Anal. Calcd. for $C_{31}H_{52}O_3S$: C, 73.76; H, 10.38; S, 6.33. Found: C, 73.45; H, 10.38; S, 6.16.

"β-Amyradiene-IV". A.—A solution of β-amyrin toluenesulfonate (530 mg.) in petroleum ether was chromatographed on alumina (Woelm, neutral, grade I). Elution with the same solvent gave a product (300 mg.) which crystallized from acetone to give "β-amyradiene-IV" as needles; m.p. 134–135°; $[\alpha]_D$ +157° (*c* 1.8); ν^{CS_2} 1650, 893 (vinylidene), and 730 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{48}$: C, 88.16; H, 11.84. Found: C, 88.00; H, 12.00.

Elution with chloroform gave β-amyrin (204 mg.), crystallized from chloroform–methanol as needles, m.p. and m.m.p. 194–195°, $[\alpha]_D$ +95°.

B.—In a similar experiment, β-amyrin methanesulfonate (300 mg.) gave 249 mg. of crude "β-amyradiene-IV" and 20 mg. of β-amyrin.

C.—In an experiment using Woelm basic alumina, the methanesulfonate (500 mg.) gave 300 mg. of "β-amyradiene-IV."

D.—A solution of β-amyrin methanesulfonate (650 mg.) in dry pyridine (7 ml.) was heated under reflux for 7 days and worked up as in the corresponding preparation (A) of "α-amyradiene-IV" to give "β-amyradiene-IV" as needles, m.p. 137–138°, $[\alpha]_D$ +152°, after three recrystallizations from acetone.

Separation of Constituents of "β-Amyradiene-IV."—"β-Amyradiene-IV" (90 mg.) was subjected to thin layer chromatography under the same conditions as applied to the separation of "α-amyradiene-IV." Again, two principal spots were detected. The fraction (R_f 0.37, 70 mg.) was crystallized from acetone as needles to give oleana-2,12-diene; m.p. 145–147°; $[\alpha]_D$ +136° (*c* 0.6); ν^{KBr} 1667, 730, and 725 cm.$^{-1}$; lit.[8] m.p. 150–153°, $[\alpha]_D$ +140°.

Anal. Calcd. for $C_{30}H_{48}$: C, 88.16; H, 11.84. Found: C, 88.10; H, 11.65.

The second fraction (R_f 0.15, 13 mg.) was crystallized from acetone to give β-amyradiene-IV as prismatic needles; m.p. 167–169°; $[\alpha]_D$ +167° (*c* 0.4); ν^{KBr} 1656 and 893 cm.$^{-1}$; n.m.r. signals (in CCl_4) at δ 5.17, 4.69, and 4.41, each with integrated intensity of one proton.

Anal. Calcd. for $C_{30}H_{48}$: C, 88.16; H, 11.84. Found: C, 88.36; H, 11.67.

Recrystallization of "β-amyradiene-IV" six times from acetone or three times from chloroform–methanol gave oleana-2,12-diene as needles, m.p. and m.m.p. 154–155°, $[\alpha]_D$ +145° (*c* 1.8).

Solvent Effects in Quantitative Structure–Reactivity Correlations of Esters

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Received March 23, 1964

The rates of alkaline hydrolysis of eight ethyl esters have been correlated by the extended Taft linear free-energy relationship in both 85% aqueous ethanol and 85% aqueous dimethyl sulfoxide. The solvent dependence of the polar, steric, and hyperconjugative resonance reaction constants are discussed in terms of differences in transition-state solvation mechanisms. An increased importance of steric interference with solvation of the activated complex in aqueous dimethyl sulfoxide relative to aqueous ethanol is suggested by the data.

The dependence of substituent effects upon reaction medium has attracted increasing attention over the past few years. Thus, Grunwald and Berkowitz[1] found the variation with solvent of the reaction constant ρ for the dissociation of *meta*- and *para*-substituted benzoic acids is given quantitatively as a linear function of the activity function *Y*. Fuchs and Nisbett[2] reported that ρ for the reaction of *para*-substituted α-chlorotoluenes with thiosulfate anion varies linearly with $1/D$ in a variety of organic solvents.

In a related study Ritchie and Lewis[3] demonstrated that the solvent dependence of substituent effects on the acidities of a series of 4-substituted bicyclo[2,2,2]-octane-1-carboxylic acids is attributed to factors other than direct interaction of substituent and reaction site.

Most recently Taft and co-workers[4] observed the effect of four specific solvent–substituent interactions based on extensive measurements of fluorine nuclear magnetic resonance shielding in the *meta*-substituted fluorobenzenes. Of particular interest to the present study, their data reveal a solvent interaction between dimethyl sulfoxide and ester functions based on solvent polarity but no definite evidence for a complex between an ester function and dimethyl sulfoxide.

Previously, it was reported[5] that the rate of alkaline hydrolysis of ethyl benzoate exhibits a significantly different dependency upon solvent composition when aqueous dimethyl sulfoxide is substituted for aqueous ethanol. The presence of microscopic solvent–solute interactions were proposed as an explanation for these observations.[6]

In order to further delineate the specific solvation interactions, it was decided to study solvent effects on a quantitative structure–reactivity relationship. Such an investigation permits a more discriminating assessment of the medium effects by measuring the susceptibility of the reaction to polar, resonance, and steric substituent effects.

For a series of esters, RCO_2R', where the R′ group is fixed while the R group is varied, the saponification rate constants, *k*, are defined by the following (eq. 1[7])

$$\log k = \log k_0 + \rho^*\sigma^* + \delta E_s \qquad (1)$$

where k_0 is the regression value for the saponification constant of CH_3CO_2R', ρ^* is the polar reaction constant,[8a] σ^* is the polar substituent constant[8b] for the R group, δ is the steric reaction constant,[8c] and E_s is the steric substituent constant[8c] for the R group.

Hancock[9] modified the steric substituent constant by quantitative separation of hyperconjugation effects according to the expression shown in eq. 2 following

$$E_s^c = E_s - h(n - 3) \qquad (2)$$

(1) E. Grunwald and B. J. Berkowitz, *J. Am. Chem. Soc.*, **73**, 4939 (1951).

(2) R. Fuchs and A. Nisbett, *ibid.*, **81**, 2371 (1959).

(3) C. D. Ritchie and E. S. Lewis, *ibid.*, **84**, 591 (1962).

(4) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *ibid.*, **85**, 709 (1963).

(5) D. D. Roberts, *J. Org. Chem.*, **29**, 2039 (1964).

(6) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 263 ff.

(7) W. H. Pavelich and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4935 (1957).

(8) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956: (a) p. 606, (b) p. 587, (c) p. 643, (d) p. 599, (e) p. 591, and (f) p. 636.

(9) C. K. Hancock, E. A. Meyers, and B. J. Yaeger, *J. Am. Chem. Soc.*, **83**, 4211 (1961).

where E_s^c is a corrected steric substituent constant,[9] h is the reaction constant for hyperconjugation, and n is the number of α-hydrogens. For several reaction series[9,10] it has been shown that eq. 3 following

$$\log k = \log k_0 + \rho^*\sigma^* + \delta E_s^c + h(n - 3) \quad (3)$$

gives a better fit in a multiple-regression analysis of log k on σ^*, E_s^c, and $(n - 3)$.

In Table I, values of second-order saponification rate constants, k, are given for nine esters, $RCO_2C_2H_5$, in both 85% aqueous ethanol and 85% aqueous dimethyl sulfoxide, and in Table II Taft's polar (σ^*)[8b] and steric (E_s)[8c] substituent constants, the corrected steric substituent constant (E_s^c),[9] and the number of α-hydrogens in R relative to the number in the methyl group $(n - 3)$ are given for eight ethyl esters, $RCO_2C_2H_5$.

TABLE I

SECOND-ORDER SAPONIFICATION RATE CONSTANTS[a] FOR NINE ETHYL ESTERS

$RCO_2C_2H_5$

R	$k \times 10^3$ (l./mole/sec.) Aq. EtOH	$k \times 10^3$ (l./mole/sec.) Aq. DMSO
CH_3	18.7	1360[b]
n-C_3H_7	5.3	430[c]
i-C_3H_7	1.77	354[d]
n-C_5H_{11}	4.7	280[e]
$C_6H_5CH_2(CH_3)CH$	1.6	300
$C_6H_5C(CH_3)_2CH_2$	0.29	30
Cyclo-C_6H_{11}	1.07	152[f]
Cyclo-(1-CH_3)C_6H_{10}	0.0145	5
Cyclo-$C_6H_{11}(CH_3)_2C$	0.005	1.4

[a] In 85% aqueous ethanol and 85% aqueous dimethyl sulfoxide at 35°. [b] Extrapolated from data in Table IV. [c] Extrapolated from the following rate data (temperature, $k_2 \times 10^3$ l./mole/sec.): 10°, 95; 15°, 130; 20°, 182; 25°, 242; $\Delta H^* = 9900$ cal./mole and $\Delta S^* = -28$ e.u. [d] Extrapolated from the following rate data (temperature, $k_2 \times 10^3$ l./mole/sec.): 10°, 68; 15°, 99; 20°, 136; 25°, 189; $\Delta H^* = 10{,}800$ cal./mole and $\Delta S^* = -26$ e.u. [e] Extrapolated from the following rate data (temperature, $k_2 \times 10^3$ l./mole/sec.): 15°, 91; 20°, 121; 25°, 165; 30°, 212; $\Delta H^* = 9300$ cal./mole and $\Delta S^* = -31$ e.u. [f] Extrapolated from the following rate data (temperature, $k_2 \times 10^3$ l./mole/sec.): 10°, 26; 15°, 38; 20°, 55; 25°, 78; $\Delta H^* = 11{,}600$ cal./mole and $\Delta S^* = -25$ e.u.

TABLE II

SUBSTITUENT CONSTANTS

Substituent	σ^*[a]	E_s[b]	$(n - 3)$[c]	E_s^c[d]
n-C_3H_7	−0.115	−0.36	−1	−0.67
i-C_3H_7	−0.19	−0.47	−2	−1.08
n-C_5H_{11}	−0.16[e]	−0.40	−1	−0.71
$C_6H_5CH_2(CH_3)CH$	+0.025[f]	−1.13[g]	−2	−1.75
$C_6H_5C(CH_3)_2CH_2$	−0.043[h]	−1.70[g]	−1	−2.01
Cyclo-C_6H_{11}	−0.15[i]	−0.79	−2	−1.40
Cyclo-(1-CH_3)C_6H_{10}	−0.44[j]	−2.03[g]	−3	−2.95
Cyclo-$C_6H_{11}(CH_3)_2C$	−0.44[k]	−2.49[g]	−3	−3.41

[a] Ref. 8e. [b] Ref. 8d. [c] n is the number of α-hydrogens in R of $RCO_2C_2H_5$. [d] Calcd. from Taft's steric substituent constant (ref. 9) by eq. 2. [e] A. B. Hoefelmeyer and C. K. Hancock, *J. Am. Chem. Soc.*, **77**, 4746 (1966). [f] Calcd. by the method in ref. 8b (rate of acid-catalyzed hydrolysis in 70% aqueous acetone at 35° = 0.80×10^{-5} l./mole/sec.). [g] Calcd. by the method in ref. 8d. [h] Calcd. by the method in ref. 8b (rate of acid-catalyzed hydrolysis in 70% aqueous acetone at 35° = 0.216×10^{-5} l./mole/sec.). [i] P. R. Wells, *Chem. Rev.*, **63**, 171 (1963). [j] Calcd. by the method in ref. 8b (rate of acid-catalyzed hydrolysis in 70% aqueous acetone at 35° = 0.104×10^{-5} l./mole/sec.). [k] Calcd. by the method in ref. 8b (rate of acid-catalyzed hydrolysis in 70% aqueous acetone at 35° = 0.035×10^{-5} l./mole/sec.).

Statistical treatment of the saponification rate constants in 85% aqueous ethanol at 35° given in Table I for eight esters, $RCO_2C_2H_5$, and the corresponding substituent constants given in Table II yield eq. 4 and 5

$$\log k = \underset{(0.001)}{-1.68} + \underset{(0.001)}{2.39}\sigma^* + \underset{(0.001)}{1.037}E_s, \quad R = 0.995,\ s = 0.011 \quad (4)$$

$$\log k = \underset{(0.001)}{-1.57} + \underset{(0.001)}{2.09}\sigma^* + \underset{(0.001)}{0.99}E_s^c - \underset{(0.025)}{0.18}(n - 3), \quad R = 0.997,\ s = 0.008 \quad (5)$$

where R is the multiple correlation coefficient[11a] and s is the standard deviation from regression.[11b] The numbers in parentheses below the two coefficients of eq. 4 and the three coefficients of eq. 5 are the significance levels determined by Students' t-tests.[11c]

Similar statistical treatment of the saponification-rate constants in 85% aqueous dimethyl sulfoxide at 35° given in Table I for eight ethyl esters, $RCO_2C_2H_5$, and the corresponding substituent constants given in Table II yield eq. 6 and 7.

$$\log k = \underset{(0.001)}{0.21} + \underset{(0.001)}{1.88}\sigma^* + \underset{(0.001)}{0.88}E_s, \quad R = 0.990,\ s = 0.022 \quad (6)$$

$$\log k = \underset{(0.001)}{0.01} + \underset{(0.001)}{1.25}\sigma^* + \underset{(0.001)}{0.957}E_s^c - \underset{(0.001)}{0.512}(n - 3), \quad R^c = 0.996,\ s = 0.008 \quad (7)$$

These results indicate that all three independent variables are highly significant [with the possible exception of $(n - 3)$ in eq. 5] and that the deviation of experimental log k values from log k values calculated by eq. 1 or 3 is of the same order of magnitude as the experimental error in measurement of log k. Analysis of variance (F-test)[11d] reveals approximately equivalent fits of the data in eq. 4 and 5 while eq. 7 represents a significant improvement of eq. 6 by the inclusion of $(n - 3)$ as an additional variable in the multiple-regression analysis.

Somewhat surprising is the fact that the linear free-energy equation is obeyed in the solvent 85% aqueous dimethyl sulfoxide. There is good evidence[4] for assuming that the polar substituent constants listed in Table II are invariant with solvent composition. However, owing to the nonadditivity of steric substituent constants,[8b] steric interaction mechanisms occur

TABLE III

CORRELATION OF ALKALINE HYDROLYSIS REACTIONS OF VARIOUS ETHYL ESTERS AT 35° WITH THE TAFT LINEAR FREE-ENERGY RELATIONSHIP

Reaction series no.	Solvent	log k_0[a]	$-\Delta\Delta F^*$[b]	ρ^*	δ	h
1	85% aq. ethanol	−1.57		2.09	0.99	−0.18
2	70% aq. acetone[c]	−1.17	400	1.66	1.09	
3	85% aq. DMSO	0.21	1130	1.25	0.96	−0.51

[a] The log of the rate constant for ethyl acetate. [b] The differences in free energy of activation of ethyl acetate in the respective solvent systems. [c] Taken from data of G. Davies and D. P. Evans, *J. Chem. Soc.*, 339 (1940).

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(12) A. J. Parker, *Quart Rev.* (London), **16**, 163 (1962).

TABLE IV

RATES OF ALKALINE HYDROLYSIS OF ETHYL ACETATE IN AQUEOUS DIMETHYL SULFOXIDE

Solvent (% by vol.)	Mole fraction[a]	Temp., °C.	$k_2 \times 10^4$, l./mole/sec.	Rel. rate
85% aq. EtOH	0.63	25.0	75[b]	1.0
85% aq. DMSO[c]	0.59	25.0	7500[d]	100
		20.0	5400 ± 90[e]	
		17.0	4550 ± 140	
		15.0	3960 ± 120	
		10.0	2850 ± 80	
		5.0	2000 ± 75	
80% aq. DMSO	0.51	25.0	3880 ± 50	52
		20.0	2880 ± 47	
		15.0	2190 ± 16	
		10.0	1570 ± 8	
		5.0	1160 ± 40	
75% aq. DMSO	0.43	25.0	3320 ± 20	44
		20.0	2600 ± 35	
		15.0	2010 ± 28	
		10.0	1520 ± 20	
70% aq. DMSO	0.37	25.0	2780 ± 30	37
		20.0	2150 ± 25	
		15.0	1550 ± 15	
		10.0	1130 ± 18	
65% aq. DMSO	0.32	30.0	3100 ± 90	
		25.0	2220 ± 45	30
		15.0	1240 ± 30	
		10.0	900 ± 15	
60% aq. DMSO	0.275	30.0	2530 ± 40	
		25.0	1950 ± 14	26
		20.0	1460 ± 15	
		10.0	815 ± 12	
50% aq. DMSO	0.20	35.0	2600 ± 45	
		30.0	2000 ± 20	
		25.0	1500 ± 22	20
		15.0	850 ± 14	
30.5% aq. DMSO	0.10	35.0	2160 ± 14	
		30.0	1710 ± 35	
		25.0	1350 ± 17	18
		15.0	780 ± 11	

[a] Mole fraction of organic component of solvent. [b] Obtained from data of ref. 14. [c] Dimethyl sulfoxide. [d] Extrapolated. [e] One standard deviation unit from the mean.

in greater variety and are expected to be more sensitive to changes in solvent composition.

The similar susceptibility to steric substituent effects coupled with variable susceptibility to polar effects suggests an increased importance of transition-state solvation in dimethyl sulfoxide. Thus by equating the magnitude of ρ^* with the degree of negative charge developed in the transition state or alternatively the degree of "tightness" of the transition state complex implies that the attacking hydroxide ion and the carbonyl carbon are separated by a greater distance in aqueous dimethyl sulfoxide than in aqueous ethanol and that reaction series 3 should be less susceptible (lower δ-value) to steric effects of structural changes adjacent to the carbonyl group. The fact that the value of δ for reaction series 3 is not smaller can be ascribed to an increased importance of steric interference with solvation of the transition state in aqueous dimethyl sulfoxide (see Table III).

While the multiple regression analysis data do not permit a quantitative assessment of the contribution of the transition state solvation to the $-\Delta\Delta F^*$ term, the importance of the contribution is further corroborated by an extended investigation of the alkaline hydrolysis of ethyl acetate in aqueous dimethyl sulfoxide. Table IV presents the kinetic findings of this study which, in agreement with the previously reported investigation,[5] show that substitution of aqueous dimethyl sulfoxide for aqueous ethanol leads to an enhanced rate of reaction.

More importantly, however, the data reported in Table V show the expected dependence of the activation parameters on the solvent composition predicted by the Hughes–Ingold theory.[13] Both the reduced enthalpy and entropy of activation support the involvement of a more highly solvated transition state of ethyl acetate in dimethyl sulfoxide.

TABLE V

THERMODYNAMIC ACTIVATION PARAMETERS FOR ALKALINE HYDROLYSIS OF ETHYL ACETATE IN AQUEOUS ETHANOL AND AQUEOUS DIMETHYL SULFOXIDE

Solvent	Mole fraction[a]	ΔH^*, cal./mole	ΔS^*, e.u.
Aq. EtOH	0.00[b]	11,100	−25.8
	0.09	10,350	−31.0
	0.14	10,700	−30.5
	0.29	12,500	−26.0
	0.42	13,700	−23.0
	0.60	14,900	−20.0
Aq. DMSO	0.10	8,600 ± 100[c]	−34 ± 1
	0.20	9,200 ± 100	−31 ± 1
	0.28	9,400 ± 100	−31 ± 1
	0.32	9,700 ± 100	−29 ± 1
	0.37	9,600 ± 90	−29 ± 1
	0.43	8,100 ± 60	−35 ± 1
	0.51	9,400 ± 100	−29 ± 1
	0.59	10,800 ± 100	−25 ± 1

[a] Mole fraction of organic component of solvent. [b] Obtained from the data of ref. 14. [c] One standard deviation unit from the mean.

Also, it is noted that the data in Table V indicate the presence of a minimum activation enthalpy at approximately 0.45 mole fraction of dimethyl sulfoxide, while a similar energy well deviation reported by Tommila[14] for the alkaline hydrolysis of ethyl acetate in aqueous ethanol occurs at approximately 0.9 mole fraction of ethanol (*cf.* Table V). This dissimilar influence of changing composition in the two binary solvent systems on the partitioning of the activation parameters lends further support to a significantly different medium effect in aqueous dimethyl sulfoxide relative to aqueous ethanol.

Experimental

All boiling points are uncorrected for stem exposure and all microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Purity of all distilled chemicals was established by gas chromatography.

Ethyl esters [ethyl acetate, b.p. 77° (760 mm.); ethyl *n*-butyrate, b.p. 120° (760 mm.); ethyl isobutyrate, b.p. 109–110° (760 mm.); and ethyl hexanoate, b.p. 165° (760 mm.)] were commercial samples fractionally distilled prior to use.

Ethyl cyclohexanecarboxylate was prepared from cyclohexanecarboxylic acid by Fischer esterification[15] with ethanol; b.p.

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(14) E. Tommila, A. Koivisto, J. P. Lyyra, K. Antell, and S. Heims, *Ann. Acad. Sci. Fennicae, Ser. A*, **47**, 3 (1952).

(15) L. F. Feiser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p. 77.

80–81° (12 mm.), $n^{25}D$ 1.4395; lit.[16] b.p. 82–83° (12 mm.), $n^{25}D$ 1.4396.

Ethyl α-methyldihydrocinnamate was prepared from α-methyldihydrocinnamic acid [b.p. 103° (0.5 mm.), $n^{23}D$ 1.5143; lit.[17] b.p. 152° (10 mm.), $n^{25}D$ 1.5135] by Fischer esterification[14] with ethanol; b.p. 68° (0.6 mm.), lit.[18] b.p. 130–131° (17 mm.).

Ethyl 1-methylcyclohexanecarboxylate was prepared from 1-methylcyclohexanecarboxylic acid [b.p. 63° (1 mm.), $n^{23}D$ 1.4921; lit.[19] b.p. 132.5° (20 mm.)] by Fischer esterification[15] with ethanol; b.p. 77–79° (10 mm.), $n^{25}D$ 1.4406; lit.[16] b.p. 82–83° (12 mm.), $n^{28}D$ 1.4430.

Ethyl cyclohexanedimethylacetate was prepared in 64% yield from cyclohexanedimethylacetic acid [b.p. 98° (0.5 mm.), lit.[19] b.p. 146° (10 mm.)] *via* the interaction of the silver salt with ethyl bromide; b.p. 64° (0.6 mm.), $n^{25}D$ 1.4500.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.80; H, 11.25. Found: C, 72.80; H, 11.42.

Ethyl β,β-dimethyldihydrocinnamate was prepared from β,β-dimethyldihydrocinnamic acid (m.p. 57–58°, lit.[20] m.p. 57.5–58°) by Fischer esterification[15] with ethanol; b.p. 89° (0.4 mm.), $n^{25}D$ 1.4916.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.65; H, 8.80. Found: C 75.41; H, 8.72.

Rate Measurements.—The kinetic experiments were carried out using both ester and sodium hydroxide in equal concentrations (about 0.05 *M*). The ester was weighed out in a volumetric flask, rapidly brought up to volume with the appropriate solvent mixture (pre-equilibrated to the reaction temperature, zero time was recorded as the time when one-half the solvent had been added), and placed in a constant temperature bath (accurate to ±0.1°.). Aliquots were removed periodically; the reaction was quenched by addition to an excess of hydrochloric acid of known normality and finally back-titrated with standardized sodium hydroxide to a bromthymol blue end point. The values of k_2 were calculated from the second-order reaction rate equation

$$k_2 = x/at(a - x)$$

where a is the initial concentration of each reactant and $(a - x)$ is the concentration of each reactant at time t. All of the measured reactions followed strictly second-order kinetic law with the exception of the first 10% conversion of ethyl cyclohexanedimethylacetate. This deviation was corrected for by assuming "0" reaction time at 10% conversion.

Treatment of the Kinetic Data.—The multiple regression analyses were performed through the courtesy of the Computer Center, Louisiana Polytechnic Institute, employing an IBM 1620 computer.

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1H-2,1,3-Benzothiadiazin-4(3H)-one 2-Oxides

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Received April 16, 1964

Several 1-methyl-3,6-disubstituted 1H-2,1,3-benzothiadiazin-4(3H)-one 2-oxides have been prepared by the reaction of suitably substituted 2-methylaminobenzamines with thionyl chloride. Certain infrared spectral characteristics of these compounds are discussed.

In an attempt to prepare 5-chloro-N-(2-chloroethyl)-2-methylaminobenzamide by the reaction of 5-chloro-N-(2-hydroxyethyl)-2-methylaminobenzamide (Ia) with thionyl chloride, we obtained, instead, 6-chloro-3-(2-chloroethyl)-1-methyl-1H-2,1,3-benzothiadiazin-4-(3H)-one 2-oxide (IIa) (see Chart I). This new and unexpected ring closure to the benzothiadiazine with thionyl chloride was found to proceed smoothly with other suitably substituted 2-methylaminobenzamides (Ia–h, Table I). In these compounds, R = alkyl, substituted alkyl, or cycloalkyl, and X is an electronegative substituent, *e.g.*, Cl, NO_2, or $SO_2NHC_2H_5$. The correspondingly substituted benzothiadiazines (IIa–h) are given in Table II.

An attempt to displace the chloro group in the alkyl chain of IIa with a morpholino group was successful, but cleavage of the thiadiazine ring occurred, giving 5-chloro-2-methylamino-N-(2-morpholinoethyl)benzamide (Ii). The latter product was more easily prepared by the reaction of 5-chloro-N-methylisatoic anhydride with N-(3-aminoethyl)morpholine. Treatment of Ii with thionyl chloride in the usual manner, however, failed to give the desired benzothiadiazine.

The compounds shown in Table I were readily prepared in satisfactory yield by the reaction of a suitably substituted N-methylisatoic anhydride[1] with the appropriate amine. The previously undescribed 5-chlorosulfonyl-N-methylisatoic anhydride (III) used in the synthesis of Ih was prepared by chlorosulfonation of N-methylisatoic anhydride with chlorosulfonic acid. Treatment of the anhydride with excess aqueous ethylamine afforded Ih, which upon reaction with thionyl chloride gave the expected benzothiadiazine (IIh).

In contrast to these results, 2-methylaminobenzamide reacted with thionyl chloride to give a gummy residue which was not readily purified. The presence of a strong nitrile band at 4.54 μ in the infrared spectrum of this material indicated that dehydration of the amide group to the nitrile had occurred. Attempts to prepare the corresponding benzothiadiazines from N-ethyl-2-methylaminobenzamide and 2-amino-5-chloro-N-ethylbenzamide by reaction with thionyl chloride were unsuccessful. Similarly, 2-anilino-N-ethylbenzamide failed to give the expected ring closure. The results of these experiments make it clear that specific structural features in 2-aminobenzamides are essential for the success of the reaction. Both the amino and amido nitrogen atoms must be mono-

(1) N-Methylisatoic, 5-chloro-N-methylisatoic, 5-nitro-N-methylisatoic, and 5-chloroisatoic anhydrides were obtained from Maumee Chemical Co., Toledo, Ohio. The last three anhydrides, however, are offered by Maumee as the 6-chloro, 6-nitro, and 6-chloro derivatives, respectively, because a different numbering system was used. Since the compounds are derivatives of isatoic acid, we have numbered the substituents in accordance with the manner prescribed by *Chemical Abstracts*.