with its tetrahedral intermediate, which has a constant NH_2 group.

A comparison of ψ values for sets 3, 11, 31, and 35 shows that the effect of solvent on the ψ value for the basic hydrolysis of alkyl acetates is small.

At the suggestion of a referee, we have examined the correlation of data for the alkaline hydrolysis of ZCO_2X in 40% aqueous dioxane at 35 °C with the equation

$$\log k = \psi_1 \upsilon_Z + \psi_2 \upsilon_{OX} + h \quad (12)$$

The data used were a combination of set 3 from Table I and set 5 from ref 4. The results of the correlation with eq 12 are: multiple correlation coefficient, 0.995; F test for significance of regression, 64.30 (99.9% CL); s_{est}, 0.0609; s_{ψ_1}, 0.0805 (99.9% CL); s_{ψ_2}, 0.0741 (00.0% CL); s_h, 0.0822 (99.9% CL); partial correlation coefficient of υ_Z on υ_{OX}, 0.479 (90.0% CL); ψ_1, −2.06; ψ_2, −2.54; h, 3.23; number of points in set, 15; range in log k, 2.27. Thus, the rates of hydrolysis of esters substituted in both the acyl and alkoxy moieties can be successfully treated by means of eq 12.

The success of this work in evaluating υ_{OX} constants which are on the same scale as, and can therefore be used in the same correlation as, υ constants for alkyl, halogen, haloalkyl, oxyalkyl, and other groups is not yet completely established. We hope to demonstrate in future work that the υ_{OX} values reported here are indeed applicable to data sets containing a mixture of substituent types.

Supplementary Material Available: the results of the correlations with eq 7 and 8 and values of σ_I and σ_R for OR groups and complete statistics for the correlations of the data in Table I with eq 10 (5 pages). Ordering information is given on any current masthead page.

Registry No.—Acetic acid, 64-19-7; 4-nitrobenzoyl chloride, 122-04-3.

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Steric Effects. 10. Substituents at Nitrogen in Carbonyl Compounds

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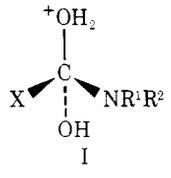
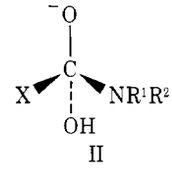
Twelve sets of carbonyl addition reactions including rate constants for acidic and basic hydrolysis of N-substituted amides, rate constants for the reaction of methyl acetate with alkylamines, and rate constants for the reaction of piperonal with alkylamines were correlated with the modified Taft equation using $\upsilon_{CHX^1X^2}$ constants; 16 sets of data were correlated with $\upsilon_{NX^1X^2}$ constants. Very good results were obtained. The $\upsilon_{NX^1X^2}$ constants were defined in this work. Eighteen values of $\upsilon_{NX^{12}}$ are given. The results verify the validity and generality of the equation $\upsilon_{Z_1X^1X^2} = \upsilon_{Z_2X^1X^2} + c$. The variation of ψ with structure is discussed for a variety of acid-catalyzed and base-catalyzed hydrolyses of carbonyl derivatives.

In the preceding paper of this series,[1] steric substituent constants were developed for alkoxy groups. These constants were applicable to addition reactions of carbonyl compounds. In this work we consider the application of the techniques we have developed to the definition of steric substituent constants for alkylamino and dialkylamino substituents. Let us consider substituent effects upon rates of acid and alkaline hydrolysis of N-substituted amides. The tetrahedral intermediates involved in the acid and alkaline hydrolysis are I and II, respectively. The X group represents a constant substituent; the NR^1R^2 group varies. We have shown that the electrical effects of alkyl groups in base-catalyzed ester hydrolysis reactions are constant,[2] as are electrical effects of alkoxy groups.[1] It seems likely that the electrical effects of alkylamino and dialkylamino groups are also constant in addition reactions of the carbonyl group. In support of this contention, the σ_m and σ_p substituent constants of NHX groups are given by the equations[3]



I



II

$$\sigma_{m\text{-NHX}} = 1.11\,\sigma_{m\text{-X}} - 0.187 \quad (1)$$

$$\sigma_{p\text{-NHX}} = 1.33\,\sigma_{m\text{-X}} - 0.476 \quad (2)$$

According to Taft

$$\sigma_{INHX} = (3\,\sigma_{m\text{-NHX}} - \sigma_{p\text{-NHX}})/2 \quad (3)$$

and

$$\sigma_{RNHX} = \sigma_{p\text{-NHX}} - \sigma_{INHX} \quad (4)$$

From eq 1, 2, and 3

$$\sigma_{INHX} = (3.33\,\sigma_{m\text{-X}} - 0.561 - 1.33\sigma_{m\text{-X}} + 0.476)/2 \quad (5)$$

$$= (2\sigma_{m=X} - 0.085)/2 = \sigma_{m\text{-X}} - 0.043 \quad (6)$$

Now, according to Taft,[4]

$$\sigma_{m\text{-X}} = \sigma_{IX} + \sigma_{RX}/3 \quad (7)$$

We are interested in the case in which X is alkyl. For values of σ_I and σ_R for alkyl groups, see the paragraph at the end of this paper. The average value of σ_I is −0.01 ± 0.02. Since the error in the σ_I values is probably 0.05, we conclude that σ_I values for alkyl groups are constant. Examination of the σ_R values for alkyl groups shows that they average 0.16 ± 0.03; the error in σ_R is not less than 0.05; therefore these values are again constant. Then from eq 7, σ_m for alkyl groups is con-

Table I. Data Used in the Correlations

1. *kr*, AcNHX + H_3O^+ in H_2O at 65 °C[a]
   Me, 2.23; Et, 1.40; Pr, 1.14; *i*-Pr, 0.437; Bu, 1.12; *i*-Bu, 0.808; *s*-Bu, 0.261; *i*-$PrCH_2CH_2$, 1.44; $BuCH_2CH_2$, 1.12; c-C_6H_{11}, 0.472; $PhCH_2$, 1.28
2. *kr*, AcNHX + H_3O^+ in H_2O at 75 °C[a]
   Me, 5.74; Et, 3.83; Pr, 2.82; *i*-Pr, 1.11; Bu, 2.98; *i*-Bu, 2.09; *s*-Bu, 0.684; *i*-$PrCH_2CH_2$, 2.84; $BuCH_2CH_2$, 2.78; c-C_6H_{11}, 1.24; $PhCH_2$, 3.17
3. *kr*, AcNHX + H_3O^+ in H_2O at 85 °C[a]
   Me, 13.0; Et, 9.53; Pr, 6.77; *i*-Pr, 2.84; Bu, 6.93; *i*-$PrCH_2CH_2$, 6.72; $BuCH_2CH_2$, 6.53; c-C_6H_{11}, 2.98; $PhCH_2$, 7.61
4. *kr*, AcNHX + H_3O^+ in H_2O at 95 °C[a]
   Me, 26.3; Et, 21.2; Pr, 15.3; *i*-Pr, 6.71; Bu, 14.8; *i*-Bu, 10.8; *s*-Bu, 3.96; *i*-$PrCH_2CH_2$, 15.0; $BuCH_2CH_2$, 14.9; c-C_6H_{11}, 7.59; $PhCH_2$, 19.3
5. *kr*, $AcNX^1X^2$ + H_3O^+ in 1.0 N aq HCl at 75 °C[b]
   H, H, 511; Me, H, 25.5; Et, H, 14.0; Ph, H, 11.9; *i*-Pr, H, 5.40; Bu, H, 10.1; *i*-Bu, H, 8.09; Me_2, 22.6; Me, Et, 6.10; Et_2, 1.36; Pr_2, 0.68
6. *kr*, AcNHX + H_3O^+ in 1.0 N aq HCl at 80 °C[b]
   Et, 22.2; Pr, 17.2; Bu, 15.6; *i*-Bu, 11.3
7. *kr*, AcNHX + H_3O^+ in 1.0 N aq HCl at 85 °C[b]
   Me, 59.0; Et, 32.7; Pr, 23.2; Bu, 24.1; *i*-Bu, 17.5
9. *kr*, AcNHX + OH^- in 1.0 N aq NaOH at 60 °C[b]
   Me, 6.78; Et, 3.83; Pr, 2.24
10. *kr*, AcNHX + OH^- in 1.0 N aq NaOH at 65 °C[b]
    Me, 10.1; Et, 5.42; Pr, 3.37; *i*-Pr, 1.05; Bu, 2.83
11. *kr*, $AcNX^1X^2$ + OH^- in 1.0 N aq NaOH at 70 °C[b]
    Et, H, 7.72; Pr, H, 4.50; Bu, H, 3.58; Me, Et, 4.25; Et_2, 0.51
12. *kr*, $AcNX^1X^2$ + OH^- in 1.0 N aq NaOH at 75 °C[b]
    H, H, 112; Me, H, 21.5; Et, H, 10.8; Pr, H, 6.62; *i*-Pr, H, 2.20; Bu, H, 6.17; *i*-Bu, H, 3.85; Me_2, 31.1; Me, Et, 5.90; Et_2, 0.70; Pr_2, 0.40
14. *kr*, $AcNX^1X^2$ + OH^- in 1.0 N aq NaOH at 85 °C[b]
    Me, Et, 1.12; Et_2, 1.49; Pr_2, 0.75
15. *kr*, $AcNX^1X^2$ + OH^- in 1.0 N aq NaOH at 90 °C[b]
    Me, Et, 15.0; Et_2, 2.12; Pr_2, 0.87
16. 10^4kr, MeOAc + XNH_2 in dioxane 5 M in $(CH_2OH)_2$[c]
    Me, 853; Et, 111; Bu, 106; $BuCH_2$, 98.7; Pr, 87.9; *i*-Bu, 43.5; *i*-Pr, 4.22; *s*-Bu, 2.27
17. 10^2kr, piperonal + XNH_2 in MeOH at 0.00 °C[d]
    Me, 1.92; Et, 0.952; Pr, 1.04; *i*-Pr, 0.267; Bu, 1.15; *i*-Bu, 1.13; *s*-Bu, 0.292; *t*-Bu, 0.0267
18. 10^2kr, piperonal + XNH_2 in MeOH at 24.97 °C[d]
    Me, 5.55; Et, 2.88; Pr, 3.15; *i*-Pr, 0.895; Bu, 3.37; *i*-Bu, 3.16; *s*-Bu, 0.940; *t*-Bu, 0.115
19. 10^2kr, piperonal + XNH_2 in MeOH at 45.00 °C[d]
    Me, 11.4; Et, 6.00; Pr, 6.40; *i*-Pr, 1.98; Bu, 6.83; *i*-Bu, 6.23; *s*-Bu, 2.00; *t*-Bu, 0.299

[a] P. D. Bolton, J. Ellis, R. D. Frier, and P. C. Nancarrow, *Aust. J. Chem.*, **25**, 303 (1972). [b] T. Yamana, Y. Mizukami, A. Tsuji, Y. Tasuda, and K. Masuda, *Chem. Pharm. Bull.*, **20**, 881 (1972). [c] E. M. Arnett, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **72**, 5635 (1950). [d] R. I. Hill and T. I. Crowell, *J. Am. Chem. Soc.*, **78**, 2284 (1956).

Table II. Values of $\upsilon_{NX^1X^2}$

NX^1X^2	$\upsilon_{NX^1X^2}$	Set[a]	NX^1X^2	$\upsilon_{NX^1X^2}$	Set[a]
NHMe	0.39	*b*	NEt_2	1.37	5
NHEt	0.59	5	NPr_2	1.60	5
NHPr	0.64	5	NH-*s*-Bu	1.12	2
NH-*i*-Pr	0.91	5	$NHCH_2CH_2$-*i*-Pr	0.65	2
NHBu	0.70	5	$NHCH_2CH_2Bu$	0.66	2
NH-*i*-Bu	0.77	5	NH-c-C_6H_{11}	0.92	2
NMe_2	0.43	5	$NHCH_2Ph$	0.62	2
NMeEt	0.87	5	N-*i*-Pr_2	2.01	14
$NHCH_2Bu$	0.64	16	NH-*t*-Bu	1.83	19

[a] Set from which $\upsilon_{NX^1X^2}$ was calculated. [b] By definition.

Table III. Values of ψ, h, and $100r^2$ Obtained from Correlation with Equation 11

Set	$-\psi$	h	$100r^2$	Set	$-\psi$	h	$100r^2$
1	1.37	0.952	97.0	11	1.37	1.63	92.0
2	1.34	1.33	94.5	12A	1.50	1.90	94.5
3	1.30	1.68	95.8	14	1.63	2.45	99.6
4	1.21	1.97	96.6	15	1.69	2.65	100.
6	1.54	2.24	96.8	16	3.69	4.35	94.7
7	1.37	2.30	96.6	17	1.31	0.854	94.7
9	1.73	1.52	90.4	18	1.19	1.25	95.3
10	1.92	1.79	98.4	19	1.12	1.52	84.0

stant. It follows then, for eq 6, that σ_{INHX} is constant. From eq 2 we conclude that $\sigma_{p\text{-}NHX}$ is constant, and therefore from eq 4 that σ_{RNHX} is constant. Thus, the electrical effects of alkylamino groups are independent of the nature of the alkyl group. As to the electrical effect of dialkylamino groups as compared with alkylamino groups, we would expect them to behave in a similar manner. The evidence for this is more tenuous, however. A number of successful correlations have been reported in which the value $\sigma_I = 0.10$ has been used for both MHMe and NMe_2.[5] Using the σ_p values given by McDaniel and Brown[6] σ_R values of −0.94 and −0.93 are obtained for NHMe and $NHMe_2$. Thus, at least in the case of the dimethylamino group the electrical effects are comparable to those of alkylamino groups.

The arguments we have presented for the constancy of the electrical effects of alkylamino and dialkylamino groups lead to the inexorable conclusion that the only effect of these substituents on carbonyl addition reactions will be steric.

In order to correlate data for carbonyl addition reactions involving variable NR^1R^2 groups, steric substituent constants for these groups are required. Such constants are not available. We have shown, however,[1] that a substituent may be written in the form ZX, where Z joins X and the skeletal group to which X is attached. Then, for two sets of substituents, one with constant Z_1 and the other with constant Z_2, the equation

$$\upsilon_{Z_1X} = \upsilon_{Z_2X} + c \tag{8}$$

is obeyed, where the υ values are steric substituent constants. We propose to extend this equation to

$$\upsilon_{Z_1X^1X^2} = \upsilon_{Z_2X^1X^2} + c \tag{9}$$

where $Z_1 = N$, $Z_2 = CH$.

Thus, rate data for sets of carbonyl addition reactions involving variable NR^1R^2 groups have been correlated with the modified Taft equation in the form[1]

$$\log k_{NX^1X^2} = \upsilon_{CHX^1X^2} + h' \tag{10}$$

The data used in the correlations are set forth in Table I. The values required are from our previous work.[7] For results of the correlations with eq 10, see the paragraph at the end of this paper. Sets 6, 7, 9, 14, and 15 were excluded from the correlations because the substituents in these sets have at most only two significantly different υ_{CH_2R} values.

The results for set 5 were considerably improved by the exclusion of the value for X^1X^2 = H, H (set 5A). The further exclusion of the value for $X^1X^2 = Me_2$ improved the results somewhat. The results for set 12 were not significantly improved by exclusion of the value for X^1X^2 = H, H (set 12A). Further exclusion of the value for $X^1X^2 = Me_2$ gives better results (set 12B).

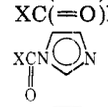
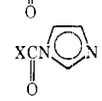
Of the 12 sets correlated with eq 10, ten sets gave excellent

Table IV. Correlations of $\upsilon_{NX^1X^2}$ with $\upsilon_{CHX^1X^2}$ [a]

Set	m	c	r	F	s_{est}	s_m	s_c	n
A	1.21	−0.218	0.918	80.82	0.164	0.134	0.127	17
B	1.05	−0.107	0.943	112.3	0.112	0.0991	0.0905	16
C	1.03	−0.0691	0.964	169.3	0.0887	0.0789	0.0728	15

[a] All correlations were significant at the 99.9% confidence level (CL).

Table V. Comparison of ψ Values

Substrate	Reagent	T, °C	ψ	υ^k	Source
MeC(=O)NHX	H_3O^+	75	−1.34	0.52	*a*
MeC(=O)NX^{1}X^2	H_3O^+	75	−1.30	0.52	*b*
MeC(=O)NX^{1}X^2	OH^-	75	−1.50	0.52	*c*
MeC(=O)OX	OH^-	30	−2.61	0.52	*d*
HC(=O)OX	OH^-	35	−1.40	0	*e*
XC(=O)NH$_2$	OH^-	75	−1.87	0.32	*f*
XC(=O)NH$_2$	H_3O^+	75	−2.07	0.32	*g*
	H_3O^+	30	−1.53	0.71[l]	*h*
	OH^-	30	−1.50	0.71[l]	*i*
XC(=O)NHOH	H_3O^+	50.5	−2.16	0.48[m]	*j*

All reactions were studied in water. [a] This work, set 2. [b] This work, by definition. [c] This work, set 12A. [d] Reference 1, set 35. [e] Reference 1, set 20. [f] Reference 8, set 7. [g] Reference 8, set 4A. [h] Reference 8, set 12A. [i] Reference 8, set 27A. [j] Reference 8, set 28A. [k] υ of constant substituent in substrate. [l] υ for c-C_5H_9. [m] Calculated from $\upsilon_{NX^1X^2} = 1.03, \upsilon_{CHX^1X^2} = 0.0691$.

(>99.5% CL), one gave good (97.5% CL), and one gave fair correlation (95.0% CL). Thus the validity of eq 9 is again substantiated. Our results now make it possible to define υ constants for alkylamino groups. As was the case in our previous definition of υ_{OX} groups, we are interested in defining $\upsilon_{NX^2X^2}$ groups which can be used together with the other υ values we have previously calculated in order to make possible the application of the modified Taft equation to sets containing a wide range of substituent type. It is therefore vital that the $\upsilon_{NX^1X^2}$ values be on the same scale as our other υ constants. Otherwise, the $\upsilon_{NX^1X^2}$ constants would only be applicable to sets in which the sole substituent type is NX^1X^2. In order to do this we must choose a reference set. As a reference set we have chosen the rate constants for acidic hydrolysis of N-substituted amides in 1.0 N aqueous HCl at 75 °C (set 5). This set was chosen because it gave an excellent correlation with eq 10 and included a large number of substituents. A value of 0.39 was then assigned to the NHMe group. This value was obtained by means of the same type of argument we used in the previous work in this series[1] in assigning a value to the OMe group. Ideally, we would have liked to simply use the value $\upsilon_{NH_2} = 0.35$, but the rate constant for the NH_2 group does not fit the correlation obtained with eq 10. The value of ψ chosen for set 5 is the value obtained from correlation of set 5B with eq 10. In choosing this value for ψ we are putting the $\upsilon_{NX^1X^2}$ values on the same scale as the other υ values. This is shown by writing the modified Taft equation for the use of true $\upsilon_{NX^1X^2}$ values

$$\log k_{NX^1X^2} = \psi\upsilon_{NX^1X^2} + h \quad (11)$$

and then writing eq 9 for $\upsilon_{NX^1X^2}$ and $\upsilon_{CHX^1X^2}$

$$\upsilon_{NX^1X^2} = \upsilon_{CHX^1X^2} + c \quad (12)$$

Now substituting in eq 11, we obtain

$$\log k_{NX^1X^2} = \psi(\upsilon_{CHX^1X^2} + c) + h \quad (13)$$

$$= \psi\upsilon_{CHX^1X^2} + \psi c + h \quad (14)$$

which is equivalent to eq 10 with $h' = \psi c + h$

We may now obtain the equation for defining $\upsilon_{NX^1X^2}$ constants from set 5B.

$$\upsilon_{NX^1X^2} = -0.769 \log k_{NX^1X^2} + 1.47 \quad (15)$$

Values of $\upsilon_{NX^1X^2}$ obtained from set 5B and other sets are reported in Table II. Data for all sets other than set 5 were then correlated with eq 11. Values of ψ, h, and $100r^2$ (which represents the percent of the data accounted for by the correlation) are reported in Table III. For other statistics see the paragraph at the end of this paper. One set did not correlate. As the two sets which gave the poorest results had only three points, it is not surprising that good correlations were not obtained. Overall, the results are very good, and support the utility of the $\upsilon_{NX^1X^2}$ constants.

To verify eq 12, we have correlated the $\upsilon_{NX^1X^2}$ values with $\upsilon_{CHX^1X^2}$ values. The results of these correlations are set forth in Table IV. The equation used is

$$\upsilon_{NX^1X^2} = m\upsilon_{CHX^1X^2} + c \quad (16)$$

Set A includes all available $\upsilon_{NX^1X^2}$ values. The value for X^1X^2 = H, *t*-Bu is excluded from Set B. Further exclusion of the value $X^1X^2 = Me_2$ results in set C. All three sets give excellent correlation. Best results are obtained with set C, however. Furthermore, with set C the value of m obtained is not significantly different from the value of 1 predicted by eq 12. The results obtained support the validity of eq 12 and together with our previous results for OX groups support the generality of eq 9. It is now possible to estimate values of $\upsilon_{NX^1X^2}$ from values of $\upsilon_{CHX^1X^2}$.

It is of interest to compare the magnitude of the steric effect upon the basic hydrolysis of N-substituted amides with that upon the acidic hydrolysis of amides under similar reaction conditions. This can be done by comparing the ψ values for sets 5B and 12A. The values are −1.30 and −1.50, respectively. The application of the "Student's *t*" test shows that the two values are not significantly different. This is in accord with our findings for the hydrolysis of amides substituted in the acyl moiety.[8] By contrast, the hydrolysis of alkyl acetates and benzoates showed a distinct difference in steric effects between acid-catalyzed and base-catalyzed reactions,[1] as did the hydrolysis of esters substituted in the acyl moiety.[2,7]

We have also compared the magnitude of the steric effect for N-substituted amide hydrolysis with that for other carbonyl addition reactions under similar reaction conditions. Values of ψ are given in Table V. Although the values of ψ are at different temperatures, the results obtained in this work and previous work[1,8] suggest that this will not cause large differences in ψ. We had previously suggested that the ψ values might depend on the size of the constant substituent in the substrate. Plots of ψ values for acid-catalyzed hydrolyses and for base hydrolyses against the υ values of the constant substituent in the substrate show no discernable relationship between ψ and υ. The ψ values lie in the range −1.30 to −2.16 for acidic hydrolysis and −1.40 to −2.61 for basic hydrolysis. Possibly, the value of ψ will depend on the extent to which the transition state resembles the tetrahedral intermediate. Further data are required before any conclusion can be reached.

At the suggestion of a referee we have examined the corre-

lation of data for the acid hydrolysis of ZCONHX in water at 75 °C with

$$\log k = \psi_1 \upsilon_Z + \psi_2 \upsilon_{NHX} + h \quad (17)$$

The data used were a combination of set 2 in Table I and set 4 of ref 8. Results of the correlation are: multiple correlation coefficient, 0.969; F test for significance of regression, 176.8 (99.9% CL); s_{est}, 0.126; s_{ψ_1}, 0.109 (99.9% CL); s_{ψ_2}, 0.128 (99.9% CL); s_h, 0.125 (99.9% CL); partial correlation coefficient of υ_Z on υ_{NHX}, 0.497 (98.0% CL); $\psi_1 = -1.93$; $\psi_2 = -1.82$; $h = 2.73$; number of points in the set, 26; range in log k, 1.84. The high confidence level for the correlation of υ_Z on υ_{NHX} indicates that the separation of steric effects is less than is desirable. It seems probable, however, that rates of hydrolysis of amides substituted in both the acyl and amino moieties can be successfully correlated by eq 17.

Supplementary Material Available. The results of the correlations with eq 10, values of σ_I and σ_R for alkyl groups, and complete statistics for the correlation of the data in Table I with eq 11 (3 pages). Ordering information is given on any current masthead page.

Registry No.—Methyl acetate, 79-20-9; piperonal, 120-57-0.

References and Notes

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(6) Footnote *b*, Table I.
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Chemistry of Nitrosoureas. Decomposition of 1,3-Bis(*threo*-3-chloro-2-butyl)-1-nitrosourea and 1,3-Bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea

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1,3-Bis(*threo*-3-chloro-2-butyl)-1-nitrosourea and 1,3-bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea were synthesized and decomposed in buffered water. The products were analyzed by GC and GC/MS. The stereochemistry of the product 3-chloro-2-butanols and 2-chloro-2-butenes indicates that a significant fraction of these products are formed via reactions of 3-chloro-2-butyldiazo hydroxide with S_N2 and E2 stereochemistry, as well as by S_N1 and El reactions involving the secondary 3-chloro-2-butyl carbonium ion. Since primary carbonium ions are higher energy species than secondary ones, we predict that the decomposition of the antitumor agent 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) to 2-chloroethanol and vinyl chloride occurs predominantly by way of S_N2 and E2 reactions of 2-chloroethyldiazo hydroxide and not by way of S_N1 and E1 reactions involving the primary 2-chloroethyl carbonium ion.

BCNU [1,3-bis(2-chloroethyl)-1-nitrosourea] is a useful agent for the treatment of certain malignant diseases. The major products of the decomposition of BCNU in buffered aqueous solution (pH 7.4) are vinyl chloride, acetaldehyde, 1,2-dichloroethane, and 2-chloroethanol.[1] Recently, we reported the synthesis and decomposition of specifically deuterated BCNUs.[2] The results excluded the intermediacy of diazochloroethane and the vinyl carbonium ion and were consistent with the intermediacy of the 2-chloroethyl carbonium ion. However, the results did not definitively distinguish between the S_N1–E1 path through the 2-chloroethyl carbonium ion and the S_N2–E2 path in which the various reactions and rearrangements occur concerted with the loss of nitrogen from the 2-chloroethyldiazo hydroxide. Because the decomposition of BCNU to 2-chloroethanol involves a primary carbon atom, there is no stereochemistry by which an S_N1 process could be distinguished from an S_N2 process. We report here the synthesis and decomposition of the substituted BCNU derivatives 1,3-bis(*threo*-3-chloro-2-butyl)-1-nitrosourea and 1,3-bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea in which there is stereochemistry to follow.

Chemistry. 1,3-Bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea (*erythro*-BCBNU, **5**) was synthesized as shown in Scheme I. 1,3-Bis(*threo*-3-chloro-2-butyl)-1-nitrosourea (*threo*-BCBNU) was synthesized by the same route, only starting from *cis*-2-butene. The unnitrosated ureas can exist as a mixture of a meso compound and a *dl* pair and the nitrosated ureas as a mixture of two *dl* pairs, but these facts do not affect any of the stereochemistry in this paper. The first three steps of the syntheses are known stereospecific reactions[3] and the last step does not involve making or breaking any bonds to carbon atoms. The remaining step, the reaction of dimethylaziridine with phosgene, is expected to go with one inversion by analogy with other aziridine ring openings.[4] This

Scheme I