TLC was developed. Upon completion of the reaction, the acid solution was cooled and poured into 10% ice-cold $NH_4OH$ (250 mL) with stirring (final pH 8.0). The precipitate was filtered and dissolved in ether; the ether solution was dried ($K_2CO_3$) and evaporated. The resulting oil was crystallized from pentane to give **5** (2.0 g, 65%) containing **2** as an impurity (18% from NMR), mp 70–80 °C. Recrystallization with petroleum ether gave **5** (1.0 g, 32%): mp 84–86 °C (lit.[3] 90.5–92.0 °C); $R_f$ 0.40.

**(*E*)- and (*Z*)-2-[2-(3-Chlorophenyl)-1-phenyl-1-propenyl]pyridine (2a,b).** A solution of **1b** (1.16 g, 0.005 mol) in 85% $H_3PO_4$ (10 mL) was heated at 75–80 °C with stirring for 48 h and then at 110 °C for additional 48 h. The mixture was cooled and poured into ice-cold 10% $NH_4OH$ (250 mL), and the precipitate was collected on a filter, washed, and dried to yield **2** (0.93 g, 62%), mp 109–110 °C (lit.[3] 107–108 °C).

**Separation of (*E*)-2-[2-(3-Chlorophenyl)-1-phenyl-1-propenyl]pyridine (2a) and (*Z*)-2-[2-(3-Chlorophenyl)-1-phenyl-1-propenyl]pyridine (2b).** The $E$ and $Z$ mixture (**2a,b**) (1.5 g, 0.0049 mol) was chromatographed on a column of 20% $AgNO_3$ impregnated silica gel using ethyl acetate–acetic acid (9:1) as the eluting solvent. The first fraction contained **2a**. The solvent was removed under reduced pressure at ≤40 °C to leave a residue

Table II. Hypocholesteremic and Estrogenic Activity of Metabolites of 1-(3-Chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)ethanol in Rats

| | Hypocholesteremic[a] | | | | |
|---|---|---|---|---|---|
| Compd | Serum cholesterol,[b] mg/100 mL | No. of animals | Depression, % | $p$[c] | Estrogenicity[d] |
| Control | 77.1 ± 10.5 | 6 | | | 0.01 ± 0.02 |
| 1a | 36.0 ± 5.9[e] | 8 | 49.5 | <0.001 | 0.49 ± 0.05 |
| 2a | 49.3 ± 11.9 | 6 | 36.1 | <0.001 | 0.22 ± 0.04 |
| 2b | 28.7 ± 13.0 | 6 | 62.8 | <0.001 | 0.92 ± 0.12 |
| 3a | 41.0 ± 5.6[e] | 8 | 43.5 | <0.001 | 0.92 ± 0.07 |
| 4a | 47.7 ± 6.5 | 6 | 38.1 | <0.001 | 0.03 ± 0.03 |
| 4b | 53.6 ± 8.5 | 6 | 30.5 | <0.001 | 0.02 ± 0.02 |
| 5 | 69.3 ± 15.0 | 3 | 10.1 | NS | |
| 8 | 74.0 ± 15.1 | 3 | 4.0 | NS | |

[a] Dose, 25 mg/kg in 200-g rat for 7 days. [b] See ref 2 for method of determination. Recorded as the mean ± standard deviation. [c] Student's $t$ test (two-tailed test). [d] The number of micrograms of 17$\beta$-estradiol given sc that produces an estrogenic response equivalent to that produced by 25 mg of the test compound. Seven animals were used for each compound. Components **5** and **8**, without significant hypochloestermic effect, were not tested for estrogenicity. [e] Data reported from an earlier study. See ref 8.

of a few milliliters and the acetic acid was neutralized with ice-cold saturated $NaHCO_3$ solution (100 mL); the mixture stirred at 10 °C overnight, and the precipitate was removed by filtration and recrystallized from ether–petroleum ether to yield **2a** (0.41 g, 27%): mp 125–126 °C; TLC $R_f$ 0.43; NMR ($CDCl_3$) $\delta$ 2.23 (s, $CH_3$), 7.00–8.00 (m, ArH), 8.50–8.70 (m, ArH); IR (KBr) 1595, 1585, 1565, 1475, 1430, 1380, 1315, 785, 705, 700 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ ($\epsilon$) 263 nm (7540). Anal. ($C_{20}H_{16}ClN \cdot 0.5H_2O$) C, H, N.

The second fraction contained a small amount of a mixture of **2a** and **2b** and was not pursued further. The third fraction was worked up in the same manner as the first fraction and recrystallized from ether–petroleum ether to yield **2b** (0.42 g, 28%): mp 110–111 °C; TLC $R_f$ 0.27; NMR ($CDCl_3$) $\delta$ 2.19 (s, $CH_3$), 7.15–8.00 (m, ArH), 8.87–9.05 (m, ArH); IR (KBr) 1590, 1585, 1565, 1465, 1430, 700, 800, 790, 770, 750 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ ($\epsilon$) 270 nm (5660). Anal. ($C_{20}H_{16}ClN \cdot 0.5H_2O$) C, H, N.

**2-[2-(3-Chlorophenyl)-1-(4-hydroxyphenyl)-2-propenyl]pyridine (8).** A solution of **3b** (1.7 g, 0.005 mol) in 85% $H_3PO_4$ (5 mL) was heated at 75–80 °C with stirring for 48 h, cooled, and poured into ice-cold 10% $NH_4OH$ solution (150 mL, final pH 8.0). The white precipitate was filtered, washed, and dried to yield **8** (1.5 g), contaminated with 27% of **4** (based upon NMR). Recrystallization from ethanol gave **8** (0.7 g, 43%): mp 154–157 °C; TLC $R_f$ 0.3; NMR ($Me_2SO$-$d_6$) $\delta$ 4.88 (br s, CH), 5.57 (br s, $CH_2$), 6.70–8.20 (m, ArH), 8.65–8.75 (m, ArH). Anal. ($C_{20}H_{16}ClNO$) H, N; C: calcd, 74.64; found, 74.16.

**(*E*)- and (*Z*)-2-[2-(3-Chlorophenyl)-1-(4-hydroxyphenyl)-1-propenyl]pyridine (4a,b).** A solution of **8** (0.64 g, 0.002 mol) in 85% $H_3PO_4$ (5 mL) was heated at 110 °C with stirring for 48 h. Workup with 10% $NH_4OH$ gave a mixture of **4a** and **4b** (0.44 g, 69%), mp 160–165 °C.

In another experiment, heating a solution of **3b** (1.0 g, 0.0029 mol) at 75–80 °C with stirring for 48 h and then 110 °C for 72 h and working up with 10% $NH_4OH$ gave a mixture of **4a** and **4b** (0.86 g, 91%), mp 160–165 °C.

**Separation of (*E*)-2-[2-(3-Chlorophenyl)-1-(4-hydroxyphenyl)-1-propenyl]pyridine (4a) and (*Z*)-2-[2-(3-Chlorophenyl)-1-(4-hydroxyphenyl)-1-propenyl]pyridine (4b).** The *E* and *Z* mixture of **4a** and **4b** (0.50 g, 0.0016 mol) was dissolved in acetone (100 mL), silica gel (10 g) was added, and solvent was removed in vacuo at 25 °C. The silica gel was placed on top of a column of 20% $AgNO_3$ impregnated silica gel (100 g) and eluted with ethyl acetate–acetic acid (9:1). The fractions were worked up as for **2a,b**. The first fraction was recrystallized with acetone to give **4a** (0.08 g, 16%): mp 238–239 °C; TLC $R_f$ 0.39; NMR ($Me_2SO$-$d_6$) $\delta$ 2.20 (s, $CH_3$), 6.80–7.90 (m, ArH), 8.55–8.70 (m, ArH), OH not discernible; UV (MeOH) $\lambda_{max}$ ($\epsilon$) 243 nm (15 700), 270 (13 300). Anal. ($C_{20}H_{16}NClO$) C, H, N.

The second fraction contained a mixture of **4a** and **4b**. Recrystallization from acetone gave additional **4a** (0.032 g, 6.4%) mp 239–240 °C. The filtrate was evaporated and the residue was recrystallized with acetone–water to give **4b** (0.18 g, 36%): mp 120–125 °C (remelts at 228–230 °C); TLC $R_f$ 0.22; NMR ($Me_2SO$-$d_6$) $\delta$ 2.08 (s, $CH_3$), 6.55–8.20 (m, ArH), 8.80–8.95 (m, ArH); UV (MeOH) $\lambda_{max}$ ($\epsilon$) 240 nm (17 100), 277 (10 400). Anal. ($C_{20}H_{16}ClNO$) C, H, N.

The third fraction, rich in **4b**, was recrystallized from acetone–water (0.042 g, 8.4%): mp 123–125 °C.

Alternatively, 0.5 g of a mixture of **4a** and **4b** was recrystallized from acetone–water (5 mL) at 25 °C, filtered, again triturated with acetone, filtered, and recrystallized from acetone to give **4a** (0.21 g, 42%), mp 234–236 °C.

The filtrates from above were evaporated in vacuo and the residue was resuspended in acetone (5 mL) and removed by filtration. A second extraction with acetone and recrystallization of the resulting residue from acetone–water gave **4b** (0.16 g, 32%), mp 123–125 °C.

**Metabolite Identification.** Three male Sprague–Dawley rats (400 ± 10 g) were housed in separate 20 × 11.5 cm stainless steel metabolic cages with Mouse/Rat Diet (Teklad, Inc.) and water supplied ad libitum. Rats were intraperitoneally administered 1 mL of an aqueous Tween 80 (0.26%) suspension of compound **1a** containing tritium uniformly disributed in the 2-phenyl ring[6] (25 mg/kg, 1.94 mCi). Urine and feces were collected for 72 h for one rat. Feces were air-dried, powdered, and extracted for 48 h with *n*-pentane in a Soxhlet extractor. The pentane was evaporated, and the residue was dissolved in methanol (1 mL) for HPLC determination.

The urine was frozen as collected and lyophilized to remove $^3H_2O$; the residue was dissolved in 0.2 M $NH_4OAc$ solution (40 mL) and placed on a Pharmacia Sephadex column (2.5 × 50 cm) containing 70 g of Sephadex G-10 in 0.2 M $NH_4OAc$ solution.[9] The sample was eluted with 0.2 M $NH_4OAc$ and aliquots of the eluent were assayed for radioactivity and corrected for quenching. The first 100 mL (fraction I) contained no radioactivity; the second 100 mL, fraction II, contained some radioactivity, but on the basis of reducing an aliquot to dryness was found to be contaminated with urine constituents. A third 150 mL, fraction III, contained radioactivity without appreciable urine-constituents contamination. Elution with 0.2 M $NH_4OAc$ (500 mL, fraction IV) contained no radioactive material. Elution with water (200 mL, fraction V) produced another fraction containing radioactive material. The third and fifth fractions were individually lyophilized to remove water and $NH_4OAc$ and the residues were dissolved in methanol (1.0 mL) for HPLC determinations.

Blood was obtained by closed chest cardiac puncture from three rats at 72, 10, or 2 h with the serum separated by centrifugation (1700g for 30 min). Part of the 72-h serum was hydrolyzed for 48 h with aryl sulfatase and glucuronidase as described previously.[2] The hydrolyzed and nonhydrolyzed fraction was deproteinized with methanol, the methanol evaporated under a $N_2$ stream, and the residue subjected to HPLC determination.

**High-Pressure Liquid Chromatography.** HPLC was performed on an assembled apparatus consisting of a Milton Roy Minipump Model 396-89, a Precision Science Valveseal septumless injector, a 250 × 2.3 mm Varian Aerograph Micro Pak-CH reverse phase column preceded by a 100 × 2.13 mm i.d. precolumn packed with Vydak C-18 reverse phase, and a Varian Aerograph UV

detector equipped with a 5 ft × 0.01 mm i.d. back pressure coil (total volume 0.033 $cm^3$). The solvents used were Burdick and Jackson methanol and glass-distilled water in a ratio of 65:35. Pressures used varied from 1000 to 2500 lb with flow rates (18–50 mL/h) maintained constant in a given determination. Fractions (30 s each) were collected directly into glass liquid scintillation vials and counted with a Beckman Model LS 200 spectrometer employing 15 mL of a fluid containing 8 g of PPO and 0.4 g of POPOP in 1 L of toluene and 100 mL of Scintisol GP. Injected samples (20.0 μL) contained a 1.0-L solution with $5.0 \times 10^{-6}$ g each of **1a**, **2a,b**, **3a**, **4a,b**, **5**, and 11 in order to compare retention times of standards and $^3H$ metabolites. Results of the HPLC determinations are given in Table I.

**Estrogenicity.** The following modification of the estrogen assay described by Dorfman and Dorfman[8] was employed. Twenty-one-day-old female Sprague–Dawley rats of approximately 35 g were ovariectomized. After 7 days and for 7 consecutive days these rats were administered aqueous suspensions of compounds **1a**, **2a,b**, **3a**, and **4a,b** (25 mg/kg) by oral intubation. On day 8 uteri were removed and freed of surrounding tissue. The uteri were weighed after pressing out the intrauterine fluid on blotting paper and results were expressed as weight of the uterus in milligrams per gram of body weight times 100. Additional rates were treated in a similar manner following subcutaneous injection of 17β-estradiol in peanut oil for preparation of a standard curve.

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# 5-O-Alkylated Derivatives of 5-Hydroxy-2′-deoxyuridine as Potential Antiviral Agents. Anti-Herpes Activity of 5-Propynyloxy-2′-deoxyuridine

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Alkylation of 5-hydroxyuridine or 5-hydroxy-2′-deoxyuridine with various activated alkylating agents in the presence of 1 equiv of NaOH gave a series of new nucleoside analogues which were evaluated for antiviral activity against vaccinia virus, herpes simplex-1 virus, and vesicular stomatitis virus in both primary rabbit kidney cells and human skin fibroblasts. One of these analogues, 5-propynyloxy-2′-deoxyuridine, was a potent inhibitor of herpes simplex virus. Structure–activity considerations suggest that the anti-herpes activity is dependent on the integrity of the acetylene group since substitution of phenyl, *p*-nitrophenyl, vinyl, carboxamido, or carboxyl for the triple bond led to diminished antiviral activity.

Certain 5-substituted pyrimidine deoxyribonucleosides show potent in vitro and/or in vivo antiviral properties. Among the 5-substituents that endow 2′-deoxyuridine with in vitro antiviral activity are iodo, bromo, chloro, fluoro,[2] trifluoromethyl,[3] ethyl,[4] methoxymethyl,[5] methylthio,[6] methylamino,[7] cyano,[8] nitro,[9] thiocyano,[10,11] vinyl,[12] propyl,[12] and allyl.[12] These substituents vary considerably in steric bulk and electronic properties, rendering it difficult to dissociate one effect from the other when attempting to ascertain structure–activity trends that might be used to design other effective nucleoside antivirals. In this study, we have sought to examine the relationship between antiviral activity and the steric bulk and configuration of the 5-substituent. 5-O-Alkylated derivatives of 2′-deoxyuridine provided a useful approach to this problem, since a number of different substitutents could be introduced at the 5 position with relative ease.

**Chemistry.** The synthetic approach used herein is based on the observations of Otter et al.[13,14] in their approach to 6-substituted pyrimidine nucleosides. They found that 5-hydroxyuridine may, in the presence of base, be selectively 5-O-alkylated by activated alkylating agents. Indeed, compounds **2** and **4** reported here are but 2′-deoxyribonucleoside analogues of the 5-propenyloxy- and 5-propynyloxyuridines reported in their study. Thus, when either 5-hydroxyuridine or 5-hydroxy-2′-deoxyuridine was treated with 1 equiv of NaOH (to form the monoanion of the 5-hydroxyl function) and then reacted with 1.5–2.0 equiv of a properly substituted activated alkyl halide, the corresponding 5-O-alkylated nucleoside was formed in an isolable yield of 40–60%. All products were negative to $FeCl_3$ which gives a blue color with 5-hydroxyuridine or its deoxyribonucleoside analogue. The structures presented in Table I and Chart I were supported by elemental analysis, molecular weight (by chemical ionization mass spectrometry), and $^1H$ NMR.

**Evaluation of Antiviral Activity.** Antiviral activity was determined as inhibition of cytopathogenicity induced by three different viruses [herpes simplex-1 (KOS strain), vaccinia, and human skin fibroblasts (VGS strain)]. The

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