3b structure was solved with heavy-atom Patterson techniques, while **3d** was determined with direct methods.[15] The structures were refined by full-matrix least-squares techniques with minimization of $\sum w(F_o - F_c)^2$. Anisotropic temperature factors were used for C, N, O, and Br; isotropic terms were used for H. Few of the H atoms in **3d** refined well, and these atoms were fixed at idealized positions for the last several least-squares cycles. The F_c's were corrected for isotropic secondary extinction,[16] and only those terms for which $I_c > 3\sigma(I)$ were included in the calculations. The f curves for C, N, O, and Br were obtained from the analytical functions of Cromer and Mann;[17] the H values were interpolated from data tabulated by Stewart, Davidson, and Simpson.[18]

(15) All of the crystallographic calculations were performed on a UNIVAC 1108 computer at the University of Maryland's Computer Science Center, with the X-ray 72 system [J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickinson, and S. R. Hall, Report TR-192, Computer Science Center, University of Maryland, College Park, MD, 1972] of programs.

(16) A. C. Larson, "Crystallographic Computing", F. R. Ahmed, S. R. Hall, and C. P. Huber, Eds., Munksgaard, Copenhagen, Denmark, 1970, p 291.

(17) D. T. Cromer and J. B. Mann, *Acta Crystallogr., Sect. A*, **24**, 321 (1968).

Acknowledgment. Financial support was received from the National Science Foundation under Grant No. GP-37528 and from the Gillette Research Institute. The computer work for this project was supported in part through the facilities of the Computer Science Center of the University of Maryland.

Registry No. 1a, 1916-70-7; **3a**, 73198-81-9; **3b**, 73210-17-0; **3c**, 73198-82-0; **3d**, 58805-28-0; **3e**, 73198-83-1; **3f**, 73210-18-1; **3g**, 58805-30-4; 1-methyl-2-bromopyridinium bromide, 52693-57-9; 2-bromopyridine, 109-04-6; 1-methyl-4-bromopyridinium bromide, 73198-84-2; 4-bromopyridine, 1120-87-2; indene, 95-13-6; cyclopentadiene, 542-92-7; 1-benzyl-4-cyclopentadienylidene-1,4-dihydropyridine, 729-28-2; 1-methyl-4-indenylidene-1,4-dihydropyridine, 1916-68-3; 1-benzyl-4-indenylidene-1,4-dihydropyridine, 58805-29-1.

Supplementary Material Available: Tables of the atomic coordinates and temperature factors and crystal packing diagrams for **3b** and **3d** (8 pages). Ordering information is given on any current masthead page.

(18) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

Synthesis of 3,4-Dihydro-4-(2-hydroxyphenyl)pyrido[2,3-*d*]pyrimidin-2(1*H*)-ones by a Novel Rearrangement of a 5*H*-[1]Benzopyrano[2,3-*b*]pyridine Derivative

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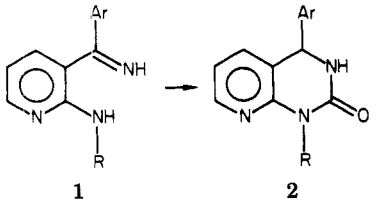
The benzopyrano[2,3-*b*]pyridine **4** undergoes a facile base-induced ring rearrangement in the form of its monoanion derivatives **5** or **7** to afford the pyrido[2,3-*d*]pyrimidin-2(1*H*)-ones **8a** and **8b**, respectively. Deuteration experiments confirm the formation of the urea dianion **6** which does not rearrange but initially reacts with iodomethane at 0–20 °C and subsequently rearranges to **8b**.

As part of an investigation of the chemistry and biological activity of a series of 5*H*-[1]benzopyrano[2,3-*b*]-pyridin-5-ylureas,[1] we have observed a novel base-induced ring rearrangement of the 1,3-dimethylurea derivative **4** to give the 3,4-dihydro-4-(2-hydroxyphenyl)pyrido[2,3-*d*]pyrimidin-2(1*H*)-ones **8a** and **8b** (Scheme I). The only previously reported synthesis of this class of compounds has involved the cyclization of a 2-aminopyridine derivative (**1**) followed by reduction of the 3,4 double bond to give **2**.[2]



1 **2**

In the present case, reaction of 5*H*-[1]benzopyrano-[2,3-*b*]pyridin-5-ol (**3**) with 1,3-dimethylurea under acid-catalyzed conditions ($HOAc/CH_3CN$) gave **4** in 65% yield. Treatment of **4** with 1 molar equiv of LiN-*i*-Pr_2 (LDA) in THF at −40 °C gave the monoanion **5** which afforded **8a** (62%) after warming to room temperature. When **5** was treated at −40 °C with excess iodomethane and warmed to 20 °C, rearrangement also occurred to give **8a** and not the 1,1,3-trimethylurea derivative.

The formation of a carbanion α to nitrogen in amides with LDA has been reported recently.[3] By contrast, we are unaware of any examples of metalation on carbon α to a urea nitrogen. When **4** was treated with 2 molar equiv of LDA in THF at −40 °C to form the dianion **6** followed by the addition of 2 molar equiv of iodomethane and warming to 25 °C, **8b** was isolated (44%). TLC of the crude product before recrystallization showed one major component corresponding to **8b**.

The ^1H NMR spectrum of **4** is reported in the Experimental Section and is readily interpretable. In the mass spectrum, the molecular ion at m/e 269 is abundant, and

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(1) A complete description of this research will be published separately.

(2) G. E. Hardtmann, B. Huegi, G. Koletar, S. Kroin, H. Ott, J. W. Perrine, and E. I. Takesue, *J. Med. Chem.*, **17**, 636 (1974).

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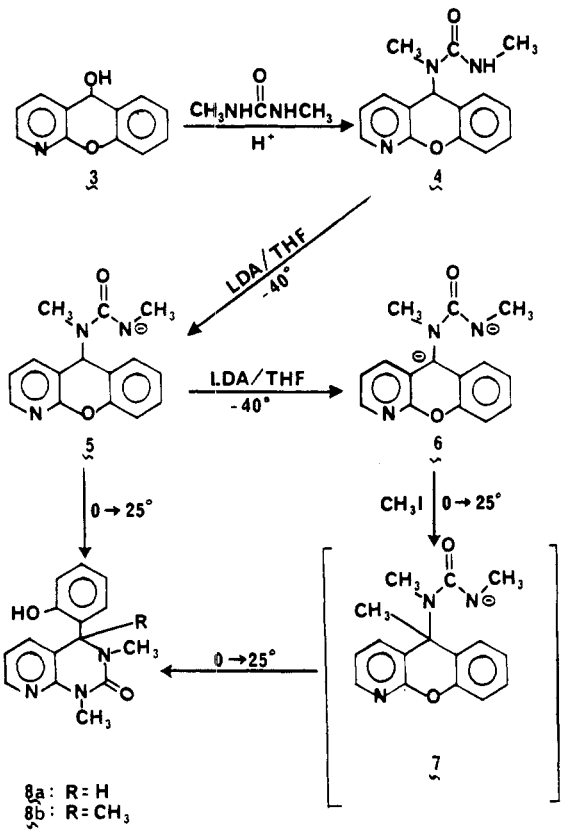
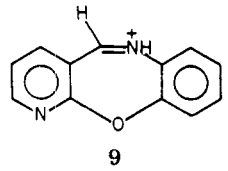
Scheme I



the base peak is the ion at m/e 182 resulting from loss of the urea moiety. Another abundant ion is formed at m/e 197. High-resolution mass measurement shows this ion to have the formula $C_{12}H_9N_2O$ which we assign to **9**.



9

The ^1H NMR spectrum of the rearranged products **8a** and **8b** are also readily interpretable. The two NCH_3 resonances are singlets and the C_4 H in **8a** appears at δ 5.83, 1 ppm upfield from the methine proton of **4**. In **8b**, the C_4 CH_3 resonance appears at δ 1.84. The mass spectra of **8a** and **8b** show molecular ions at m/e 269 and 284, respectively, with abundant P - 1 peaks. For **8a**, the base peak appears at m/e 176 for $M^+ \cdot - C_6H_4OH$, while for **8b** the base peak is m/e 268 ($M^+ \cdot - CH_3$).

In order to better understand the sequence of events taking place in the rearrangement of **4** to **8a** and **8b** and to confirm the formation of dianion **6**, several deuteration experiments were performed (Table I). The urea **4** was treated with 1, 2, or 3 (excess) equiv of LDA at -78, 0, and 25 °C and subsequently quenched with D_2O after the period of time shown. Percent deuterium incorporation at C-5 of recovered **4** was determined from the relative abundance of isotopic masses in the mass spectrum at m/e 270/269, 198/197, and 183/182. No deuteration at C-5 occurs with 1 equiv of LDA, and only a negligible amount of rearranged product, **8a**, is formed at 0 °C.

When **4** is treated with 2 or 3 equiv of LDA, the dianion **6** is clearly formed as shown by deuterium incorporation at C-5. No attempts were made to maximize deuterium incorporation by extending the reaction time or by heating above 25 °C. As expected, dianion **6** does not rearrange due to the deactivating influence of the second negative charge. Even after 16 h at 25 °C, **4** is recovered unrearranged upon D_2O quenching (75% deuterated).

Table I. Deuteration Experiments

LDA, molar equiv	temp, °C	time, h	% deuteration of 4	8a, % yield
1.0	-78	0.5	0	0
1.0	0	0.5	0	<5[a]
2.0	-78	0.5	42	0
2.0	0	0.5	67	0
3.0	25	16	75	0

[a] ^1H NMR spectrum of crude product mixture and TLC show **8a** as a minor component.

When **6** was formed at -40 °C, treated with iodomethane, and allowed to warm to 0 °C and stir for 0.5 h, only starting material (**4**) was observed after treatment with H_2O; however, when an identical reaction was allowed to warm to 20 °C, **8b** was the sole reaction product. Since **6** does not rearrange, **8b** must form via C-alkylation of **6** between 0 and 20 °C followed by rapid rearrangement of the resulting monoanion **7**.

Nucleophilic ring opening of benzopyrano[2,3-*b*]pyridin-5-one by hydroxide in boiling ethanol to give a pyridone has been reported previously by Villani and coworkers.[4] In the present case, an intramolecular ring-opening rearrangement of a benzopyrano[2,3-*b*]pyridine nucleus occurs under exceedingly mild conditions. It should be noted that this ring rearrangement corresponds to a favored 6-exo-trig process according to Baldwin's rules for ring closure.[5]

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on Varian T60A and CFT 20 spectrometers, and chemical shift values are reported in parts per million downfield from internal Me_4Si. IR spectra were recorded on a Perkin-Elmer 221 spectrophotometer, and mass spectra were obtained with a Varian MAT CH5 spectrometer. UV spectra were recorded on a Cary 118 spectrophotometer. All distillative concentration of solvents was done with a rotary evaporator under reduced pressure. *n*-Butyllithium in hexane (2.4 M) was obtained from Alfa Inorganics, Inc.

1-(5*H*-[1]Benzopyrano[2,3-*b*]pyridin-5-yl)-1,3-dimethylurea (4). A solution of **3**[6] (19.9 g, 0.10 mol) and 1,3-dimethylurea (8.8 g, 0.10 mol) in 250 mL of CH_3CN and 10 mL of HOAc was heated under reflux for 1 h. The solution was cooled and concentrated to remove the CH_3CN. Ice was added to the residual liquid followed by aqueous K_2CO_3 solution, and this mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with saturated NaCl solution, dried (K_2CO_3), and concentrated to give an oil which crystallized upon standing. This was recrystallized from 75 mL of toluene to give 17.4 g (65%) of **4**, sinters at 140 °C, melts at 145–150 °C. A second recrystallization from 75 mL of toluene gave 15.17 g of pure **4**: sinters at 147 °C, melts at 166–168 °C; IR (Nujol) 3290, 1625 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.33 (s, 3 H, N_1CH_3), 2.72 (d, 3 H, N_3CH_3), 6.50 (q, 1 H, NH), 6.80 (s, 1 H, C_5H), 7.00–7.45 (m, 5 H, ArH), 7.68 (q, 1 H, C_4H), 8.39 (q, 1 H, C_2H); UV (CH_3OH) 235 nm (log ϵ 3.77), 269 (3.36), 290 (3.44); mass spectrum, m/e 269 ($M^+ \cdot$, 49.3%), 197 ($M^+ \cdot - C_2H_5NO$,

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(5) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).
(6) M. Nakanishi, O. Takanori, and M. Tsuruda, German Patent 2 337 052; *Chem. Abstr.*, **80**, 108503g (1974).

93%), 182 (M^+· – $CH_3NHCONCH_3$, 100%).

Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.59; H, 5.81; N, 15.36.

3,4-Dihydro-1,3-dimethyl-4-(2-hydroxyphenyl)pyrido[2,3-*d*]pyrimidin-2(1*H*)-one (8a). To a solution of 9.0 mL (0.064 mol) of freshly distilled diisopropylamine in 150 mL of dry THF held at –40 °C under a N_2 atmosphere was added 26.5 mL of 2.4 M *n*-butyllithium/hexane (0.064 mol). After being stirred at –20 °C for 0.5 h, the LDA solution was cooled to –40 °C and a solution of 16.0 g (0.059 mol) of **4** in 50 mL of dry THF was added over 0.25 h. The reaction mixture was allowed to warm to 25 °C, stirred for 8 h, and finally heated at 35–40 °C for 0.5 h. The resultant black mixture was poured into 1000 mL of cold H_2O. The aqueous mixture was acidified with 12 N HCl, then rendered basic with $NaHCO_3$ to pH 8, and extracted with three 500-mL portions of CH_2Cl_2. The CH_2Cl_2 extract was concentrated and the residual oil repeatedly diluted with EtOAc and concentrated until a semisolid material remained. This was triturated with two 50-mL portions of EtOAc and finally was dissolved in 50 mL of Me_2SO and 50 mL of H_2O on a steam bath, allowed to cool, and filtered to give 9.9 g (62%) of **8a**: mp 219–221 °C; IR (Nujol) 3125, 1630, 1590 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.78 (s, 3 H, N_1CH_3), 3.37 (s, 3 H, N_3CH_3), 5.83 (s, 1 H, C_4H), 6.60–7.30 (m, 6 H, ArH), 7.55 (q, 1 H, C_7H), 11.83 (br s, 1 H, OH); UV (CH_3OH) 263 nm (log ϵ 3.78), 285 (3.90); mass spectrum, *m/e* 269 (M^+·, 32%), 176 (M^+· – C_6H_4OH, 100%).

Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.51; H, 5.39; N, 15.26.

3,4-Dihydro-4-(2-hydroxyphenyl)-1,3,4-trimethylpyrido-[2,3-*d*]pyrimidin-2(1*H*)-one (8b). To a solution, under N_2, of 0.127 mol of LDA in 150 mL of dry THF, prepared as described above and held at –40 °C, was added a solution of 16.0 g (0.059 mol) of **4** in 150 mL of THF over 0.25 h. After the solution was warmed to 25 °C over 0.5 h, 3.9 mL (0.063 mol) of CH_3I was added, producing a temperature rise to 35 °C. After the solution was stirred for 2 h at ambient temperature, an additional 3.9 mL of CH_3I was added. The reaction mixture was allowed to stir for 6 h and then poured into 1000 mL of cold H_2O. The aqueous solution was acidified with 12 N HCl, rendered basic with $NaHCO_3$, and extracted with three 500 mL-portions of $CHCl_3$. The $CHCl_3$ solution was concentrated and the residual oil repeatedly treated with EtOAc and concentrated until a semisolid residue remained. This was triturated with two 50-mL portions of EtOAc and recrystallized from 50 mL of Me_2SO and 50 mL of H_2O at 100 °C to give 7.3 g (44%) of **8b**: mp 250–252 °C; IR (Nujol) 3115, 1618, 1595, 1585 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.84 (s, 3 H, C_4CH_3), 2.55 (s, 3 H, N_1CH_3), 3.38 (s, 3 H, N_3CH_3), 6.55–7.30 (m, 6 H, ArH), 7.44 (q, 1 H, C_7H), 11.43 (s, 1 H, OH); UV (CH_3OH) 240 nm (log ϵ 4.21), 271 (3.96), 283 (3.90), 324 (3.85); mass spectrum, *m/e* 283 (M^+·, 12.5%), 268 (M^+· – CH_3, 100%), 190 (M^+· – C_6H_4OH, 55.6%).

Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 68.05; H, 5.88; N, 14.49.

Deuteration Experiments. General Procedure. See Table I for results. To LDA (1, 2, or 3 molar equiv) in THF under N_2 at –40, 0, or 25 °C was added 0.50 g (0.00187 mol) of **4**. After the solution was stirred for the period of time noted, D_2O was added and the reaction mixture was poured into 100 mL of 5% aqueous NH_4Cl. The product was extracted into $CHCl_3$ and the chloroform was evaporated to give 0.45–0.48 g of crude product. This was recrystallized from 2.5 mL of EtOAc to give pure material which was analyzed for percent deuterium incorporation by mass spectral analysis.

Acknowledgment. We thank the staff of the Department of Physical and Analytical Chemistry, Schering-Plough Corporation, for microanalytical and spectral data. In particular we wish to thank Mr. Peter Bartner for his assistance in mass spectral interpretation.

Registry No. **3**, 6722-09-4; **4**, 73018-17-4; **8a**, 73018-18-5; **8b**, 73018-19-6; 1,3-dimethylurea, 96-31-1.

Useful Route to 1,6-Dioxaspiro[4.4]nonane and 1,6-Dioxaspiro[4.5]decane Derivatives[1]

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A wide variety of derivatives of 1,6-dioxaspiro[4.4]nonane and 1,6-dioxaspiro[4.5]decane, including certain insect pheromones, can be conveniently prepared by reaction of the lithium salts of protected alkynols with equimolar amounts of lactones followed by hydrogenation and acid-catalyzed deprotection and cyclization. Alkynols are satisfactorily protected either as their tetrahydropyranyl or as their 1-ethoxyethyl ethers; intermediates need not be isolated. Yields are variable, but products are readily obtainable in high purity regardless of yield.

Steroidal sapogenins[3a,b] and other moderately complex compounds such as monensin[3c] containing the 1,6-dioxaspirononane structure have been known for many years, but the discovery of simple 1,6-dioxaspironone and -decane natural products has occurred only recently. Derivatives of this class of compounds have been found in several plant species, of which chrysanthemum and hops are two examples.[3d] The discovery that this class of compounds includes insect pheromones is also a recent development, although various other acetal and ketal structures are well-known beetle pheromone components.[4] W. Francke and his collaborators have established the presence of 2-ethyl-1,6-dioxaspiro[4.4]nonane (**5**, **6**) in the aggregation pher-

(1) Approved as TA 15435 by the director of the Texas Agricultural Experiment Station in cooperation with ARS-USDA. Supported by the Texas Department of Agriculture Interagency Agreement IAC-0487 (78–79).

(2) (a) Oberlin College. (b) Texas A&M University.

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