(s) and 2.96 (s) (for total 3 H, 1.47/1/1.87 ratio), 2.94–2.77 (m, 1.43 H), 2.58 (dq, 0.34 H, J = 14.0 and 2.9 Hz), 2.34–1.03 (m, 6.66 H), 0.92 (s), 0.89 (s), and 0.88 (s) (for total 9 H, 1.87/1/1.47); ^{13}C NMR (carbon assignment of diastereoisomers was made in the mixture, on the basis of DEPT and two-dimensional ^{13}C–^{1}H correlation experiments) δ (**16**] (68.02),[a] 63.70, (47.45),[b], 39.40, (33.17),[c] (32.62),[d] 27.33, 20.94, 19.60, [**14**] 69.28, (66.96),[a] (46.68),[b] 41.93, (34.94),[c] (32.40),[d] 27.11, 25.01, 24.63, [**13**] 70.77, 63.72, 45.19, 41.47, 32.26, 30.90, 27.22, 25.70, 25.15 [the chemical shifts of signals in parentheses labeled a–d can be exchanged for compounds **16** and **14**. Signals corresponding to compound **13** were unequivocally assigned before]; IR (KBr) 3480, 2966, 2868, 1352, 1292, 1108, 1084, 987.

Registry No. **1**, 52190-35-9; **2**, 62151-61-5; **3**, 108920-15-6; **4**, 16096-71-2; **5**, 84613-31-0; **6**, 108920-16-7; **7**, 108920-17-8; **8**, 41578-04-5; **9**, 108920-18-9; **10**, 108920-19-0; **11**, 108920-20-3; **12**, 108920-21-4; **13**, 108920-22-5; **14**, 108920-23-6; **15**, 108945-94-4; **16**, 108920-24-7; cyclohexanone, 108-94-1; dimethyl disulfide, 624-92-0; 4-*tert*-butylcyclohexanone, 98-53-3.

Linear Free Energy Relationship Studies of 5-Substituted 2,4-Dioxopyrimidine Nucleosides

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The development of a direct and efficient palladium(0)-catalyzed biaryl coupling reaction permitted the synthesis of a series of N1-substituted 5-aryl-2,4-dioxopyrimidines. The physical and spectral properties of these compounds were determined and correlated by various linear free energy relationships. The relationships between the physical and spectral data with Hammett σ constants proved useful in analyzing the electron distribution of the heterocycle. Although a significant degree of orbital overlap and interaction between the substituents and the pyrimidine ring was observed, it is doubtful that the interactions are comparable to those of a benzene ring system.

The biochemical significance of 2,4-dioxopyrimidines and their N1-substituted derivatives and their polymeric products (RNA, DNA) is evident in the role played in metabolism, control, and regulation. For this reason, the electronic structure of these molecules has been the subject of extensive investigation.

In an earlier study of 5-substituted 2,4-dioxopyrimidines Tarpley and Goldstein[1] found that the ^{13}C chemical shifts of these compounds correlated reasonably well with the total electron charge densities calculated with extended Hückel theory (EHT). In addition, good correlation between the ^{13}C chemical shifts of 5-halo-2,4-dioxopyrimidines and substituent electronegativity (E_X) was observed. Ellis and co-workers[2] using a more complete list of 5-substituted derivatives found that the linear relationship between ^{13}C chemical shifts and E_X no longer holds. Instead, they rationalized the data by considering 5-substituted 2,4-dioxopyrimidines as trisubstituted ethylenes. On the other hand, Chandrasekaran and coworkers,[3] in studying the ^{17}O NMR of the 5-substituted heterocycle, found good correlation between chemical shifts of the 2- and 4-oxygen atoms and Hammett σ values of the substituents. These results indicate that there is considerable interaction between the 5-substituents and both the 2- and 4-oxygen atoms. The ground electronic state of 2,4-dioxopyrimidine has been characterized by O'Donnell and co-workers,[4] using the ab initio molecular fragment floating spherical Gaussian orbital (MF-FSGO) method. The resonance structure that is usually drawn places double bonds along the C2=O2, C4=O4, and C5=C6, resulting in $\sim 3\pi$ bonds. Yet they found a net bond order of $\sim 4.4\pi$ bonds indicating a higher degree of orbital overlap.[4]

While these studies have concentrated on 2,4-dioxopyrimidines, the application of the results to the properties of their biological derivatives is tenuous since the natural derivatives are substituted at N1 with either ribose, 2′-deoxyribose, or their 5′-phosphates. This critical structural change, N1-substitution, effectively limits the resonance contribution of the 5-substituents and seriously hampers the direct application of these results to the heterocyclic structure as it is found in nature.

In an effort to model N1-substitution found in the natural molecules, we have analyzed the physical and spectral properties of 13 2,4-dioxopyrimidine nucleosides substituted at C5 of the pyrimidine ring. The models chosen may be written in the form XGY, where X represents a substituent, Y represents the site at which the observed phenomenon takes place, and G is a skeletal group to which X and Y are attached (Table I). In the classical ionization constant study of substituted benzoic acids by Hammett, X is a set of substituents, G is a phenyl ring, and Y, the reactive site, is the carboxyl moiety. In an analogous manner, the entire 2,4-dioxopyrimidine ring can be considered as the reactive site Y, a phenyl ring as the skeletal group G, and a series of substituents X, attached on the phenyl ring.

The advantages in the proposed model system are as follows:

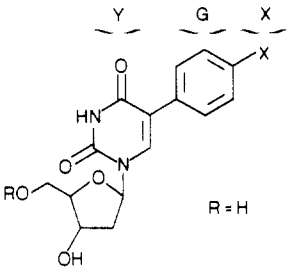
(1) The planarity of the two rings allows for the transmission of the electronic properties of the substituents to the pyrimidine ring.

(2) The insertion of the phenyl ring between the substituent and the heterocycle should simplify the NMR

(1) Tarpley, A. R., Jr.; Goldstein, J. H. *J. Am. Chem. Soc.* **1971**, *93*, 3573–3578.
(2) Ellis, P. D.; Dunlap, R. B.; Pollard, A. L.; Seidman, K.; Cardin, A. D. *J. Am. Chem. Soc.* **1973**, *95*, 4398–4403.
(3) Chandrasekaran, S.; Wilson, W. D.; Boykin, D. W. *J. Org. Chem.* **1985**, *50*, 829–831.
(4) O'Donnell, T. J.; LeBreton, P. R.; Shipman, L. L. *J. Phys. Chem.* **1978**, *82*, 343–347.

0022-3263/87/1952-3625$01.50/0

Table I. Substituent Constants for a Series of N1-Substituted 5-Aryl-2,4-dioxopyrimidines[11]



compd	X	π^a	σ^b	F[c]	R[c]	MR[d]
3	$N(CH_3)_2$	0.18	−0.83	0.10	−0.92	1.56
4	NH_2	−1.23	−0.66	0.02	−0.68	0.54
5	OH	−0.67	−0.37	0.29	−0.64	0.29
6	OCH_3	−0.02	−0.27	0.26	−0.51	0.79
7	$OCH_2C_6H_5$	1.66	−0.23	0.26	−0.51	3.22
8	CH_3	0.56	−0.17	−0.04	−0.13	0.57
9	H	0.00	0.00	0.00	0.00	0.10
10	Br	0.86	0.23	0.44	−0.17	0.89
11	$CONH_2$	−1.49	0.36	0.24	0.14	0.98
12	CO_2CH_3	−0.01	0.45	0.33	0.15	1.29
13	CF_3	0.88	0.54	0.38	0.19	0.50
14	CN	−0.57	0.66	0.51	0.19	0.63
15	NO_2	−0.28	0.78	0.67	0.16	0.74

[a] π values represent hydrophobic interactions. [b] σ values represent electronic effect. [c] The terms F and R represent field-inductive and resonance effects, respectively. [d] MR values represent steric effects. The MR values were scaled by 0.1 to make them commensurable with the other parameters.

studies. Shielding effects such as neighboring group anisotropic effect, steric effect, and heavy atom effect are not of concern.

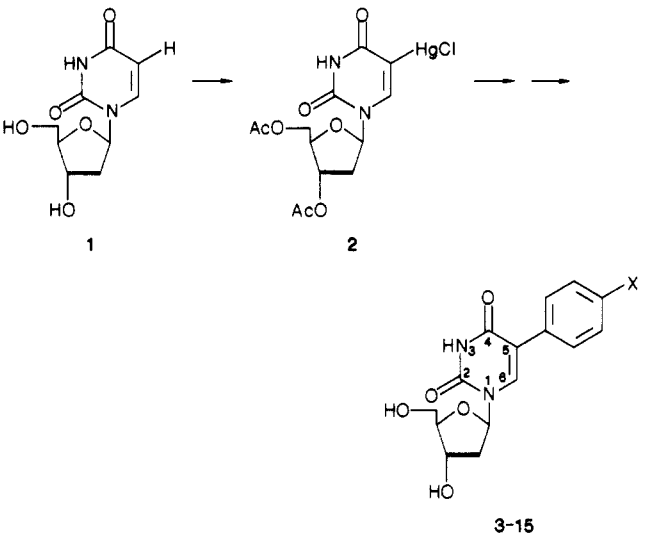
(3) The presence of the phenyl ring should eliminate intramolecular interactions (i.e., hydrogen bonding) between the substituents and the carbonyl group of the pyrimidine ring.

Physical and spectral properties were used to examine in greater detail the electron distribution of the pyrimidine ring in the models. Good to excellent correlations were found between Hammett σ values and ^1H and ^{13}C NMR chemical shifts for the N3 and C6 protons, C4, C5, and C6. The results of this study have shown that there is a considerable degree of interaction between the substituted aromatic ring on carbon-5 and the pyrimidine ring.

Results

Previous methods examined for the direct synthesis of 5-aryl derivatives of pyrimidine nucleosides employed a biaryl photochemical coupling reaction[5] and a palladium(II)-catalyzed coupling reaction.[6] Low yields and the lack of regioselectivity in the former and mechanistic questions raised in the latter prompted a study of a palladium(0)-catalyzed reaction. A direct and efficient synthetic procedure employing a palladium(0)-catalyzed biaryl coupling reaction was developed for the preparation of a wide variety of 5-aryl-substituted nucleosides[7] (**6–15**, Scheme I). Studies of the reaction using both the nucleoside and the protected derivative showed the reaction to be compatible with a variety of functional groups on the nucleoside and the aromatic derivative. The use of the more soluble di-*O*-acetyl derivative of 5-(chloromercurio)-2′-deoxyuridine (**2**) significantly increased the yield of the reaction. From the results, solubility rather than the electronic nature of the *p*-phenyl substituent appeared to influence the reaction efficiency. Three compounds (**3–5**) were prepared in high yields by modification of derivatives **15** and **7** by using standard procedures.

Scheme I. Synthesis of 5-(*p*-Substituted-phenyl)-2′-deoxyuridines[a]



[a] **6**, X = OCH_3, 62%; **7**, X = $OCH_2C_6H_5$, 65%; **8**, X = CH_3, 55%; **9**, X = H, 58%; **10**, X = Br, 42%; **11**, X = $CONH_2$, 45%; **12**, X = $COOCH_3$, 52%; **13**, X = CF_3, 53%; **14**, X = CN, 55%; **15**, X = NO_2, 42%; **3**, X = $N(CH_3)_2$, 90% from **15**; **4**, X = NH_2, 98% from **15**; **5**, X = OH, 97% from **7**.

The chemical shifts of the N3 and C6 protons[8] for the pyrimidine ring in nucleosides **3–15** are listed in Table II along with the chemical shifts of the C1′ proton and the Hammett σ values. The order of presentation in Table II and compound numbering is that of increasing sigma

(5) Al-Razzak, L.; Mertes, M. P. *Nucleosides Nucleotides* **1983**, *2*, 243–248.
(6) Bigge, C. F.; Mertes, M. P. *J. Org. Chem.* **1981**, *46*, 1994–1997.
(7) Chang, G.; Mertes, M. P. *Tetrahedron Lett.* **1985**, *25*, 2431–2434.

(8) Due to an error is setting the transmitter offset value, the ^1H NMR chemical shifts of the C6 protons reported in Chang and Mertes (Chang, G.; Mertes, M. P. *Tetrahedron Lett.* **1985**, *25*, 2431–2434) are incorrect. The corrected values are as follows: ^1H NMR for C6-H (CD_3OD, in ppm): **2**, 8.26; **3**, 8.13; **4**, 8.28; **5**, 8.21; **6**, 8.55.

Table II. ^{1}H Chemical Shifts of 5-(*p*-Substituted-phenyl)-2′-deoxyuridines 3–15[a]

compd	X	C6-H[b]	N3-H[b]	Cl′-H[b]	σ
3	$N(CH_3)_2$	8.00	11.31	6.24	−0.83
4	NH_2	7.94	11.26	6.23	−0.66
5	OH	8.03	NA[c]	6.23	−0.37
6	OCH_3	8.09	11.37	6.24	−0.27
7	$OCH_2C_6H_5$	8.10	11.42	6.25	−0.23
8	CH_3	8.13	11.39	6.24	−0.17
9	H	8.18	11.43	6.24	0.00
10	Br	8.26	11.48	6.22	0.23
11	$CONH_2$	8.29	11.50	6.23	0.36
12	CO_2CH_3	8.40	11.53	6.23	0.45
13	CF_3	8.39	NA[c]	6.23	0.54
14	CN	8.41	11.57	6.22	0.66
15	NO_2	8.51	11.61	6.22	0.78

[a] All spectra were obtained in Me_2SO-d_6. [b] Chemical shifts are reported in parts per million and with respect to Me_4Si. [c] Chemical shifts for these protons were not observed.

values. The observed ranges of the ^{1}H chemical shifts for the nucleosides studied were 0.57 and 0.35 ppm for C6-H and N3-H, respectively; there was little change in the C1′-H chemical shifts.

Listed in Table III are the ^{13}C chemical shifts of C6, C5, C4, and C2 of the pyrimidine ring and the Hammett σ values of the paraphenyl substituents. The observed ranges of ^{13}C chemical shifts for the nucleosides studied were 0.25, 0.67, 3.17, and 5.08 ppm for C2, C4, C5, and C6, respectively.

The infrared stretching frequency of the carbonyl groups at C2 and C4 of the 5-(*p*-substituted-phenyl)-2′-deoxyuridines are listed in Table IV. A review of the literature[9] revealed that for 2,4-dioxopyrimidine, the bands at 1661 and 1696 cm^{-1} were assigned to the C4 and C2 carbonyl stretching vibrations. The C2 carbonyl bands of the samples studied covered a range of 21.2 cm^{-1}, while the range for the C4 carbonyl was limited to two values for C4 carbonyl shifts, one centering at 1653 cm^{-1} and the other at 1662 cm^{-1}.

The compounds examined in this study were sparingly soluble in water; hence determination of apparent ionization constants (Table V) was accomplished by ultraviolet spectrophotometry.[10] The values ranged from 9.01 (X = CN) to 9.47 nm (X = NH_2) for the compounds examined.

Discussion

The results from the ^{1}H NMR studies were useful in the analysis of the electronic effects of the substituents on the N3 and C6 protons. The data from the plots of chemical shifts vs. Hammett σ values and the regression analysis data for the N3 and C6 protons (Table VI) showed excellent correlations (r = 0.98 for N3-H, r = 0.99 for C6-H). In going from electron-donating to electron-withdrawing substituents (increasing σ values), corresponding downfield shifts (increasing ppm) of both N3 and C6 protons were observed as indicated by positive slopes. As expected, electron-withdrawing groups decreased the electron density at the N3 and C6 regions, resulting in a deshielding effect on the protons. The greater slope for the C6 than the N3 proton plot indicates that conjugation and closer proximity render C6 more sensitive to the electronic properties of the substituents. However, the high correlation between N3-H chemical shifts and Hammett σ values indicates a significant degree of orbital overlap and interaction between the substituents and the N3 proton.

The N3 and C6 proton chemical shifts of the *N*,*N*-dimethylamino compound **3** gave a large deviation from the Hammett lines. An examination of the ^{1}H NMR spectra in different deuteriated solvents (methanol-d_4 and acetonitrile-d_3) and a replot of the chemical shifts vs. Hammett σ values revealed that the *N*,*N*-dimethylamino compound **3** was still a deviate, indicating that solvent interaction was not the cause of the deviation. On the basis of the NMR shifts of the N3-H and C6-H, the graphically determined σ value for the *N*,*N*-dimethylamino group is −0.53 instead of the normal −0.83 value.[11] A σ value of −0.53 indicates that in the aryl pyrimidine system studied, the *N*,*N*-dimethylamino group has a smaller electronic contribution than the amino group (σ = −0.66). A similar effect was observed in the alkaline hydrolysis of para-substituted ethyl β-phenylpropionates.[12] In this example the experimental σ value for the amino group was determined to be −0.33 while a higher σ value of −0.27 was determined for the *N*,*N*-dimethylamino group.[12] The reasons for this deviation are not immediately obvious.

In an earlier ^{13}C NMR study of 5-substituted 2,4-dioxopyrimidines the substituents (X = NH_2, OH, OCH_3, CH_3, CH_2OH, H, F, I, Cl, Br, CHO, $COOCH_3$, COOH, CF_3, CN, NO_2) were attached directly to the C5 carbon of the heterocyclic ring.[2] No obvious correlation was found between the ^{13}C chemical shifts of the C5 and C6 carbons and the substituent electronegativity. In an attempt to explain the data, the authors considered the 5-substituted heterocycles as trisubstituted ethylenes and rationalized the data in terms of the ability of the C5 substituent to behave as a mesomeric acceptor or donor.[2] They noted that the lack of correlation between the C5 carbon and the substituent electronegativity was due largely to magnetic anisotropy effects. Application of a correction for the magnetic anisotropy contribution did result in a high correlation between substituent electronegativity and the ^{13}C chemical shifts of the aromatic carbon atom directly attached to the substituent.[13] The ^{13}C chemical shifts of the C6 carbon atoms in the ortho position are not readily predictable. In addition to magnetic anisotropy effects, the ring carbon in the C6 position is subject to steric and other local effects of the attached substituents.

In the models used in the present study, a phenyl ring separates the substituents and the heterocyclic ring; thus magnetic anisotropy effects and varying steric effects are eliminated. The results of the plots of the ^{13}C NMR chemical shifts of the C6, C5, C4, and C2 carbons vs. Hammett σ values and the regression analysis data are shown in Table VI. Similar to the ^{1}H NMR studies, the *N*,*N*-dimethylamino compound **3** was a deviate. High correlations with σ values were obtained for the ^{13}C chemical shifts of C6 and C5. However, attempts to correlate the ^{13}C chemical shifts of C4 and C2 with substituent sigma values proved to be less successful.

Comparison of the ^{13}C NMR data of these heterocycles with those of 4-substituted biphenyls was diagnostic. The ^{13}C chemical shifts of 4-substituted biphenyls **16** have been determined and correlated by various linear free energy relationships.[14] Table VII summarizes the results of the

(9) (a) Miles, H. T. *Biochim. Biophys. Acta* **1956**, *22*, 247–253. (b) Lafleur, L.; Rice, J.; Thomas, G. J., Jr. *Biopolymers* **1972**, *11*, 2423–2437. (c) Lord, R. C.; Thomas, G. J., Jr. *Spectrochim. Acta, Part A* **1967**, *23A*, 2551–2591. (d) Susi, H.; Ard, J. S. *Ibid.* **1971**, *27A*, 1549–1562. (e) Susi, H.; Ard, J. S. *Ibid.* **1974**, *30A*, 1843–1853. (f) Bandekar, J.; Zundel, G. *Ibid.* **1983**, *39A*, 337–341. (g) Bandekar, J.; Zundel, G. *Ibid.* **1983**, *39A*, 343–355.

(10) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman-Hall: London, 1971.

(11) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207–1216.

(12) Fuchs, R.; Caputo, J. A. *J. Org. Chem.* **1966**, *31*, 1524–1526.

(13) Spiesecke, H.; Schneider, W. G. *J. Chem. Phys.* **1961**, *35*, 731–738.

Table III. ^{13}C Chemical Shifts of 5-(*p*-Substituted-phenyl)-2′-deoxyuridines 3–15[a]

compd	X	C2[b]	C4[b]	C5[b]	C6[b]	σ
3	$N(CH_3)_2$	149.88	162.34	113.83	135.67	−0.83
4	NH_2	149.88	162.37	114.24	135.32	−0.66
5	OH	149.91	162.28	113.65	136.42	−0.37
6	OCH_3	149.89	162.20	113.23	136.89	−0.27
7	$OCH_2C_6H_5$	149.91	162.22	113.20	136.95	−0.23
8	CH_3	149.85	162.07	113.39	137.41	−0.17
9	H	149.87	162.04	113.41	137.94	0.00
10	Br	149.76	161.84	112.10	138.32	0.23
11	$CONH_2$	149.92	162.10	112.50	138.71	0.36
12	CO_2CH_3	149.72	161.81	111.98	139.34	0.45
13	CF_3	149.84	161.94	111.78	139.36	0.54
14	CN	149.67	161.70	111.43	139.76	0.66
15	NO_2	149.72	161.78	111.07	140.40	0.78

[a] All spectra were obtained in Me_2SO-d_6. [b] Chemical shifts are reported in parts per million and with respect to Me_4Si.

Table IV. Infrared Absorption of the C2 and C4 Carbonyl Groups of 5-(*p*-Substituted-phenyl)-2′-deoxyuridines 3–15[a]

compd	X	C2=O[b]	C4=O[b]	σ
3	$N(CH_3)_2$	1697.6	1654.7[c]	−0.83
4	NH_2	1697.6	1657.6[c]	−0.66
5	OH	1699.5	1653.2[c]	−0.37
6	OCH_3	1713.0	1662.8	−0.27
7	$OCH_2C_6H_5$	1697.6	1676.4[c]	−0.23
8	CH_3	1711.1	1660.9	−0.17
9	H	1713.0	1662.8	0.00
10	Br	1711.1	1664.8	0.23
11	$CONH_2$	1699.5	1653.2	0.36
12	CO_2CH_3	1714.9	1653.2	0.45
13	CF_3	1718.8	1660.9	0.54
14	CN	1718.8	1660.9	0.66
15	NO_2	1716.9	1662.8	0.78

[a] All samples were examined as potassium bromide pressed disks. [b] Carbonyl stretching bands are reported in wavenumbers (cm^{-1}). [c] Center of broad or ill-defined band.

Table V. Apparent Ionization Constants of N3 Protons of 5-(*p*-Substituted-phenyl)-2′-deoxyuridines[a]

compd	X	pK_a	σ
3	$N(CH_3)_2$	9.39	−0.83
4	NH_2	9.47	−0.66
7	$OCH_2C_6H_5$	9.38	−0.23
8	CH_3	9.27	−0.17
9	H	9.25	0.00
14	CN	9.01	0.66

[a] Ionization constants were determined by spectrophotometric methods.[10] The ionic strength of the buffers was 0.5.

biphenyl study and our aryl nucleoside study. The data revealed that there are little similarities between aryl nucleosides and biphenyls. Carbons 5 and 6 on the heterocyclic ring are similar to aromatic carbons in that the electronic properties of the substituents have effects on C5 and C6 of 2,4-dioxopyrimidine which are similar to the effects observed on C1′ and C2′ of biphenyl. These are indicated by the same sign of the slopes observed for C1′ and C2′ with those of C5 and C6, respectively (Table VI, entries 1, 2 and 4, 5). However, C6 of the heterocycle rather than C5, was observed to be more sensitive to the electronic effects of the substituents as indicated by the greater range of chemical shifts for the C6 carbon atom. The reverse is true for the C1′ and C2′ carbons of the biphenyl compounds.

The lack of similarities of the ^{13}C data of C4 and C2 carbons of the heterocycle with those of C2′ and C4′ of biphenyl (Table VII, entries 6, 7 and 2, 3) is an indication that the C4 and C2 carbons of N1-substituted 2,4-dioxopyrimidines are no longer in conjugation with the substituents, and the resonance contribution of the substituents is drastically reduced. In this case, the decrease in correlation between the ^{13}C chemical shifts of the C4 and C2 carbon atoms and Hammett σ values would be expected, since the σ values are a combination of inductive and resonance effects. A qualitative analysis of the data however, was possible. A plot of the chemical shifts of the C2 and C4 carbon atoms with σ values resulted in negative slopes for both plots. This is unexpected since a negative slope indicates that changing from electron-donating to electron-withdrawing groups, a shielding effect or increase in electron density is observed. If it is assumed that the resonance contribution of the substituents is no longer a factor, then it is possible to view the substituents purely in terms of inductive effects. Thus, in going from a less electron-attracting substituent (i.e., NH_2) to a more electron attracting substituent (i.e., NO_2), the carbonyl bond length is reduced at C2 and C4, resulting in a shielding effect on the ^{13}C NMR signals of the carbons. A comparison of the ^{13}C NMR chemical shift of the carbonyl carbon of 1-chloro-2-propanone (Charton "inductive" substituent constant, σ_I of Cl = 0.44,[15] δ 200.1[16]) and 2-butanone (σ_I of CH_3 = −0.04,[15] δ 208.7[16]) revealed a similar effect. The compensating interaction of oxygens O2 and O4 with carbons C2 and C4 resulting in local electronic effects may be another factor for the decrease in correlation between the ^{13}C chemical shifts of C2 and C4 carbon atoms and σ values.

Attempts to determine a quantitative relationship between IR carbonyl shifts and σ constants were less successful. Again, the Hammett σ values may not be the appropriate descriptors, due to the decreased resonance contribution of the substituents. However, qualitative analyses were informative. The C2 carbonyl bands of the nucleosides studied covered a range of 21.2 cm^{-1}. A plot of C2 carbonyl shifts and σ values resulted in a positive slope (Table VI). With the inductive contribution as the major electronic effect, a more electron attracting substituent (i.e., NO_2) would reduce the length of the C=O bond, thus increase its force constant and the frequency of absorption. A similar effect was not observed for the C4 carbonyl, where essentially only two carbonyl shift values (1653 and 1662 cm^{-1}) were observed. This is not an unusual observation since the direct through-space inductive effect or field effect has proven in many cases to be predominant over the σ-inductive effect.[15] This trend also was observed in the ^{17}O NMR studies of 5-substituted

(14) Schulman, E. M.; Christensen, K. A.; Grant, D. M.; Walling, C. *J. Org. Chem.* **1974**, *39*, 2686–2690.

(15) Topsom, R. D. In *Progress in Physical Organic Chemistry*; Taft, R. W., Ed.; Wiley-Interscience: New York, 1976; Vol. 12, pp 1–20.

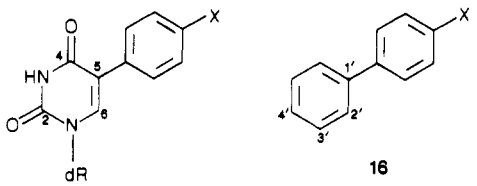
(16) *The Sadtler Standard Spectra*; Sadtler Research Laboratories: Philadelphia, 1976; 1074c.

Table VI. Plot of Physical Measurements vs. Hammett σ Constants in a Series of 5-(p-Substituted-phenyl)-2′-deoxyuridines[a]

measurement	slope	intercept	n^b	r^c	s^d
N3-H ^{1}H NMR chem shift, ppm	0.224	11.43	10	0.987	0.017
C6-H ^{1}H NMR chem shift, ppm	0.383	8.19	12	0.993	0.022
C6-C ^{13}C NMR chem shift, ppm	3.303	137.71	12	0.994	0.173
C5-C ^{13}C NMR chem shift, ppm	−2.099	112.90	12	0.970	0.253
C4-C ^{13}C NMR chem shift, ppm	−0.432	162.08	12	0.913	0.093
C2-C ^{13}C NMR chem shift, ppm	−0.138	149.84	12	0.724	0.063
C2 carbonyl IR stretching frequency, cm^{-1}	14.38	1709	11[e]	0.834	4.74
N3-H apparent ionization constants	−0.356	9.25	6	0.984	0.032

[a] The data for the plots are found in Tables I–V. The dimethylamino derivative 3 was excluded from these determinations. [b] n = number of data points. [c] r = correlation coefficient. [d] s = standard deviation. [e] The amide, compound 11, was excluded from this determination.

Table VII. Comparison of ^{13}C NMR Data of 5-(p-Substituted-phenyl)-2′-deoxyuridines and 4-Substituted Biphenyls 16



16

entry	position	range of chem shifts, ppm[a]	slope from plots of chem shifts vs. σ
1	1′	2.81	−
2	2′	1.52	+
3	4′	3.11	+
4	5	3.17	−
5	6	5.08	+
6	4	0.67	−
7	2	0.25	−

[a] The range was determined by subtracting the chemical shift of the nitro-substituted compound from the amino-substituted compound.

2,4-dioxopyrimidines, where a larger chemical shift range was observed for the O2 than the O4 oxygen.[3] From the IR study, it can be inferred that less electron-attracting substituents result in higher electron density at O2. It should be noted that the IR data indicate that the electronic properties of the substituents have a greater effect on the C2 than the C4 carbonyl. Yet in the ^{13}C NMR study, a greater range of chemical shifts was observed for the C4 than the C2 carbon.

A high correlation was observed for the ^{1}H chemical shifts of the N3 proton and the apparent ionization constant for that proton. A comparison of the K_a values with those of N3-H chemical shifts gave a correlation coefficient of 0.969 (eq 1).

$$K_a\ (\times 10^9) = 4.78\ (\text{N3-H chemical shift}) + 6.14 \quad (1)$$

$$n = 6,\ r = 0.969,\ s = 0.640$$

The regression equation comparing K_as and N3-H chemical shifts could be useful for estimating the ionization constants of the nucleosides in this series. A correlation of the apparent ionization constants with σ values also was obtained. The results of the plot of pK_a vs. σ constants are shown in Table VI. As expected, electron-withdrawing groups decrease pK_a values.

There is some uncertainty regarding the electronic structure of the 2,4-dioxopyrimidine ring. As noted, Tarpley and Goldstein,[1] using a limited number of 5-substituted heterocycles, were able to correlate the ^{13}C chemical shifts with substituent electronegativity (E_X). However, Ellis and co-workers[2] could not correlate their larger set of NMR data directly with E_X and rationalized the data in terms of the ability of the substituent to behave as a mesomeric acceptor or donor. In contrast, Chandrasekaran and co-workers[3] using ^{17}O NMR analysis, showed good correlation between chemical shifts of the O2 oxygen and Hammett σ values. In addition, good correlation of the ^{17}O NMR shifts of para-substituted anisoles with the O2 oxygen of 5-substituted 2,4-dioxopyrimidines was observed. The authors suggested that these results support the contention that considerable interaction between the 5-substituent and the O2 oxygen atom exists and compares with substituent effects noted for the benzene ring system. The chemical shift data for the O4 oxygen, which is in an ortho-type relationship to the 5-substituent, did not give as good a correlation with σ values. Nevertheless, qualitatively the same type of general trend noted for O2 oxygen was observed. The results from the ^{17}O NMR studies indicate that previous conclusions regarding the electronic structure of 2,4-dioxopyrimidine should be revised since there was considerable interaction between the 5-substituents and both O2 and O4 oxygen atoms.[3]

Conclusions

In the present study, we have utilized spectroscopic data to analyze the interaction between the substituent and the N1-substituted 2,4-dioxopyrimidines. In contrast to a previous ^{13}C NMR study, good correlations of ^{13}C chemical shifts of the C5 and C6 carbon atoms with substituent electronic properties (as defined by Hammett σ values) were observed. In support of the conclusions from the ^{17}O NMR study, good correlations of the N3-H chemical shifts and apparent ionization constants with σ values indicate a significant degree of orbital overlap and interaction between the substituent and the ring. Correlations of the C2 and C4 ^{13}C chemical shifts and infrared carbonyl bands with σ constants were less successful. However, the data were readily analyzed qualitatively. The results indicate that there is considerable interaction between the 5-substituent and the heterocycle. However, it is doubtful that the interactions between the substituent and the ring are comparable to those of a benzene ring system, as suggested by Chandrasekaran and co-workers.[3] This is further indicated by the lack of similarities between the ^{13}C NMR data of these models and 4-substituted biphenyls. However, the presence of quantitative and qualitative relationships between physical/spectral data and σ constants permits the use of the former to analyze the electron distribution of N1-substituted 2,4-dioxopyrimidines.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were determined at 80 MHz on a Varian FT80A Spectrometer in 99.9% Me_2SO-d_6. The Me_2SO-d_6 furnished the internal lock while the 0.1% Me_2SO was used for a chemical shift reference; the proton chemical shifts for the sugar portion of these molecules did not vary significantly and are not reported. ^{13}C NMR were determined at 75.43 MHz, using a Varian XL300 spectrometer.

Infrared (IR) spectra were determined on an IBM IR-32 with Fourier transform capabilities. All samples were examined as potassium bromide pressed disks. UV spectra were determined with a Cary Model 219 recording spectrophotometer. Microanalyses were obtained from a Hewlett-Packard 185B and mass spectra from a Reibermag GC-MS instrument.

3′,5′-Di-*O*-acetyl-5-(chloromercurio)-2′-deoxyuridine (2). To a solution of 2′-deoxyuridine (2.0 g, 8.7 mmol) in 30 mL of pyridine was added 8 mL (85 mmol) of acetic anhydride. After the mixture was stirred under an inert atmosphere at room temperature for 12 h, the solvents were evaporated under vacuum. The residue was dissolved in 20 mL of methanol and 100 mL of water. A solution (100 mL) of mercuric acetate (4.6 g, 14.4 mmol) was added, followed by stirring at 60 °C for 12 h. After the mixture was cooled, a 200-mL aqueous solution of sodium chloride (2.8 g, 48 mmol) was added. The reaction was filtered after 4 h, and the precipitate was washed with 0.1 N NaCl solution, water, ethanol, and finally ether to give 4.25 g (90% yield) of **2**.

Anal. Calcd for $C_{13}H_{15}N_2O_7HgCl$: C, 28.53; H, 2.76; N, 5.12. Found: C, 28.90; H, 3.08; N, 5.30.

General Coupling Procedure: 5-Phenyl-2′-deoxyuridine (9). The general procedure used in the preparation of 5-aryl-2′-deoxyuridines **6**–**15** was the following, which describes the preparation of **9**. A solution containing tetrakis(triphenylphosphine)palladium(0) (311 mg, 0.27 mmol) and iodobenzene (51 mg, 0.25 mmol) in 4 mL of tetrahydrofuran was stirred at room temperature for 15 min. This solution was added to a suspension of 3′,5′-di-*O*-acetyl-5-(chloromercurio)-2′-deoxyuridine (**2**, 110 mg, 0.20 mmol) in 10 mL of diglyme. The mixture was heated to 120 °C for 12 h under an inert atmosphere. After cooling to 25 °C, the black suspension was filtered through Celite. The Celite pad was washed with 20 mL of methanol, and the combined organic layers were evaporated to give a viscous brown residue. This was dissolved in 40 mL of methanol partially saturated with ammonia and stirred at 25 °C for 12 h to remove the acetyl-protecting groups. Separation of the mixture on silica gel was accomplished by eluting with 20% ethanol in dichloromethane to give a 58% yield of **9**: mp 192.5–194 °C (methanol) [lit.[6] mp 193–194.5 °C]. The ultraviolet, mass spectra, elemental analysis, and ^1H NMR spectra of compound **9** matched the reported values.[6]

5-(*p*-Methoxyphenyl)-2′-deoxyuridine (6): 62% yield; mp 172–174 °C (methanol); UV (H_2O) λ_{max} 287 nm (ϵ 9400), λ_{min} 267 nm (ϵ 7600), (0.1 N HCl) λ_{max} 287 nm (ϵ 9500), λ_{min} 267 nm (ϵ 7700), (0.1 N NaOH) λ_{max} 278 nm (ϵ 9400), λ_{min} 272 nm (ϵ 9300); ^1H NMR (Me_2SO) 11.37 (br s, 1 H, N3-H), 8.09 (s, 1 H, C6-H), 7.49 (d, 2 H, J = 8.7 Hz, Ar), 6.92 (d, 2 H, J = 8.7 Hz, Ar), 6.24 (t, 1 H, J = 6.6 Hz, C1′-H), 3.77 ppm (s, 3 H, OCH_3); EIMS, m/e (relative intensity) 334 (M^+, 1.6), 218 (5-(*p*-methoxyphenyl)uracil, 100), 188 (20), 175 (13), 117 (2′-deoxyribose, 17).

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.48; H, 5.49; N, 8.40.

5-[*p*-(Benzyloxy)phenyl]-2′-deoxyuridine (7): 65% yield; mp 210–211.5 °C (methanol); UV (H_2O) λ_{max} 286 nm (ϵ 10 100), λ_{min} 269 nm (ϵ 8500), (0.1 N HCl) λ_{max} 286 nm (ϵ 10 100), λ_{min} 269 nm (ϵ 8500), (0.1 N NaOH) λ_{max} 279 nm (ϵ 10 200); ^1H NMR (Me_2SO) 11.42 (s, 1 H, N3-H), 8.10 (s, 1 H, C6-H), 7.55–6.95 (m, 9 H, Ar), 6.25 (t, 1 H, J = 6.6 Hz, C1′-H), 5.12 ppm (s, 2 H, OCH_2Ar); EIMS, m/e (relative intensity) 410 (M^+, 0.2), 294 (5-[*p*-(benzyloxy)phenyl]uracil, 13), 117 (2′-deoxyribose, 5.8).

Anal. Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.10; H, 5.40; N, 6.81.

5-(*p*-Methylphenyl)-2′-deoxyuridine (8): 55% yield; mp 197.5–198 °C (methanol); UV (H_2O) λ_{max} 283 nm (ϵ 10 100), λ_{min} 263 nm (ϵ 7700), (0.1 N HCl) λ_{max} 283 nm (ϵ 10 300), λ_{min} 263 nm (ϵ 8000), (0.1 N NaOH) λ_{max} 274 nm (ϵ 9700); ^1H NMR (Me_2SO) 11.39 (br s, 1 H, N3-H), 8.13 (s, 1 H, C6-H), 7.45 (d, 2 H, J = 8.2 Hz, Ar), 7.16 (d, 2 H, J = 8.2 Hz, Ar), 6.24 (t, 1 H, J = 6.6 Hz, C1′-H), 2.31 ppm (s, 3 H, CH_3); EIMS, m/e (relative intensity) 318 (M^+, 1.6), 202 (5-*p*-methylphenyl)uracil, 100), 156 (18), 117 (2′-deoxyribose, 15).

Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.10; H, 5.50; N, 8.90.

5-(*p*-Bromophenyl)-2′-deoxyuridine (10): 42% yield; mp 195–197 °C (methanol); UV (H_2O) λ_{max} 283 nm (ϵ 12 000), λ_{min} 265 nm (ϵ 9900), (0.1 N HCl) λ_{max} 283 nm (ϵ 12 000), λ_{min} 265 nm (ϵ 9900), (0.1 N NaOH) λ_{max} 276 nm (ϵ 11 600); ^1H NMR (Me_2SO) 11.48 (br s, 1 H, N3-H), 8.26 (s, 1 H, C6-H), 7.54 (s, 4 H, Ar), 6.22 ppm (t, 1 H, J = 6.6 Hz, C1′-H); EIMS, m/e (relative intensity) 382/384 (M^+, 1/1, 0.6), 266/268 (5-(*p*-bromophenyl)uracil, 60), 222/224 (13), 117 (2′-deoxyribose, 64).

Anal. Calcd for $C_{15}H_{15}N_2O_5Br$: C, 47.02; H, 3.95; N, 7.31. Found, C, 47.40; H, 4.30; N, 7.20.

5-[*p*-(Aminocarbonyl)phenyl]-2′-deoxyuridine (11): 45% yield; mp >230 °C (methanol); UV (H_2O) λ_{max} 286 nm (ϵ 16 300), λ_{min} 233 nm (ϵ 6900), (0.1 N HCl) λ_{max} 286 nm (ϵ 16 500), λ_{min} 233 nm (ϵ 6900), (0.1 N NaOH) λ_{max} 286 nm (ϵ 15 300), λ_{min} 242 nm (ϵ 8600); ^1H NMR (Me_2SO) 11.50 (br s, 1 H, N3-H), 8.29 (s, 1 H, C6-H), 7.87 (d, 2 H, J = 8.4 Hz, Ar), 7.63 (d, 2 H, J = 8.4 Hz, Ar), 7.29 (br s, 2 H, $CONH_2$), 6.23 ppm (t, 1 H, J = 6.6 Hz, C1′-H); CIMS (2-methylpropane), m/e (relative intensity) 348 (M^+ + 1, 1.2), 232 (5-[*p*-(aminocarbonyl)phenyl]uracil, 26), 117 (2′-deoxyribose, 74).

Anal. Calcd for $C_{16}H_{17}N_3O_6$: C, 55.33; H, 4.93; N, 12.10. Found: C, 55.38; H, 5.00; N, 12.06.

5-[*p*-(Methoxycarbonyl)phenyl]-2′-deoxyuridine (12). Compound **12** was obtained from 600 mg (1.10 mmol) of **2**, 1.0 g (0.87 mmol) of tetrakis(triphenylphosphine)palladium(0), and 580 mg (2.21 mmol) of methyl *p*-iodobenzoate by using the general procedure described for the preparation of **9**. The deoxyribose was deacetylated by stirring in anhydrous methanolic HCl for 12 h. The solution then was made basic with methanolic ammonia and concentrated under vacuum. The ammonium chloride salt was removed by adding tetrahydrofuran to the residue and filtering the precipitate. The filtrate was chromatographed on silica gel (20% ethanol in dichloromethane) to give 207 mg (52% yield) of compound **12**: mp >230 °C (methanol); UV (H_2O) λ_{max} 289 nm (ϵ 17 700), λ_{min} 237 nm (ϵ 6400), (0.1 N HCl) λ_{max} 289 nm (ϵ 17 900), λ_{min} 237 nm (ϵ 6800), (0.1 N NaOH) λ_{max} 284 nm (ϵ 14 900), λ_{min} 243 nm (ϵ 9100); ^1H NMR (Me_2SO) 11.53 (s, 1 H, N3-H), 8.40 (s, 1 H, C6-H), 7.96 (d, 2 H, J = 8.4 Hz, Ar), 7.74 (d, 2 H, J = 8.4 Hz, Ar), 6.23 (t, 1 H, J = 6.6 Hz, C1′-H), 3.86 ppm (s, 3 H, CO_2CH_3); CIMS (NH_3), m/e (relative intensity) 363 (M^+ + 1, 4.5), 247 (5-[*p*-(methoxycarbonyl)phenyl]uracil, 100), 215 (12), 117 (2′-deoxyribose, 49).

Anal. Calcd for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 5.01; N, 7.73. Found: C, 56.30; H, 5.20; N, 7.80.

5-[*p*-(Trifluoromethyl)phenyl]-2′-deoxyuridine (13): 53% yield; mp >215 °C (methanol); UV (H_2O) λ_{max} 281 nm (ϵ 11 900), λ_{min} 261 nm (ϵ 9500), (0.1 N HCl) λ_{max} 281 nm (ϵ 11 900), λ_{min} 261 nm (ϵ 9500), (0.1 N NaOH) λ_{max} 276 nm (ϵ 11 100), λ_{min} 271 nm (ϵ 11 000); ^1H NMR (Me_2SO) 8.39 (s, 1 H, C6-H), 7.83 (d, 2 H, J = 9 Hz, Ar), 7.69 (d, 2 H, J = 9 Hz, Ar), 6.23 ppm (t, 1 H, J = 6.6 Hz, C1′-H); CIMS (NH_3), m/e (relative intensity) 373 (M^+ + 1, 13), 256 (5-[*p*-(trifluoromethyl)phenyl]uracil, 56), 212 (10), 117 (2′-deoxyribose, 100).

Anal. Calcd for $C_{16}H_{15}N_2O_5F_3$: C, 51.62; H, 4.06; N, 7.52. Found: C, 51.60; H, 4.24; N, 7.48.

5-(*p*-Cyanophenyl)-2′-deoxyuridine (14): 55% yield; mp >250 °C (methanol); UV (H_2O) λ_{max} 287 nm (ϵ 18 100), λ_{min} 236 nm (ϵ 6300), (0.1 N HCl) λ_{max} 287 nm (ϵ 18 500), λ_{min} 236 nm (ϵ 6600), (0.1 N NaOH) λ_{max} 289 nm (ϵ 16 400), λ_{min} 244 nm (ϵ 7800); ^1H NMR (Me_2SO) 11.57 (br s, 1 H, N3-H), 8.41 (s, 1 H, C6-H), 7.80 (s, 4 H, Ar), 6.22 ppm (t, 1 H, J = 6.6 Hz, C1′-H); IR (KBr) 2234 cm^{-1} (CN stretching); EIMS, m/e (relative intensity) 329 (M^+, 5.9), 213 (5-(*p*-cyanophenyl)uracil, 22), 169 (19), 117 (2′-deoxyribose, 36).

Anal. Calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76. Found: C, 58.49; H, 4.65; N, 12.60.

5-(*p*-Nitrophenyl)-2′-deoxyuridine (15): 45% yield; mp >250 °C (methanol); UV (H_2O) λ_{max} 315 nm (ϵ 13 400), λ_{min} 248 nm (ϵ 4500), (0.1 N HCl) λ_{max} 315 nm (ϵ 13 600), λ_{min} 248 nm (ϵ 4900), (0.1 N NaOH) λ_{max} 335 nm (ϵ 11 300), 273 (7600), λ_{min} 291 nm (ϵ 6800), 256 (6900); ^1H NMR (Me_2SO) 11.61 (br s, 1 H, N3-H), 8.51 (s, 1 H, C6-H), 8.22 (d, 2 H, J = 9 Hz, Ar), 7.89 (d, 2 H, J = 9 Hz, Ar), 6.22 ppm (t, 1 H, J = 6.6 Hz, C1′-H); CIMS (NH_3), m/e (relative intensity) 350 (M^+ + 1, 28), 233 (5-(*p*-nitrophenyl)uracil, 10), 117 (2′-deoxyribose, 30).

Anal. Calcd for $C_{15}H_{15}N_3O_7$: C, 51.58; H, 4.33; N, 12.03. Found: C, 51.50; H, 4.39; N, 11.90.

5-[*p*-(*N*,*N*-Dimethylamino)phenyl]-2′-deoxyuridine (3). 5-(*p*-Nitrophenyl)-2′-deoxyuridine (**15**, 184 mg, 0.53 mmol) was dissolved in 50 mL of hot methanolic tetrahydrofuran. Upon

cooling to room temperature, 0.5 mL of concentrated HCl and 205 mg of 10% palladium on carbon were added. After shaking under 50 psi of hydrogen, the reaction mixture was filtered through Celite, and the filtrate was evaporated under vacuum. The residue was dissolved in 40 mL of 50:1 acetonitrile–methanol. To this solution was added 2 mL (27 mmol) of 37% aqueous formaldehyde and 120 mg (1.91 mmol) of sodium cyanoborohydride. After 15 min of being stirred, the solution was neutralized with glacial acetic acid. The resulting mixture was allowed to stir for 12 h. The sodium cyanoborohydride was quenched with aqueous methanol–ammonia. Chromatography (SiO_2, 10% ethanol–dichloromethane) afforded 166 mg (90% yield) of **3**: UV (H_2O) λ_{max} ~305 nm (ϵ ~7700), 260 (16600), λ_{min} 231 nm (ϵ 7400), (0.1 N HCl) λ_{max} 279 nm (ϵ 10700), λ_{min} 260 nm (ϵ 8300), (0.1 N NaOH) λ_{max} ~295 nm (ϵ ~9300), 263 (16400), λ_{min} 237 nm (ϵ 11200); ^1H NMR (Me_2SO) 11.31 (s, 1 H, N3-H), 8.00 (s, 1 H, C6-H), 7.40 (d, 2 H, J = 8.7 Hz, Ar), 6.71 (d, 2 H, J = 8.7 Hz, Ar), 6.24 (t, 1 H, J = 6.6 Hz, C1'-H), 2.90 ppm (s, 6 H, $N(CH_3)_2$); EIMS, m/e (relative intensity) 347 (M^+, 6.6), 231 (5-[*p*-(*N*,*N*-dimethylamino)-phenyl]uracil, 100), 188 (11), 160 (19), 117 (2'-deoxyribose, 4.0).

Anal. Calcd for $C_{21}H_{25}N_3O_7 \cdot H_2O$ (3',5'-di-*O*-acetyl derivative of **3**): C, 56.12; H, 6.06; N, 9.35. Found: C, 56.20; H, 5.99; N, 9.30.

5-(*p*-Aminophenyl)-2'-deoxyuridine (4). 5-(*p*-Nitrophenyl)-2'-deoxyuridine (**15**, 81 mg, 0.23 mmol) was dissolved in 50 mL of warm ethanol. Upon cooling to room temperature, 0.5 mL of concentrated HCl and 100 mg of 10% palladium on carbon were added. After shaking under 50 psi of hydrogen for 12 h, the mixture was filtered through Celite, and the filtrate was concentrated under vacuum. An aliquot of methanolic–ammonia solution was added to convert the amine salt to the free base. Chromatography (SiO_2, 10% ethanol–dichloromethane) afforded 80 mg (98% yield) of **4**: UV (H_2O) λ_{max} 295 nm (ϵ 8100), 252 (15600), λ_{min} 283 nm (ϵ 7700), 235 (7700), (0.1 N HCl) λ_{max} 280 nm (ϵ 10300), λ_{min} 261 nm (ϵ 7600), (0.1 N NaOH) λ_{max} ~286 nm (ϵ ~8800), 253 (15000), λ_{min} 234 nm (ϵ 13000); ^1H NMR (Me_2SO) 11.26 (s, 1 H, N3-H), 7.94 (s, 1 H, C6-H), 7.22 (d, 2 H, J = 8.4 Hz, Ar), 6.54 (d, 2 H, J = 8.4 Hz, Ar), 6.23 ppm (t, 1 H, J = 6.6 Hz, C1'-H); EIMS, m/e (relative intensity) 319 (M^+, 3.0), 203 (5-(*p*-aminophenyl)uracil, 100), 160 (21), 132 (28), 117 (2'-deoxyribose, 23).

Anal. Calcd for $C_{15}H_{17}N_3O_5 \cdot 0.5EtOH$: C, 56.13; H, 5.89; N, 12.27. Found: C, 55.90; H, 5.86; N, 12.05.

5-(*p*-Hydroxyphenyl)-2'-deoxyuridine (5). 5-[*p*-(Benzyloxy)phenyl]-2'-deoxyuridine (**7**, 53 mg, 0.13 mmol) was dissolved in 50 mL of warm ethanol. Upon cooling to room temperature, 120 mg of 10% palladium on carbon was added. After shaking under 45 psi of hydrogen for 18 h, the mixture was filtered through Celite. Chromatography (SiO_2, 10% ethanol–dichloromethane) of the filtrate afforded 40 mg (97% yield) of **5**: mp 189–191 °C (methanol); UV (H_2O) λ_{max} 287 nm (ϵ 7700), λ_{min} 267 nm (ϵ 6300), (0.1 N HCl) λ_{max} 287 nm (ϵ 8000), λ_{min} 267 nm (ϵ 6500), (0.1 N NaOH) λ_{max} 292 nm (ϵ 8000); ^1H NMR (Me_2SO) 8.03 (s, 1 H, C6-H), 7.36 (d, 2 H, J = 8.4 Hz, Ar), 6.75 (d, 2 H, J = 8.4 Hz, Ar), 6.23 ppm (t, 1 H, J = 6.6 Hz, C1'-H); CIMS (NH_3), m/e (relative intensity) 321 (M^+ + 1, 3.6), 204 (5-(*p*-hydroxyphenyl)uracil, 100), 160 (8.8), 117 (2'-deoxyuridine, 30).

Anal. Calcd for $C_{15}H_{16}N_2O_6 \cdot H_2O$: C, 53.25; N, 8.28; H, 5.36. Found: C, 53.60; N, 8.10; H, 5.10.

pK_a Determination. The ionization constants were determined by ultraviolet spectrophotometry.[10] Phosphate solutions from potassium phosphate monobasic and dibasic provided buffers in the pH range of 6.0–8.0. Borate solutions from sodium borate, provided the buffers in the pH range of 8.5–10.5. The ionic strength was 0.5.

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Registry No. **1**, 951-78-0; **2**, 92510-77-5; **3**, 108664-86-4; **4**, 108664-87-5; **5**, 108664-88-6; **6**, 89647-11-0; **7**, 108664-89-7; **8**, 92510-80-0; **9**, 76756-28-0; **10**, 108664-90-0; **11**, 108664-91-1; **12**, 108664-92-2; **13**, 108664-93-3; **14**, 92524-53-3; **15**, 108664-94-4; PhI, 591-50-4; IC_6H_4-*p*-COOMe, 619-44-3.

New Iptycenes Using 2,3-Naphtho[*b*]triptycene[1] as a Synthon

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A new synthesis of the triptycene **1** (5,14-[1',2']benzeno-5,14-dihydropentacene) is described. Cycloaddition of endoxide **8** to diene **6** gave exo adduct **9**, which was successively dehydrated and dehydrogenated to give **1** in three steps and 47% overall yield. Cycloadducts **11–13** were obtained from **1** and tetracyanoethylene, dimethyl acetylenedicarboxylate, or maleic anhydride, respectively. Irradiation of **1** through Pyrex gave photodimer **26**. Pentiptycenes **16** and **18** were obtained in two steps using **1** as a synthon. Cycloaddition of 1,4-dichloro-2-butene to **1**, followed by dehydrohalogenation, gave diene **21**, which was then used as a synthon for functionalized pentiptycenes **22** and **25**. Finally, the new route to **1** was extended to the first synthesis of its naphthacene analogue **30**.

We recently summarized some of the ways in which the triptycene[2] framework can be elaborated to form iptycenes,[3] extended triptycenes that contain more than three aryl planes due to the presence of more than one bicyclo[2.2.2]octyl moiety.[4] The rigid framework, high thermal stability, and in the case of higher iptycenes, the cavities that lead to host–guest complexes[5] add interest to these structures.

In this paper we describe a new route to 2,3-naphthotriptycene **1** and make use of the anthracene moiety in **1** to construct several pentiptycenes. Certain products of these syntheses, or intermediates en route to them, are

(1) *Chemical Abstracts* nomenclature is 5,14-[1',2']benzeno-5,14-dihydropentacene.

(2) For a review of triptycene chemistry, see: Skvarchenko, V. R.; Shalaev, V. K.; Klabunovskii, E. I. *Russ. Chem. Rev. (Engl. Transl.)* **1974**, *43*, 951.

(3) Hart, H.; Bashir-Hashemi, A.; Luo, J.; Meador, M. A. *Tetrahedron* **1986**, *42*, 1641.

(4) Hart, H.; Shamouilian, S.; Takehira, Y. *J. Org. Chem.* **1981**, *46*, 4427.

(5) Bashir-Hashemi, A.; Hart, H.; Ward, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 6675.

0022-3263/87/1952-3631$01.50/0