2-Acetyl-4-bromofuran Diethyl Ketal.—To a stirred solution of 2-acetyl-4-bromofuran (50.0 g) in 50 ml of absolute ethanol was added triethyl orthoformate (75.0 g) and 25 ml of a 9% (w/w) solution of dry hydrochloric acid in absolute ethanol. The reaction mixture was stirred at room temperature for 24 hr and, after it was neutralized with sodium ethoxide, the mixture was distilled to 85° to remove excess ethanol and ethyl formate. The residual dark liquid was distilled under reduced pressure. A forerun of triethyl orthoformate was collected and 63.0 g (90%) of 2-acetyl-4-bromofuran diethyl ketal was obtained as a colorless liquid: bp 119° (16 mm); bp 95° (3 mm); ir (CCl_4) 3155 (w), 2994 (s), 1370 (m), 1271 (s), 901 (s), 860 (s), 691 cm^{-1} (m) nmr (CCl_4) δ 1.13 (t, 6, J_{CH_3,CH_2} = 7 Hz, CH_2CH_3), 1.54 (s, 3, $=CCH_3$), 3.32 (dq, 4, CH_2), 6.34 (d, 1, $J_{3,5}$ = 0.9 Hz, 3-H), 7.40 (d, 1, 5-H).

2-(5-Acetyl-3-furyl)-2-propanol.—In a nitrogen-swept flask, immersed in an acetone–Dry Ice bath, was placed a solution of 2-acetyl-4-bromofuran diethyl ketal (26.3 g, 0.1 mol) in 250 ml of anhydrous ether. A precooled hexane solution of *n*-butyllithium (62.2 ml, 0.1 mol) was added over a period of 30 min. After the addition was complete the mixture was stirred at −78° for 1 hr and then 15 ml of acetone was added. The reaction mixture was stirred for 3 hr at −78° and for 2 hr at room temperature. The contents of the flask were poured into cold water and the mixture was extracted with ether. The ethereal solution was transferred to a flask, the ether was removed on a rotary evaporator, and the residual oil was hydrolyzed with 150 ml of water containing 3 ml of 3 *N* hydrochloric acid, at room temperature for 2 hr. The reaction mixture was extracted with ether. The ethereal solution was washed with 5% sodium bicarbonate and water, dried over anhydrous magnesium sulfate, and filtered. After removal of the ether on a rotary evaporator, 11.5 g (68%) of crude 2-(5-acetyl-3-furyl)-2-propanol remained as a pale yellow oil: ir (CCl_4) 3436 (broad), 2976 (m), 1681 (s), 1504 (m), 909 cm^{-1} (s); nmr (CCl_4) δ 1.46 (s, 6, CH_3), 2.34 (s, 3, $COCH_3$), 3.63 (s, 1, OH), 7.04 (d, 1, $J_{3,4}$ = 0.7 Hz, 4-H), 7.38 (d, 1, 2-H).

2-(5-Acetyl-3-furyl)-2-propyl *p*-nitrobenzoate (**5**) was prepared directly from the crude alcohol and *p*-nitrobenzoyl chloride using the pyridine method.[3] After two recrystallizations from ether–hexane, 2-(5-acetyl-3-furyl)-2-propyl *p*-nitrobenzoate was obtained as very pale yellow crystals: mp 108°; ir ($CHCl_3$) 3012 (w), 1725 (s), 1678 (s), 1613 (m), 1524 (s), 1279 cm^{-1} (s); nmr ($CDCl_3$) δ 1.94 (s, 6, CH_3), 2.48 (s, 3, $COCH_3$), 7.28 (d, 1, 3-H), 7.65 (d, 1, 5-H), 8.22 (d, 4, phenyl H).

Anal. Calcd for $C_{16}H_{15}NO_6$: C, 60.56; H, 4.76; N, 4.42. Found: C, 60.42; H, 4.69; N, 4.27.

Kinetic Methods.—Most of the kinetic procedures have been described previously.[3] Some of the individual experiments with **3** and **4** were carried out by measuring the kinetics at controlled pH, using a Radiometer Titrator (TTTlc), Autoburette (Type ABUlc), and a Titrigraph (Type SBR2c) maintaining the pH at 7.5. Additional kinetic data are recorded in Table IV.

TABLE IV

RATE CONSTANTS UNDER VARIOUS CONDITIONS

Compd	Temp, °C	Solvent	k, sec^{-1}
4	45.00	80% EtOH	4.49×10^{-3} [a]
	45.00	70% Dioxane	1.02×10^{-3}
5	75.00	80% EtOH	7.61×10^{-4}
	25.00	80% EtOH	1.36×10^{-6} [b]

[a] $\Delta H^{\ddagger}$ = 20.9 kcal; $\Delta S^{\ddagger}$ = −3.7 eu. [b] Extrapolated assuming $\Delta S^{\ddagger}$ = −4.0 eu.

Registry No.—**1**, 34878-28-9; **2**, 34878-29-0; **3**, 34878-30-3; **4**, 34878-31-4; **5**, 34878-32-5; 1-(5-ethyl-3-furyl)ethanol, 34878-33-6; 2-methyl-4-bromofuran, 24666-43-1; 2-(5-methyl-3-furyl)-2-propanol, 34878-35-8; 2-acetyl-4-bromofuran diethyl ketal, 34878-36-9; 2-(5-acetyl-3-furyl)-2-propanol, 34878-37-0.

Notes

Transmission of Substituent Effects in Heterocyclic Systems. The Application of Molecular Orbital Parameters to the Solvolysis of 4-Substituted 1-(2-Furyl)ethyl Systems[1]

DONALD S. NOYCE* AND HERNAN J. PAVEZ[2]

Department of Chemistry, University of California at Berkeley, Berkeley, California 94720

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Recent studies from these laboratories[3–5] have shown that advanced molecular orbital calculations employing all-valence electron methods, such as CNDO/2 and INDO, provide a very useful foundation and framework for interpretation of substituent effects in heterocyclic systems.

It was shown[4] that equally good correlations were obtained for the rates of solvolysis of substituted 1-(2-thienyl)ethyl *p*-nitrobenzoates, using either Brown's electrophilic substituent constants[6] or substituent constants determined from CNDO/2 parameters incorporated in a modified Dewar–Grisdale equation. For 1-(3-furyl)ethanol derivatives only the substituent constants derived by the modified Dewar–Grisdale equation adequately accounted for the observed rates of solvolysis,[5] while for 5-substituted 1-(2-furyl)ethyl derivatives, excellent correlations are obtained with both σ^+ constants and CNDO/2 parameters. The modified Dewar–Grisdale approach is also particularly adaptable to predictions for other systems. It is the purpose of the present note to examine 1-(4-X-2-furyl)-ethanol derivatives in this context.

The equation (1) first proposed by Nichols[7] leads naturally to the predictions presented below.

$$\sigma_{ij}{}^{+} = F^{+}/r + \Delta q M^{+} \qquad (1)$$

In eq 1, an electrophilic substituent constant, $\sigma_{ij}{}^{+}$, is determined for a substituent at a position i in a heterocyclic ring system, with reference to position j as

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[1] Supported in part by a grant from the National Science Foundation, GP-6133X.

[2] Graduate Fellow on the California–Chile Cooperative Exchange Program, from funds provided by the Ford Foundation, 1966–1970.

[3] D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).

[4] D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *J. Org. Chem.*, **37**, 2615 (1972).

[5] D. S. Noyce and H. J. Pavez, *J. Org. Chem.*, **37**, 2620 (1972).

[6] H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

[7] R. W. Nichols, Ph.D. Dissertation, University of California, 1970.

Table I

Substituent Constants in Heterocyclic Systems

Heterocyclic system	Substitution pattern[a]	r	Δq CNDO/2	Δq INDO	% ℛ Calcd[b]	Typical substituent constants CH$_3$	SCH$_3$	Br	COOEt
Thiophene	5, 2	1.768	0.2051		66	−0.305		0.207	0.515
	4, 2	1.672	0.0395		33			0.416	0.382
Furan	5, 2	1.571	0.2763			−0.407	−0.803	0.182	0.617
				0.2726	66	−0.401	−0.783	0.187	0.621
	5, 3	1.605	0.1076			−0.169	−0.115		
				0.1150	49	−0.177	−0.150		
	4, 2	1.605	0.0642			−0.101	0.063	0.408	0.419
				0.0696	39	−0.114	0.047	0.404	0.423
Benzene	3, 1	1.732	0.0368	0.0353	30	−0.069[c]	0.158	0.405	0.366
	4, 1	2.00	0.2115	0.2109	65	−0.311[d]	−0.604	0.150	0.482

[a] First number is substituent position; second number is side chain position. [b] *Cf.* footnote 10. [c] By definition $\sigma_m{}^+$. [d] By definition. $\sigma_p{}^+$.

Table II

Rates of Solvolysis of 4-Substituted 1-(2-Furyl)ethyl *p*-Nitrobenzoates

Registry no.	Compd, 4 X	k, sec^{-1} (45.0°)	Log k, rel	Predicted relative rates A[a]	B[b]	C[c]
18743-95-8	X = -H	1.30×10^{-4}	0.00	(0.0)	(0.0)	(0.0)
34858-73-6	X = -SCH$_3$	3.59×10^{-5}	−0.558	−1.264	−0.359	−0.268
18743-97-0	X = -Br	8.21×10^{-7}	−2.199	−3.443	−2.326	−2.303
18743-98-1	X = -COOEt	1.46×10^{-7} [d]	−2.949	−3.011	−2.338	−2.411

[a] Using $\sigma_m{}^+$ constants for 4 substituents, $\rho = -8.5$ (ref 3). [b] Using CNDO/2 $\sigma_{ij}{}^+$ constants as given in Table I; $\rho = -5.7$, as determined in ref 4. [c] Using INDO $\sigma_{ij}{}^+$ constants, $\rho = -5.7$. [d] Extrapolated from data at higher temperatures.

the locand of a reactive side chain, by the parameters F^+ and M^+ derived for that substituent from Brown's $\sigma_m{}^+$ and $\sigma_p{}^+$, and CNDO/2 (or INDO) determined regional charges, Δq,[8,9] for benzene.

From substituent constants thus determined,[10] it is also possible to determine the balance of resonance and field effects, % ℛ and % ℱ, by relating these substituent constants to the Swain and Lupton treatment.[11] Relevant terms are presented in Table I.

It is to be noted that for the furan system, both the 3–5 relationship and the 2–4 relationship are suggested to show a larger response to the resonance capabilities of substituents than $\sigma_m{}^+$. This expectation was tested and found to be true for the 3–5 relationship in our previous paper.[5] Indications that this expectation shows up in the 2–4 relationship appear in limited data reported previously from these laboratories,[3] involving bromo and carboethoxy substituents.

To provide further data on this situation, we have synthesized and measured the rate of solvolysis of 1-(4-methylthio-2-furyl)ethyl *p*-nitrobenzoate (**1**). This ester solvolyzes somewhat more slowly than the parent 1-(2-furyl)ethyl *p*-nitrobenzoate. Table II presents these data, along with previous rates, and includes the expected rates on the basis of some other predications.

Column 3 in Table II gives the expected rates based on the use of $\sigma_m{}^+$ substituent constants, and the ρ of −8.5 as determined by Noyce and Kaiser. The match is relatively poor; in particular it is to be noted that $\sigma_m{}^+$ for -Br and -COOEt predict a relative rate sequence inverted from that observed. Further, the predicted rate for -SMe is much too slow. The situation is much improved using $\sigma_{ij}{}^+$ constants determined by either CNDO/2 or INDO calculations. The average deviation between calculated and observed rates is substantially reduced. The substituents now fall in the correct order.

Thus, these data show that the determination of electrophilic substituent constants by reference to CNDO/2 or INDO parameters in conjunction with a modified Dewar–Grisdale equation provides a much more satisfactory fit between observed and predicted rates of solvolysis. It suggests that this approach is a generally preferable one.

Experimental Section[12]

4-Methylthio-2-acetylfuran.—In a nitrogen-swept flask, immersed in an acetone–Dry Ice bath, was placed a solution of 2-acetyl-4-bromofuran diethyl ketal[5] (18.8 g, 0.0715 mol) in 250 ml of anhydrous ether. To the well-stirred ethereal solution was added a precooled hexane solution of *n*-butyllithium (44.5 ml, 0.0715 mol) over a period of 30 min. After the addition was over the mixture was stirred at −78° for 1 hr and then dimethyl disulfide (6.735 g, 0.0715 mol) was added. The Dry Ice bath was removed and the reaction mixture was stirred for an additional 6 hr. The contents of the flask were poured into cold water and the mixture was extracted with ether. The ethereal solution was extracted with 20% sodium hydroxide and washed with water, and the ether was removed on a rotary evaporator. The residual oil was treated with 150 ml of water and 5 ml of 3 *N* hydrochloric acid, and the heterogeneous mixture was stirred and refluxed for 30 min. The reaction mixture was cooled, diluted with 150 ml of water, and extracted with ether. The ethereal solution was washed with 5% sodium bicarbonate and water, dried over anhydrous magnesium sulfate, and filtered. The ether was removed on a rotary evaporator and the residual liquid was distilled under reduced pressure. 4-Methylthio-2-acetylfuran (7.9 g, 71%) was obtained as a pale yellow oil, bp

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[8] Regional charge: the sum of the charges on a carbon atom and on any hydrogen atoms bonded to it. A. Streitwieser, Jr., and R. G. Jesaitis in "Sigma Molecular Orbital Theory," O. Sinanoglu and K. B. Wiberg, Ed., Yale University Press, New Haven, Conn., 1970, p 197.

[9] A more complete description of this derivation is given in ref 4.

[10] For a set of typical substituents: $-OCH_3$, $-CH_3$, $-C_2H_5$, -Cl, -Br, -H, $-CO_2Et$, -CN, $-CF_3$, and NO_2.

[11] C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

[12] Melting points and boiling points are uncorrected. Nmr spectra were obtained using a Varian T-60 spectrometer. Analyses are by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

125° (5 mm), which solidified on standing: nmr (CCl_4) δ 2.41 and 2.42 (2 singlets, 3 each, $-SCH_3$ and $COCH_3$), 7.08 (d, 1, 3-H), 7.40 (d, 1, $J_{3,5}$ = 0.9 Hz, 5-H).

Anal. Calcd for $C_7H_8O_2S$: C, 53.82; H, 5.16; S, 20.53. Found: C, 53.66; H, 5.26; S, 20.37.

1-(4-Methylthio-2-furyl)ethanol.—To a stirred solution of 4-methylthio-2-acetylfuran (7.81 g, 0.05 mol) in 75 ml of anhydrous methanol, placed in an ice water bath, was added sodium borohydride (1.41 g, 0.0374 mol) at a rate such that the temperature was kept below 20°. The mixture was stirred for 5 hr and worked up in the usual fashion to give 7.7 g (97%) of 1-(4-methylthio-2-furyl)ethanol as a pale yellow liquid: nmr (CCl_4) δ 1.40 (d, 3, CH_3), 2.27 (s, 3, SCH_3), δ 3.60 (s, 1, OH), 4.64 (q, 1, $J_{CH_3,H}$ = 6.5 Hz, CHOH), 6.11 (d, 1, 3-H), 7.13 (d, 1, $J_{3,5}$ = 0.9 Hz, 5-H).

1-(4-Methylthio-2-furyl)ethyl *p*-nitrobenzoate (1) was prepared from 1-(4-methylthio-2-furyl)ethanol (7.60 g, 0.048 mol) in 50 ml of pyridine, cooled in an ice water bath, and *p*-nitrobenzoyl chloride (8.907 g, 0.048 mol). After work-up in the usual fashion, 1-(4-methylthio-2-furyl)ethyl *p*-nitrobenzoate (8.0 g, 54%) was obtained as yellow crystals from hexane: mp 46°; nmr ($CDCl_3$) δ 1.80 (d, 3, $J_{CH_3,H}$ = 6.5 Hz, CH_3), 2.42 (s, 3, SCH_3), 6.26 (q, 1, CHOPNB), 6.53 (d, 1, $J_{3,5}$ = 0.85 Hz, 3-H), 7.38 (d, 1, 5-H).

Anal. Calcd for $C_{14}H_{13}NO_5S$: C, 54.71; H, 4.26; N, 4.56; S, 10.43. Found: C, 54.46; H, 4.08; N, 4.32; S, 10.28.

Kinetic Procedures.—Kinetic procedures have been described previously.[3-5]

Registry No.—4-Methylthio-2-acetylfuran, 934-64-5; 1-(4-methylthio-2-furyl)ethanol, 34858-77-0.

The Reaction of Some Acyclic α,β-Unsaturated Ketone Systems with *N*-Bromosuccinimide

D. V. C. Awang* and A. Vincent

Department of National Health and Welfare,
Tunney's Pasture, Ottawa, Ontario, Canada K1A OL2

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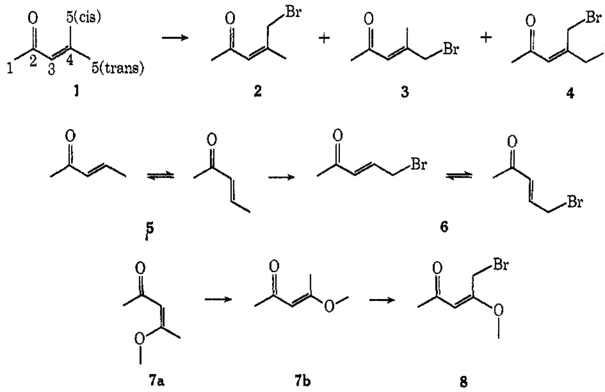
A preliminary communication by Buu-Hoi[1] in 1946 reported that mesityl oxide and 3-penten-2-one underwent bromination by *N*-bromosuccinimide (NBS) to give α-bromo ketones rather than allyl bromides; the unstable products of reaction were characterized purely on the basis of gross chemical reactivity such as ease of reaction with primary aromatic amines. These results were regarded with reservation by Djerassi,[2] who noted the possibility of allylic rearrangement of the primary products of reaction: *initial* formation of α-bromo ketones from acyclic α,β-unsaturated ketones would have belied experience to date, which indicated that substitution allylic to the olefinic bond was the general rule for cyclic systems. Later, the work of DePuy and coworkers[3] established unequivocally that 4-bromo-2-cyclopentenone was the exclusive product of reaction of 2-cyclopentenone with NBS under radical-promoting conditions.

Recent investigations of possible synthetic routes to models of the tetracycline A and B rings[4] have demonstrated that selective substitution allylic to the olefinic bond is achieved by similar bromination of cyclohex-2-enones and 3-methoxycyclohex-2-enones. It was noted also that the liquid 4-bromo-2-cyclohexenone slowly isomerized to roughly a 1:1 mixture of 6-bromo and 4-bromo ketones. In order to determine the effect of the greater conformational freedom of acyclic α,β-unsaturated ketones upon the pattern of bromine substitution and on the tendency of bromination products toward allylic rearrangement, mesityl oxide (**1**), 3-penten-2-one (**5**), and the methyl enol ethers (**7**) of acetylacetone[5] were brominated using NBS (Scheme I),

Scheme I



and the products were subjected to detailed nmr spectroscopic analysis.

No product of bromine substitution α to carbonyl could be detected from the reaction of any of these four substrates, bromination allylic to the olefinic bond being the exclusive mode of substitution. *No evidence of allylic rearrangement could be perceived in the case of these acyclic allylic bromides.* All products of bromination are obviously predominantly in the s-cis conformation.

Assignment of both configuration and conformation was possible from a consideration of either benzene-induced solvent shifts (Table I) or $Eu(thd)_3$[6]-induced chemical shift data applying the carbonyl-plane rule in the former case[5] and assuming complexation at carbonyl oxygen in the latter.[7]

Mesityl oxide (**1**) reacted with 1 molar equiv of NBS to yield a mixture of approximately equal proportions of the isomeric allylic monobromides **2** and **3** (36 and 44%,[8] respectively), contaminated with an appreciable amount of the allylic dibromide **4** (20%[8]); **1** was readily and quantitatively converted to **4** by reaction with 2 molar equiv of NBS. Table II gives Δ_{Eu} values for **2**–**8**.

It is evident that the relative percentage of **2** and **3** represent an equilibrium ratio. The product mixture could be separated by thin layer chromatography (tlc) into three distinct bands corresponding to **2**, **3**, and **4**. However, isomerization of **2** and **3** was so rapid that the fractions obtained by elution of the chromatograms were invariably mixtures of the two compounds, although significantly enriched in the respective isomers (approximately 75 and 40%[8] of **3**). The equilibrium

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(1) N. P. Buu-Hoi, *Experientia*, **2**, 310 (1946).

(2) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

(3) C. H. DePuy, M. Isaks, K. L. Eilers, and G. F. Morris, *J. Org. Chem.*, **29**, 3503 (1964); C. H. DePuy, C. E. Lyons, and L. B. Rodewald, *J. Chem. Eng. Data*, **11**, 102 (1966).

(4) D. V. C. Awang, A. Vincent, W. L. Wilson, and H. W. Avdovich, *Can. J. Chem.*, **50**, 104 (1972).

(5) D. V. C. Awang, *ibid.*, **49**, 2672 (1971).

(6) Tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium(III), also referred to as tris(dipivalomethanato)europium(III), $Eu(DPM)_3$.

(7) H. Hart and G. M. Love, *Tetrahedron Lett.*, 625 (1971)

(8) Determined by integration of the areas of nmr signal peaks.