TABLE III

p-SUBSTITUTED BENZHYDROXAMIC ACIDS

Acid	Recrystallized from	M.p., °C.[a]	Analyses, % Calculated C	H	N	Found C	H	N	pK_b[b]
p-Chlorobenzohydroxamic	EtOH; EtOH + H_2O	185	49.1	3.5	8.2	49.1	3.4	8.40	[c]
p-Nitrobenzohydroxamic	H_2O; acetone; acetone + petr. eth.; dioxane	186	46.2	3.3	15.4	46.2	3.4	15.6	8.01
p-Methylbenzohydroxamic	Acetone + petr. ether	154	63.6	6.0	9.3	63.7	6.1	9.6	8.93
p-Methoxybenzohydroxamic	Acetone + petr. eth.	163	57.4	5.4	8.4	57.7	5.2	8.1	9.03
p-Aminobenzohydroxamic	EtOH + petr. eth.	185	52.2	5.3	18.4	55.1	5.5	17.9	9.32
p-Cyanobenzohydroxamic	Water	176	59.2	3.7	17.3	58.9	3.7	17.0	8.16
p-Fluorobenzohydroxamic	Acetone + petr. eth.	165	54.2	3.9	9.1	54.7	4.0	8.8	8.70

[a] Uncorrected; determined with the Berl–Kullman copper melting point block. [b] Obtained by determination of the pH of a half-neutralized 0.01 *M* solution of the acid in 0.1 *M* KNO_3 (Dr. R. Swidler). [c] Too insol. in H_2O to determine pK_a.

TABLE IV

HETEROCYCLIC HYDROXAMIC ACIDS

Acid	Crystallized from	M.p., °C.[a]	Analyses, % Calculated C	H	N	I	Found C	H	N	I	pKa[b]
Picolinhydroxamic[12]	H_2O; acetone + petr. eth.	120	52.17	4.35	20.35	45.3	52.5	4.60	20.30	..	8.7
Methiodide	Ethanol + ether	165	30.02	3.23	10.0	45.3	30.0	3.3	9.6	45.6	5.5
Nicotinhydroxamic[12]	Ethanol; acetone + petr. eth.	165	52.17	4.35	20.35		51.8	4.40	20.0		8.3
Methiodide	Dimethylformamide + ether	187	30.02	3.23	10.0	45.3	30.4	3.20	10.0	45.6	6.5
Isonicotinhydroxamic[12]	Water	161	52.17	4.35	20.35		52.2	4.5	20.3		7.8
Methiodide	Dimethylformamide + ether	205	30.02	3.23	10.0	45.3	29.8	3.2	10.2	45.5	6.3
Isocinchomeronhydroxamic	Water	215	42.64	3.57	21.31		42.9	3.4	21.9		
Pyridine-2,6-dihydroxamic	Water	217	42.64	3.57	21.31		42.4	3.6	21.2		
Pyrazinehydroxamic	Water	168	43.16	3.62	30.2		43.3	3.6	29.8		8.1
Pyrazine-2,3-dihydroxamic	H_2O; H_2O + EtOH	163	36.4	3.05	28.3		35.8	3.3	27.7		

[a] See footnotes for Table III. [b] Determined from the potentiometric titration curve of a 0.04 *M* solution of the acid in 0.1 *M* KCl, using 0.1 *N* NaOH for neutralization. The pK_a values of the methiodides were determined (in the absence of KCl) by Dr. G. Gilbert, who will discuss their possible significance for the reaction with DFP in a later paper.

TABLE V

O-ARYLCARBAMYL ARYLHYDROXAMATES, RCONHOCONHR

R	Decomposition (melting) pt., °C.	Formula (mol. wt.)	Analyses, % Calculated C	H	N	Found C	H	N
C_6H_5–	177 (234)	$C_{14}H_{12}N_2O_3$(256.1)	65.5	4.7	10.9	65.7	4.8	11.4
p-CN–C_6H_4–	272 (277)	$C_{16}H_{10}N_4O_3$(306.1)	62.7	3.3	18.3	62.2	3.4	18.6
p-NO_2–C_6H_4–	264 (274)	$C_{14}H_{10}N_4O_7$(346.1)	48.5	2.9	16.2	48.3	3.0	15.8
p-CH_3O–C_6H_4–	168 (218–224)	$C_{16}H_{16}N_2O_5$(316.1)	60.7	5.1	8.9	61.7	5.3	9.3
2-Pyridyl	159 (170)	$C_{12}H_{10}N_4O_3$(258.1)	55.8	3.9	21.7	55.6	4.1	
3-Pyridyl	118 (204)	$C_{12}H_{10}N_4O_3$(258.1)	55.8	3.9	21.7	55.5	4.3	21.3

di-(*p*-nitrophenyl)-urea is 312°, with sublimation starting at 300°).

Pure N,N′-diphenylurea (m.p. 235°) was obtained from phenylcarbamyl benzohydroxamate by refluxing its dioxane solution. 3-Pyridylcarbamyl nicotinhydroxamate on heating to 120–130° yielded N,N′-di-(3-pyridyl)-urea, m.p. 217–219° (from aqueous alcohol).

Acknowledgments.—We are indebted to Dr. G. Steinberg and Dr. R. Tweit of this Laboratory and the following firms for supplying us with samples of certain hydroxamic acids: American Cyanamid Co., Research Division, Bound Brook, N. J.; Lederle Laboratories Division, Pearl River, N. Y.; Hoffman–LaRoche, Inc., Nutley 10, N. J.; Merck and Co., Inc., Rahway, N. J. The authors also wish to thank O. O. Owens and S. Seltzer for their skillful technical assistance.

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(12) T. S. Gardner, E. Wenis and F. A. Smith, THIS JOURNAL, **73**, 5455 (1951), described the hydrochloride of this hydroxamic acid.

Orientation in Aromatic Substitution: A Theoretical Study of the Competition between Groups

BY S. L. MATLOW[1] AND G. W. WHELAND

RECEIVED NOVEMBER 5, 1954

In 1942, there was described[2] an approximate quantum-mechanical method for calculating the orientation in aromatic substitutions by electrophilic, nucleophilic and radical reagents. More recently, Dewar[3] has developed a much simpler, but less general, procedure that is based upon the same fundamental assumptions regarding the structures of the activated complexes, and that leads to the same kinds of information. Each of these earlier papers was restricted to the study of monosubstituted benzenes; the present one, on the other hand, considers the reactions of more complex molecules in which there is competition be-

(1) Atomic Energy Commission Predoctoral Fellow, 1952–1953.
(2) G. W. Wheland, THIS JOURNAL, **64**, 900 (1942).
(3) M. J. S. Dewar, *ibid.*, **74**, 3357 (1952).

tween two or more different substituent groups. Since the method of Dewar has not been extended to such problems, only the original, relatively tedious procedure of Wheland will be used here.

The mathematical details of the treatment already have been described[2] and so need not be repeated here. Some comment is, however, necessary in regard to the choice of the numerical values assigned to the many parameters that are required. The ideal procedure would doubtless be to express the results of the calculations in the form of generally valid, continuous functions of these parameters. Such a procedure, however, is not practicable since the equations can be solved only with the use of explicitly stated parameter values. The best that can be done is therefore to carry through the calculations for several different sets of parameter values, and then to select the particular set that seems most satisfactory. The parameters used in the present work were obtained in this way, and with aid also of the following more general considerations. Each of the quantities δ_N, δ_0, δ_1, etc., is a measure of the ability of the atoms concerned to attract electrons. In other words, the more electronegative the atom, the more positive, or less negative, must be the value of the pertinent δ. For example, since a nitrogen atom with a net positive charge might be expected to be about as electronegative as an oxygen atom with a net negative charge, and since each should be more electronegative than a carbon atom of benzene, δ_N and δ_0 were assumed to be equal and positive in nitrobenzene. Similarly, since the carbon atom C_1, to which the nitro group is joined, must, as a result of the inductive effect, be somewhat more electronegative than the other ones of the ring, δ_1 was also assumed to have a small positive value. There is, however, a limit to the magnitudes of the various δ's since, if these quantities are made too large, the calculated charge distributions in the molecules will be altered greatly, and will become inconsistent with the observed dipole moments of the substances. Although, in the way just outlined, fairly reasonable values for the δ's may be obtained, it should be evident that the treatment can have only qualitative significance.

The results of the calculations for nitrobenzene, 3-nitrophenol, 3-nitrotoluene and veratraldehyde, with use of the finally selected parameter values are summarized in Table I. The quantities listed are the calculated polarization energies, ΔW, in units of the positive quantity-β_0, for attack at the specified positions by reagents of the three different types. The reactions may be expected to occur most readily at the positions with the smallest polarization energies.

With 3-nitrophenol, the treatment leads to the conclusion that all types of reagent should preferentially attack positions 2, 4 and 6, *i.e.*, the positions *ortho* and *para* to the hydroxyl group. Position 2, lying between the two substituents, is the most favored of all, but its advantage over positions 4 and 6 is small and could be masked easily by steric effects which are not here considered. When the reagent is electrophilic, the prediction that the substitution will *not* occur at position 5 is, as is well known, in complete agreement with the facts.[4] When the reagent is nucleophilic, the calculated differences between the several positions are small and, accordingly, the predicted order of increasing reactivity is somewhat dependent upon the values chosen for the several parameters. No experimental data are available for comparison with the calculations either for reagents of this type or for radical reagents.

With respect to electrophilic reagents, the methyl group in 3-nitrotoluene has a much weaker directive power than does the hydroxyl group in 3-nitrophenol. Nevertheless, with the former as with the latter substance, the substitution is found experimentally[4] to occur predominantly at the 2-, 4- and 6-positions. The calculations reported in the table are therefore in agreement with the data, whether the hyperconjugation of the methyl group with the ring is considered or not. As might, however, be expected, in view of the rather small differences among the several positions, the predicted relative reactivities are somewhat more dependent on the choice of the parameter values than is true with 3-nitrophenol.

TABLE I

POLARIZATION ENERGIES[a]

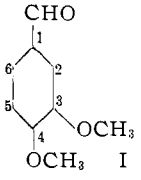
Compound	Parameter values[b]	Point of attack	Polarization energy: Electrophilic	Nucleophilic	Radical
Nitrobenzene	δ_N 0.6	*ortho*	1.86	1.72	1.79
	δ_0 .6	*meta*	1.85	1.85	1.85
	δ_1 .1	*para*	1.88	1.73	1.81
	ρ_{CN} .6				
3-Nitrophenol	δ_N .6	2	1.62	1.78	1.71
	δ_0 .8(OH)	4	1.66	1.83	1.75
	δ_0 .6(NO_2)	5	1.89	1.89	1.89
	δ_0 .2	6	1.65	1.81	1.73
	δ_1 .1				
	ρ_{CN} .6				
	ρ_{CO} .8				
3-Nitrotoluene (hyperconjugation neglected)	δ_N .6	2	1.81	1.78	1.80
	δ_0 .6	4	1.80	1.78	1.79
	δ_1 − .2	5	1.85	1.85	1.85
	δ_2 .1	6	1.83	1.80	1.82
	ρ_{CN} .6				
3-Nitrotoluene (hyperconjugation included)	δ_N .6	2	1.81	1.75	1.78
	δ_0 .6	4	1.81	1.75	1.78
	δ_H − .2(CH_3)	5	1.86	1.86	1.86
	δ_1 − .1	6	1.83	1.77	1.80
	δ_2 .1				
	ρ_{CN} .6				
	ρ_{CH} 2.0				
	ρ_{CC} 0.7(C–CH_3)				
Veratroldehyde	δ_1 .6(CHO)	2	1.69	1.56	1.63
	δ_0 .8(OCH_3)	5	2.01	1.66	1.84
	δ_C .2(CHO)	6	1.69	1.63	1.66
	δ_3 .2				
	δ_4 .2				
	ρ_{CO} .8(CHO)				
	ρ_{CO} .8($COCH_3$)				

[a] In units of $-\beta_0$, where β_0 is the value of the parameter β for two adjacent carbon atoms in benzene. For comparison with the values given in this table, it may be mentioned that the polarization energy in unsubstituted benzene is equal to $-1.85\ \beta_0$ for reaction with all three kinds of reagent (see reference 2). [b] The significance of the several parameters is the same here as in the original paper of Wheland (reference 2). For the results of several additional calculations with different choices of the parameter values, see S. L. Matlow, Thesis, University of Chicago, August, 1953.

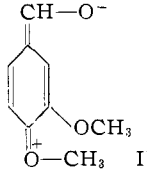
(4) For experimental data regarding orientations, see, for example, Beilstein, "Handbuch der organischen Chemie."

When the reagent is nucleophilic, the favored points of attack in 3-nitrotoluene are predicted to be 2, 4 and 6, so that the *ortho–para* directing nitro group predominates over the *meta*-directing methyl group. This prediction, which is not very sensitive to the values chosen for the parameters, is verified by experiment.[4,5] As with 3-nitrophenol, no data regarding radical attack are available; the predicted orientation must surely be correct, however, since both substituents are *ortho–para* directing.

A superficial consideration of veratraldehyde (I) leads to the conclusion that, since the two methoxy groups oppose each other, the orientation should be determined by the formyl group. On

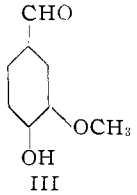


I



II

this basis, then, attack by an electrophilic reagent should occur at position 5. Experimentally,[4] however, nitration gives 6-nitroveratraldehyde, and bromination gives the analogous 6-bromoveratraldehyde. For these somewhat unexpected observations, Rây and Robinson[6] proposed an explanation which, when re-expressed in more modern terms, takes the following form. In veratraldehyde, there must be resonance not only between the two Kekulé structures that are implied by the symbol I, but also with the quinoid structure II. As a result of this resonance, only the methoxy group in position 3 is free to exert its full normal orienting effect; consequently, the entering substituent is directed largely by this one group. Although this explanation seems rather reasonable, it cannot be complete since, by centering attention upon only the normal unreacting molecule, it ignores all those respects in which the reactions at positions 5 and 6 differ from each other; it is therefore incapable of accounting for the relative rates of these competing reactions. Only by explicitly comparing the stabilities of the respective activated complexes, in fact, can we avoid this difficulty. The required comparison is shown in the table, from which it is evident that the more detailed calculations are in agreement with the earlier suggestion of Rây and Robinson. No satisfactory explanation for all the pertinent data can, however, be obtained either in this way or in any other way that is immediately apparent since the orientation observed with veratraldehyde is not always encountered with other substances of closely similar structure.[4] In both the nitration and the bromination of vanillin (III), for example, the substitution takes place at position 5, and in the bromination of protocatechualdehyde (IV), the substitution again takes place at position 5. Moreover, 4-nitroveratrole (V) is brominated at position 6 but nitrated at position 5. Clearly, no satisfactory explanation can now be offered for such conflicting data.



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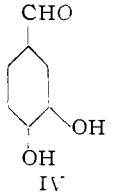
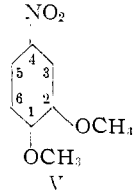


IV



V

(5) F. W. Bergstrom, I. M. Granara and V. Erickson, *J. Org. Chem.*, **7** 98 (1942).

(6) J. N. Rây and R. Robinson, *J. Chem. Soc.*, **127**, 1618 (1925).

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Higher Amino Alcohols *via* the Mannich Reaction

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In connection with studies of the reactions of higher aliphatic ketones, amino ketones have been prepared by means of the Mannich reaction. The amino ketones have been reduced to the corresponding amino alcohols and these in turn have been converted to amine and quaternary ammonium salts.

Amino ketones $RCH(COR')CH_2NMe_2$ prepared by the reaction of higher aliphatic ketones with formaldehyde and dimethylamine hydrochloride were unstable and could not be distilled. However, prompt reduction of the partially purified bases by means of lithium aluminum hydride or sodium borohydride afforded the corresponding amino alcohols which distilled without decomposition.

Exhaustive hydrogenation of the amino ketones with Raney nickel catalyst at 200° and 2000 pounds pressure gave saturated alcohols. In an experiment involving the dimethylamino ketone derived from 2-tridecanone, the alcohol obtained was not 3-tetradecanol, but was 3-methyl-2-tridecanol, indicating that aminomethylation had occurred[2] on the methylene group of the long chain adjacent to the carbonyl.

The amino alcohols were treated with hydrogen chloride, methyl chloride and benzyl chloride to give the corresponding salts.

Table I lists the conversions, properties and analyses of the bases and salts. Conversions given for the bases represent fractions of reasonable purity; the physical constants apply to center cuts.

Experimental

A typical preparation is that of 3-dimethylaminomethyl-2-heptadecanol, $C_{14}H_{29}CH(CH_2NMe_2)CHOHMe$. Methyl pentadecyl ketone (240 g., 0.95 mole), 35% formaldehyde solution (170 g., 2.0 moles) and dimethylamine hydrochloride (89.1 g., 1.1 moles) were refluxed in one liter of ethanol containing 10 ml. of concd. hydrochloric acid for five days. After removal of much of the solvent *in vacuo*, the solution was made alkaline and extracted with ether, and the extract was washed free of dimethylamine. After removal of ether, reduction of the crude amino ketone was effected at room temperature in methanol solution (250 ml.) by dropwise addition, with stirring, of sodium borohydride (16.1 g., 0.425 mole) dissolved in a mixture of methanol (100 ml.) and 5% sodium hydroxide solution (50 ml.), followed by refluxing for one hour. After dilution with 500

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(2) F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 303.