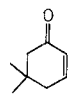
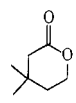
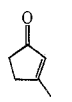
Table I
Lactones from α,β-Unsaturated Ketones

α,β-Unsaturated ketone	Lactone (yield, %)
 11	 16 (58)[a]
 12	 17 (47)[a]
 13	 18 (42)[a,b]
 14	 19 (<25)[c]
 15	 20 (<10)[d]

[a] Distilled yield. [b] Approximately a 1:1 mixture of cis and trans isomers as determined by ^{1}H NMR. [c] Determined by spectral and elemental analyses and GLC. [d] Determined by spectral analysis and comparison with a known sample.

(244 mg, 6.5 mmol) was carefully added. The solution was stirred at 0° for 1 hr, sodium borohydride (244 mg) was again added, the solution was stirred at 0° for an additional 1 hr, and a final batch of sodium borohydride (244 mg) was added. The solution was then stirred at room temperature overnight. The methanol was evaporated off, 20 ml of 10% aqueous HCl was added, and the crude product was isolated by routine ether extraction. Column chromatography [40 g Silicar CC-7, 200–325 mesh, ether–hexanes (1:9)] afforded 490 mg (45%) of lactone **6**: ^{1}H NMR ($CDCl_3$) δ 4.34 (AB q, 2, J = 12 Hz, fine splitting for A and B, $\Delta\nu_{AB}$ = 26.1 Hz), 2.37 (AB q, 2, J = 18 Hz, $\Delta\nu_{AB}$ = 34.9 Hz), 1.0–2.0 (m, 9), 1.17 (s, 3); ir (film) 1742, 1227, 1196, 1092 cm^{-1}; calcd m/e 168.1150 (M^+), found 168.1187 ($C_{10}H_{16}O_2$).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.18; H, 9.73.

Synthesis of 8aα-Octahydro-4aα-methyl-4-methylene-3*H*-2-benzopyran-3-one (4). Lactone **6** (200 mg, 1.19 mmol) was α-methylenated by Grieco's α-hydroxymethylation procedure,[5] yielding 122 mg (57%) of the desired α-methylene lactone (**4**): ^{1}H NMR ($CDCl_3$) δ 6.70 (d, 1, J = 1 Hz), 5.70 (d, 1, J = 1 Hz), 4.37 (AB q, 2, J = 11 Hz, fine splitting for A and B, $\Delta\nu_{AB}$ = 32.2 Hz), 1.3–2.1 (m, 9), 1.30 (s, 3); ir (film) 1727, 1618, 1186, 810 cm^{-1}; calcd m/e 180.1150 (M^+), found 180.1147 ($C_{11}H_{16}O_2$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found C, 73.08; H, 9.02.

General Procedure for the Preparation of δ-Lactones from Cyclohexenones. A solution of 16.1 mmol of enone in 25 ml of methanol was ozonized at −60° until 1.1 equiv of ozone had been added. After nitrogen flushing, 3 × 600 mg (16 mmol) of sodium borohydride was carefully added over 1-hr intervals at 0°, and the mixture was then stirred at room temperature overnight. The methanol was evaporated off, 40 ml of 10% aqueous HCl was added, and the product was isolated by routine ether extraction (three times). The following compounds were prepared in this manner.

5-Hydroxy-3,3-dimethylpentanoic acid δ-lactone (16) was obtained in 58% yield by bulb-to-bulb distillation [oven temperature 85–95° (0.3 mm)]: ^{1}H NMR ($CDCl_3$) δ 4.40 (t, 2, J = 6 Hz), 2.33 (s, 2), 1.72 (t, 2, J = 6 Hz), 1.13 (s, 6); ir ($CHCl_3$) 1739, 1250, 1078 cm^{-1}; m/e 128 (M^+).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.33; H, 9.50.

5-Hydroxy-3,3-dimethylhexanoic acid δ-lactone (17) was obtained in 47% yield after bulb-to-bulb distillation [oven temperature 85–95° (0.5 mm)]: ^{1}H NMR ($CDCl_3$) δ 4.50 (m, 1), 2.27 (m, 2), 1.6 (m, 2), 1.37 (d, 3, J = 6 Hz), 1.10 (s, 3), 1.07 (s, 3); ir (film) 1736, 1235, 1042, 805 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.42; H, 9.76.

5-Hydroxy-3-methylhexanoic acid δ-lactone (18) was obtained in 42% yield after bulb-to-bulb distillation [oven temperature 85–95° (0.5 mm)]: ^{1}H NMR ($CDCl_3$) δ 4.47 (m, 1), 1.40–2.80 (m, 5), 1.40 (d, 3, J = 6 Hz), 1.07 (m, 3); ir (film) 1736, 1244, 1092 cm^{-1}.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.27; H, 9.17.

5-Hydroxy-3-methylpentanoic acid δ-lactone (19) was obtained in less than 25% overall yield, as determined by ^{1}H NMR and GLC (crude recovery was only 50%): ^{1}H NMR ($CDCl_3$) δ 4.33 (m, 2), 1.2–3.0 (m, 5), 1.08 (d, 3, J = 6 Hz); ir (film) 1733, 1227, 1092 cm^{-1}; m/e 114 (M^+).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.21; H, 8.84.

4-Hydroxypentanoic acid γ-lactone (20) was obtained in less than 10% overall yield, as determined by ^{1}H NMR and GLC (crude recovery was 36%). ^{1}H NMR and ir revealed absorptions identical with those for commercially available γ-valerolactone (Aldrich); m/e 100 (M^+), 85 ($M^+ - CH_3$).

Acknowledgment. We gratefully acknowledge the National Institutes of Health (CA 12617) for financial support.

Registry No.—**4**, 56247-19-9; **5**, 32980-06-6; **6**, 56247-20-2; **11**, 4694-17-1; **12**, 78-59-1; **13**, 1123-09-7; **14**, 7214-50-8; **15**, 2758-18-1; **16**, 22791-80-6; **17**, 10603-06-2; *cis*-**18**, 24405-13-8; *trans*-**18**, 24405-14-9; **19**, 1121-84-2; **20**, 108-29-2.

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(2) (a) P. A. Grieco and K. Hiroi, *Tetrahedron Lett.*, 1831 (1973); (b) R. D. Clark and C. H. Heathcock, *ibid.*, 1713 (1974); (c) S. Danishevsky, 9th International Symposium on the Chemistry of Natural Products, Ottawa, Canada, June 24–28, 1974, Abstract 29G; (d) J. A. Marshall and D. E. Seitz, *Synth. Commun.*, **4**, 395 (1974); *J. Org. Chem.*, **40**, 534 (1975); (e) P. A. Grieco, J. J. Reap, and J. A. Noquez, *Synth. Commun.*, **5**, 155 (1975); (f) R. D. Clark and C. H. Heathcock, submitted for publication.
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(6) R. Pappo and C. J. Jung, *Tetrahedron Lett.*, 365 (1962).
(7) Although Pappo's oxidation is a variation of the classical Lemieux–Johnson hydroxylation method,[8] almost 10 mol % of OsO_4 is employed, presumably because enones react slowly toward this reagent. Even with such a large amount of catalyst, the hydroxylations are slow, typically requiring 15 days for completion. An alternative procedure, in which **7** is converted directly to **9** by using a mixture of OsO_4, $Pb(OAc)_4$, and 90% aqueous acetic acid, is more rapid, but still employs 10 mol % of OsO_4.
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A Facile Synthesis of 1-β-D-Arabinofuranosyl-2-seleno- and -4-selenouracil and Related Compounds

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2-Thiouridine and 4-thiouridine have been characterized as minor nucleoside components of transfer ribonucleic acid (t-RNA).[1,2] Later several thiopyrimidine nucleosides have been isolated or prepared by multistep syntheses.[3–12] Recently, a facile method was reported by Ueda et al.[13] for the synthesis of 4-thiopyrimidine or 6-thiopurine nucleosides. The seleno analogs, 4-selenouridine and 2-selenouridine, were also synthesized through a coupling method.[14] We have described in recent articles a one-step synthesis of

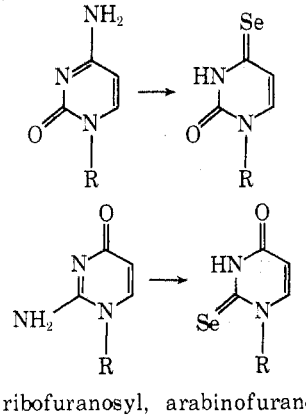
Table I
NMR Data of Some Seleno- and Thiopyrimidines and Pyrimidine Nucleosides

Compd	Registry no.	Chemical shift, ppm (coupling constants, Hz) H-6	H-5	H-1'	Solvent
1-β-D-Arabinofuranosyl-4-selenouracil (I)	56114-31-9	7.69 (7)	6.62 (7)	5.95 (4)	Me_2SO-d_6
1-β-D-Arabinofuranosyl-2-selenouracil (II)	56114-32-0	7.78 (7)	6.08 (7)	6.88 (4)	Me_2SO-d_6
4-Selenouracil (III)	56114-33-1	7.41 (7)	6.49 (7)		Me_2SO-d_6
2-Selenouracil (IV)	16724-03-1	7.35 (7)	5.95 (7)		Me_2SO-d_6
4-Selenouridine (V)	40555-30-4	7.93 (7)	6.63 (7)	5.72 (4)	Me_2SO-d_6
2-Selenouridine (VI)	40555-29-1	8.18 (7)	6.17 (7)	6.72 (4)	Me_2SO-d_6
4-Seleno-2'-deoxyuridine (VII)	56114-34-2	7.87 (7)	6.58 (7)	6.02 (6)	Me_2SO-d_6
4-Thio-2'-deoxyuridine (VIII)	5580-20-1	7.78 (7)	6.33 (7)	6.13 (6)	Me_2SO-d_6
4-Thiouridine	13957-31-8	7.85 (7)	6.33 (7)	5.80 (4)	Me_2SO-d_6
		7.85 (7)	6.63 (7)	5.97 (4)	D_2O
1-β-D-Arabinofuranosyl-4-thiouracil	32754-06-6	7.58 (7)	6.29 (7)	5.99 (4)	Me_2SO-d_6
		7.83 (7)	6.68 (7)	6.27 (4)	D_2O
4-Thiouracil[a]	591-28-6	7.33 (7)	6.18 (7)		Me_2SO-d_6
2'-Deoxycytidine	951-77-9	7.80 (7)	5.75 (7)	6.18 (6)	Me_2SO-d_6
Cytidine	65-46-3	8.17[b]	6.03[b]	6.03[b]	Me_2SO-d_6
		7.90 (7)	6.13 (7)	6.00 (4)	D_2O
1-β-D-Arabinofuranosylcytosine	147-94-4	7.68[c]	5.80[c]	6.03[c]	Me_2SO-d_6
		8.10 (7)	6.28 (7)	6.23 (4)	D_2O
Cytosine	71-30-7	7.72 (7)	5.93 (7)		D_2O-NaOD
Cytidine 5'-monophosphate-Na_2	6757-06-8	8.16 (7)	6.21 (7)	6.10 (4)	D_2O

[a] The compound was synthesized by the method of Y. Mizuno, M. Ikehara, and K. A. Watanake, *Chem. Pharm. Bull.*, 10, 647 (1962). [b] L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry", Vol. 2, W. Zorbach and R. S. Tipson, Ed., Wiley-Interscience, New York, N.Y., 1973, p 310. [c] Footnote *b*, p 312.

several 6-substituted selenopurine nucleosides and cyclic nucleotides.[15,16] In this paper we describe the application of this new synthetic method to the synthesis of selenopyrimidine and related compounds.

Treatment of 1-β-D-arabinofuranosylcytosine with excess of H_2Se in pyridine–ethylene glycol monomethyl ether at room temperature overnight afforded 1-β-D-arabinofuranosyl-4-selenouracil (I) in 20% yield. In a similar manner, treatment of 1-β-D-arabinofuranosylisocytosine[17,18] with excess of H_2Se in pyridine–DMF at room temperature for 4 days afforded 1-β-D-arabinofuranosyl-2-selenouracil (II) in 26% yield. Cytosine reacted with H_2Se to give 4-selenouracil (III) as expected. Isocytosine, however, was inert to H_2Se in DMF–pyridine, but reacted with H_2Se in pyridine–H_2O to give 2-selenouracil (IV).[19]



R = ribofuranosyl, arabinofuranosyl, 2'-deoxyribofuranosyl, or H

A mechanism of this reaction was proposed[15] and can be correlated to the method of preparation of seleno esters by the selenohydrolysis of imino esters.[20-23]

The advantages of this synthetic procedure are that it can prevent side reactions and the yields are higher than those of the conventional method.

Structures of these selenopyrimidine nucleosides were verified by elemental analysis, uv, and NMR data. The C-6 protons of selenouridines[14] were deshielded as compared with those of arabinofuranosylselenouracils. In order to generalize this effect, 4-selenouridine (V),[14] 2-selenouridine (VI),[14] 4-seleno-2'-deoxyuridine (VII), 4-thio-2'-deoxyuridine (VIII),[24] 1-β-D-arabinofuranosyl-4-thiouracil,[25] and 4-thiouridine[3,13,26] were synthesized. Treatment of cytidine with excess of H_2Se in pyridine–DMF at room temperature for 3 days gave 4-selenouridine (V) in 42% yield. Isocytidine[27] and 2'-deoxycytidine reacted with H_2Se to give 2-selenouridine (VI) and 4-seleno-2'-deoxyuridine (VII), respectively. 4-Thio-2'-deoxyuridine (VIII), 1-β-D-arabinofuranosyl-4-thiouracil, and 4-thiouridine were synthesized from the known method.[13,25] NMR data of these thio- and selenopyrimidines are listed in Table I.

The C-6 protons of the pyrimidine nucleosides are deshielded as compared with those of the corresponding arabinosyl derivatives in Me_2SO solution. Table I also indicates that the C-6 protons of arabinosyl derivatives experience a downfield shift in D_2O solution while there is almost no change for the corresponding nucleosides. This suggests that the arabinosyl derivatives of pyrimidine nucleosides exist in different conformations in Me_2SO and D_2O while pyrimidine nucleosides exist only in one conformation.

In order to determine the conformation of these pyrimidine nucleosides and the arabinosyl derivatives in both Me_2SO and D_2O, it was of interest to compare the chemical shifts of the C-6 protons of these pyrimidine nucleosides with those of known conformation. 4-Thiouridine and 4-thiouridine 5'-phosphate are known to exist in the anti con-

formation in solution.[28,29] Table I reveals that the chemical shift of the C-6 proton of 4-thiouridine in D_2O and Me_2SO is the same while it varies for 1-β-D-arabinofuranosyl-4-thiouracil. It also indicates that the chemical shifts of the C-6 protons for 4-thiouridine and the corresponding arabinosyl derivative are the same in D_2O solution. Thus, 1-β-D-arabinofuranosyl-4-thiouracil, like 4-thiouridine, exists mostly in the anti conformation in D_2O solution, while it probably exists in the syn conformation in Me_2SO. The reason for this conformational change is not clear. It is probably due to the presence of intramolecular hydrogen bonding between the 2′-OH group and the 2-keto (thio or seleno) group of pyrimidine nucleosides containing the 1-β-D-arabinofuranosyl moiety in Me_2SO. This possibility is supported by the NMR data of 4-thio-2′-deoxyuridine and 4-seleno-2′-deoxyuridine. These deoxyuridines, because of the absent of intramolecular hydrogen bonding between 2′-H and the 2-keto group, exist like 4-thiouridine, only in the anti conformation.

The deshielding of the C-6 proton in these pyrimidine nucleosides is probably due to the interaction of the 5′-OH group with the C-6 protons. Pyrimidine nucleosides containing the 1-β-D-arabinofuranosyl moiety in Me_2SO exist in the syn conformation which is free of interaction between the 5′-OH group and the C-6 proton. Similar phenomena were observed by Schweizer et al.,[30] who concluded that the 5′-phosphoryl group in nucleotides with the anti conformation exerts a specific deshielding effect on the H-8 proton of 5′-purine nucleotides and on the H-6 proton (and not H-5) of 5′-pyrimidine nucleotides. Thus the NMR spectra may provide a simple means for distinguishing between nucleosides and arabinonucleosides in pyrimidines.

Table I also indicates a deshielding effect on the anomeric proton of 2-selenouridine and 1-β-D-arabinofuranosyl-2-selenouracil as compared with the corresponding 4-seleno analogs. This is probably due to the anisotropy effect of the seleno group as suggested by Long and Townsend[31] for the thione group.

Interestingly, these selenopyrimidines were stable at pH 7 and 1 while relatively unstable at pH 11. The half-life of 1-β-D-arabinofuranosyl-2-selenouracil (II) at pH 11 is 30 min while 2-selenouridine (VI) is stable for more than 2 weeks. The instability of II in alkali is probably due to attack of the 2′-hydroxyl anion on C-2. The pK_a's of 2-seleno- and 4-selenopyrimidine nucleosides are nearly the same (7.5–7.6), but they are more acidic than their sulfur analogs (pK_a = 8.1–8.2)[9,32] and in turn more acidic than uridine (pK_a = 9.2).[33]

Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ultraviolet spectra were determined on a Perkin-Elmer Model 402 spectrophotometer. NMR spectra were measured on a Varian A-60A spectrometer in DMSO-d_6 or D_2O with Me_4Si as the internal standard. pK_a values were determined by potentiometric titration using a Radiometer pH meter 26. Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind.

1-β-D-Arabinofuranosyl-4-selenouracil (I). A solution of 550 mg (2 mmol) of arabinofuranosylcytosine in 4 ml of pyridine, 15 ml of ethylene glycol monomethyl ether, and excess of H_2Se was kept at room temperature overnight. The solution was then evaporated to dryness and the residue was dissolved in H_2O. The solution was passed through a Dowex 50 (H^+) column and eluted with H_2O. Evaporation of the solution gave 130 mg (20%) of I: mp 130° dec; uv λ_{max} (H_2O) 261 nm (ε 5131), 366 (16,482); λ_{max} (pH 1) 262 nm (ε 3798), 366 (18,355); λ_{max} (pH 11) 240 nm (ε 7095), 340 (14,915); pK_a = 7.39.

Anal. Calcd for $C_9H_{12}N_2O_5Se \cdot 0.75H_2O$: C, 33.71; H, 4.24; N, 8.74. Found: C, 34.08; H, 4.49; N, 8.32.

1-β-D-Arabinofuranosyl-2-selenouracil (II). A mixture of 170 mg (0.7 mmol) of arabinofuranosylisocytosine in 10 ml of pyridine, 10 ml of DMF, and 0.4 ml of H_2Se was stirred at room temperature for 4 days. The solution was evaporated to dryness. The residue was dissolved in H_2O and filtered. The filtrate was passed through a Dowex 50 (H^+) column and eluted with H_2O. Evaporation of the appropriate fractions and drying in vacuo gave 60 mg (26%) of II: mp 130° dec; uv λ_{max} (H_2O) 223 nm (ε 14,308), 308 (9756); λ_{max} (pH 1) 224 nm (ε 11,488), 308 (7599); λ_{max} (pH 11) 241 nm (ε 13,871), 292 (7316); pK_a = 7.53.

Anal. Calcd for $C_9H_{12}N_2O_5Se \cdot H_2O$: C, 33.24; H, 4.34; N, 8.62. Found: C, 33.10; H, 4.60; N, 8.43.

4-Selenouracil (III). A solution of 300 mg (2.8 mmol) of cytosine in 10 ml of pyridine, 25 ml of H_2O, and 0.7 ml of H_2Se was kept at 70° for 5 days. The mixture was evaporated to dryness. The residue was dissolved in H_2O and filtered. The filtrate was passed through a Dowex 50 (H^+) column and eluted with H_2O. Evaporation of the solution and drying in vacuo at 100° gave 60 mg (12%) of III: mp 235° dec; uv λ_{max} (H_2O) 260 nm (ε 7069), 368 (18,625); λ_{max} (pH 1) 260 nm (ε 6763), 368 (16,708); λ_{max} (pH 11) 235 nm (ε 7722), 348 (14,415).

Anal. Calcd for $C_4H_4N_2OSe$: C, 27.45; H, 2.30; N, 16.00. Found: C, 27.42; H, 2.45; N, 15.78.

2-Selenouracil (IV).[19] A solution of 300 mg (2.7 mmol) of isocytosine in 10 ml of H_2O, 5 ml of pyridine, and excess of H_2Se was kept at 70° for 4.5 days. The solution was evaporated to dryness. The residue was dissolved in H_2O and filtered. The filtrate was passed through a Dowex 50 (H^+) column and eluted with H_2O. The eluent was evaporated to dryness. The residue was recrystallized from EtOH to give 60 mg of IV. The filtrate was evaporated to dryness and dried in vacuo to give additional 110 mg of IV, uv λ_{max} (EtOH) 312 nm (ε 12,313).

4-Selenouridine (V).[14] A solution of 450 mg (1.85 mmol) of cytidine in 20 ml of DMF, 20 ml of pyridine, and 0.7 ml of H_2Se was kept at room temperature for 3 days and then evaporated to dryness. The residue was dissolved in H_2O and passed through a Dowex 50 (H^+) column. The column was eluted with H_2O. The solution was evaporated to dryness. The residue was dissolved in MeOH and filtered. The filtrate was evaporated to dryness and dried in vacuo to give 262 mg (42%) of V. The analytical sample was purified with Avicel plates (1000 μm) and developed with H_2O. The bands containing the compound were scraped out, dissolved in H_2O, and filtered. The filtrate was evaporated to dryness, coevaporated with EtOH, and dried in vacuo: mp 105° dec [lit.[14] mp 150–151° (anhydrous)]; uv λ_{max} (H_2O) 260 nm (ε 4532), 366 (16,332); λ_{max} (pH 1) 260 nm (ε 4320), 366 (16,362); λ_{max} (pH 11) 240 nm (ε 7401), 340 (13,568); pK_a = 7.60.

Anal. Calcd for $C_9H_{12}N_2O_5Se \cdot 0.5EtOH$: C, 36.37; H, 4.58; N, 8.48. Found: C, 35.94; H, 4.51; N, 8.71.

2-Selenouridine (VI).[14] A solution of 450 mg (1.85 mmol) of isocytidine in 10 ml of DMF, 10 ml of pyridine, and 0.6 ml of H_2Se was kept at room temperature for 3 days. The solution was evaporated to dryness. The residue was dissolved in H_2O and passed through a Dowex 50 (H^+) column. The column was eluted with H_2O. Evaporation of the appropriate fractions gave 270 mg (47%) of VI. The compound was suspended in a small amount of MeOH, filtered, and dried in vacuo to give the analytical sample: mp 170° dec [lit.[14] mp 197° dec (anhydrous)]; 225 nm (ε 16,150), 308 (13,650); λ_{max} (pH 1) 223 nm (ε 17,246), 308 (14,856); λ_{max} (pH 11) 240 nm (ε 13,988), 293 (9294); pK_a = 7.57.

Anal. Calcd for $C_9H_{12}N_2O_5Se \cdot 0.25H_2O$: C, 34.68; H, 4.04; N, 8.99. Found: C, 34.85; H, 4.30; N, 8.64.

4-Seleno-2′-deoxyuridine (VII). A solution of 300 mg (1.32 mmol) of 2′-deoxycytidine in 10 ml of DMF, 5 ml of pyridine, and excess of H_2Se was kept at room temperature for 2 days. The solvent was evaporated to dryness. The residue was dissolved in H_2O and passed through a Dowex 50 (H^+) column. The compound was eluted with H_2O. Evaporation of the solution gave 120 mg (31%) of VII: mp 135° dec; uv λ_{max} (H_2O) 260 nm (ε 3142), 368 (11,783); λ_{max} (pH 1) 260 nm (ε 2686), 368 (10,663); λ_{max} (pH 11) 239 nm (ε 5854), 340 (8960).

Anal. Calcd for $C_9H_{12}N_2O_4Se \cdot 0.5EtOH$: C, 38.23; H, 4.81; N, 8.92. Found: C, 38.16; H, 5.21; N, 9.16.

4-Thio-2′-deoxyuridine (VIII).[24] A mixture of 300 mg (1.32 mmol) of 2′-deoxycytidine in 10 ml of DMF, 5 ml of pyridine, and 5 ml of H_2S was kept at 70° for 3 days. The solution was evaporated and coevaporated with EtOH to dryness. The residue was dissolved in H_2O and passed through a Dowex 50 (H^+) column. The compound was eluted with H_2O. The solution was evaporated, coevaporated with EtOH, and dried. The residue was recrystallized from EtOH–Et_2O to give 150 mg (47%) of compound VII: mp

145–147° dec; uv λ_{max} (H_2O) 248 nm (ϵ 3638), 333 (20,789); λ_{max} (pH 1) 246 nm (ϵ 4020), 335 (21,026); λ_{max} (pH 11) 318 nm (ϵ 20,906).

Anal. Calcd for $C_9H_{12}N_2O_4S$: C, 44.25; H, 4.95; N, 11.47. Found: C, 44.49; H, 5.15; N, 11.51.

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Registry No.—Arabinofuranosylisocytosine, 10212-30-3; isocytosine, 674-97-5; isocytidine, 489-59-8; H_2Se, 7783-07-5.

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Indeno[1,2-*c*]isocoumarin

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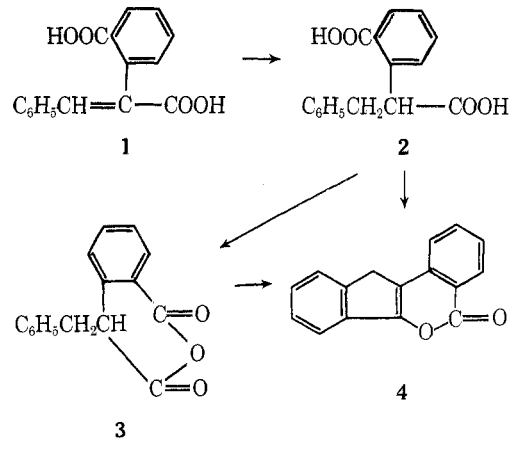
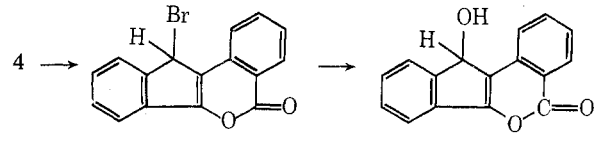
In studies dealing with the preparation of stabilized 2-arylindenones,[2,3] the synthesis of 2-*o*-carboxyphenylindanone, the precursor of 2-*o*-carboxyphenylindenone, from α-(*o*-carboxyphenyl)cinnamic acid (**1**) was investigated and found to give indeno[1,2-*c*]isocoumarin (**4**) instead of the desired product. α-(*o*-Carboxyphenyl)cinnamic acid (**1**) was prepared in two ways by the hydrolysis of α-(*o*-carboxyphenyl)cinnamonitrile and by the condensation of *o*-carboxyphenylacetic acid with benzaldehyde. Reduction of **1** with Raney nickel alloy in alkali gave α-(*o*-carboxyphenyl)-β-phenylpropionic acid (**2**), which was converted to the anhydride **3** by heating in toluene. Treatment of the acid **2** with polyphosphoric acid gave indeno[1,2-*c*]isocoumarin (**4**). The same product was formed by treating the anhydride **3** with aluminum chloride. Proofs for structure **4** were



1 **2** **3** **4**

the spectral data and the conversion of **4** to the known 11-keto[1,2-*c*]isocoumarin.[4] Bromination of **4** with *N*-bromosuccinimide gave 11-bromoindeno[1,2-*c*]isocoumarin (**5**), which when treated with alkali gave upon acidification 11-hydroxyindeno[1,2-*c*]isocoumarin (**6**). Evidence for this



5 **6**

structure was the NMR spectrum, which showed two doublets for the alcohol grouping. These doublets became a singlet in the presence of deuterium oxide.

The infrared spectrum in Nujol for **6** varied with the solvent used for recrystallization of this compound. A sample from benzene showed a sharp free hydroxyl absorption at 3484 cm^{-1} and carbonyl absorptions at 1739 and 1706 cm^{-1} with a shoulder at 1681 cm^{-1}. Compound **6** from ethanol gave two broad absorptions for the hydroxyl at 3268 and 3125 cm^{-1} and carbonyl absorptions at 1761 and 1712 cm^{-1}; the carbonyl at 1712 cm^{-1} was very small. Both samples, however, showed an absorption for the carbon–carbon double bond at 1637 cm^{-1}; its intensity when compared with that for the aromatic double bond at 1616 cm^{-1} was the same. One percent solutions of both samples in tetrahydrofuran, however, gave identical infrared spectra between 2.5 and 7 μ.

The alcohol **6** dissolved in alkali and the resulting solution when allowed to stand exposed to air for 7 days and then acidified gave 11-ketoindeno[1,2-*c*]isocoumarin.

Compound **6** was also formed by the reduction of 11-ketoindeno[1,2-*c*]isocoumarin with zinc and acetic acid.

Experimental Section

Melting points are corrected. The ir spectra were recorded with Model 21 and 137 Perkin-Elmer spectrometers, and the NMR spectra were obtained with a Varian A-60 spectrometer.

α-(*o*-Carboxyphenyl)cinnamonitrile. This nitrile was prepared from *o*-carboxyphenylacetonitrile[5] and benzaldehyde using the directions given for the preparation of α-phenylcinnamoni-