

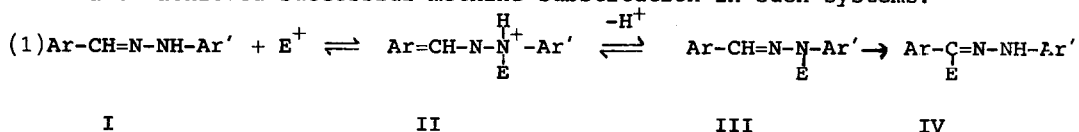
THE KINETICS OF GEOMETRICAL ISOMERISM IN N,N-DISUBSTITUTED HYDRAZONES

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Many efforts have been made to effect methine substitution in aldehydic N,N-disubstituted hydrazones and all have failed (1). Busch proposed (1) that the mechanism of successful methine attack in hydrazone systems involved first N-attack, to form an intermediate of type(III), which then rearranged to give the C-coupled product (IV), equation 1. He, and subsequent workers, regarded the fact that N,N-disubstituted hydrazones (V) did not react with electrophiles to give methine substituted products as demonstrating the necessity for the intervention in such reactions of intermediates such as (III). We have now quantitatively investigated one such electrophilic substitution for compounds (V) and we find Busch's mechanism criterion invalid. We have also achieved successful methine substitution in such systems.



We have examined the rates of bromination of the substrates (V) (in 70% acetic acid containing 0.1 m. potassium bromide at 20°) using the electro-metric technique we have described elsewhere (2). The actual substrates we used were the arylidene-N-Methyl-N-p-nitrophenylhydrazines (V, Ar' = p-NO₂C₆H₄, R = CH₃), (Table I) prepared by the reaction of the appropriate arylidene p-nitrophenylhydrazine with methyl iodide in the presence of excess 10% sodium hydroxide. When these compounds were treated with bromine under the conditions described (2) they did react, the rates of reaction (Table 2), under identical concentration conditions, being approximately one-twentieth of that for the corresponding unalkylated hydrazone. Several other major differences appeared between the results for the two systems.

First, with the N-alkyl compounds (V), (and the corresponding N-acetyl and N-benzoyl compounds), the reaction was overall first-order, being zero-order in bromine. With the corresponding unalkylated compounds, the overall reaction was second-order, first-order each in halogen and hydrazone.

TABLE 1
Substituted Benzaldehyde-N-Methyl-N-p-Nitrophenyl hydrazones
(V, R=CH₃)

Substituent	M.P.	Substituent	M.P.
H	136-137° ^(b)	3-Cl	144°
4-NO ₂	249-250°	2-F	160°
4-Cl	218°	2-Cl	191-192°
4-CH ₃	149-150°	2-Br	197°
4-(CH ₃) ₂ CH	112°	2-NO ₂	208-209°
4-Br	224-225°	2,6-di-Cl	212-213°
3-NO ₂	255-256°	2,4,6-tri-CH ₃	152-153°

(b) Lit. 137° (3).

TABLE 2

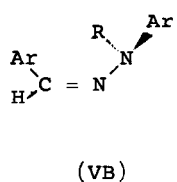
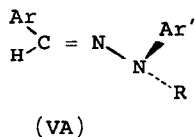
Rates of Bromination of Arylidene-N-methyl-N-p-nitrophenyl hydrazines
X. C₆H₄ = N-NCH₃-C₆H₄.NO₂ (k, in sec.⁻¹)

X	(V)	k x 10 ⁵	X	(V)	k x 10 ⁵
4-(CH ₃) ₂ CH	a	4.6	2-F	h	2.04
4-CH ₃	b	4.6	2-Cl	i	1.91
4-H	c	4.0	2-Br	j	1.76
4-Cl	d	3.2	2-NO ₂	k	1.35
4-Br	e	3.1	2,6-di-Cl	-	1.56
3-Cl	f	2.85	2,4,6-tri-CH ₃		2.68
4-NO ₂	g	2.54			

These results with the *N,N*-disubstituted compounds imply that some transformation of the hydrazone prior to bromination was actually rate-determining. The rate of bromination of compounds (V), and thence of the rate-determining pre-bromination step, proved to be relatively insensitive to the presence and the nature of the substituents we used in the *meta* and *para* positions of the arylidene (Ar) ring. From the rates of bromination of the seven compounds concerned (Va to Vg, Table 2), a Hammett ρ of -0.29 , $r = 0.95$ was calculated. The rates appeared insensitive to minor substituent variations in the hydrazine Ar' ring, since the rate of bromination of benzaldehyde-*N*-methyl-*p*-nitro-phenylhydrazone ($k = 4.0 \times 10^{-5} \text{ sec.}^{-1}$) was the same as that for benzaldehyde-*N*-methyl-2-bromo-4-nitrophenylhydrazone. In contrast, substituent variation in the arylidene portion (Ar) of compounds (I) corresponded to a Hammett ρ of -0.69 , with variation in Ar' following a ρ of -2.2 . Finally, the rates of bromination of compounds (V) were found to be somewhat sensitive to variation of substituent in the *ortho* position of the arylidene (Ar) ring (Table 2). From the data concerned (Vh to Vk), a Taft plot of $\log k$ against E_s values gives a steric susceptibility constant δ of 0.145 ($r = 0.998$). This again contrasts with the behaviour of the unalkylated hydrazones (I) where substituents in the arylidene *ortho* position produce a simple electronic effect ($\rho^* \approx -0.7$), with $\delta = 0$.

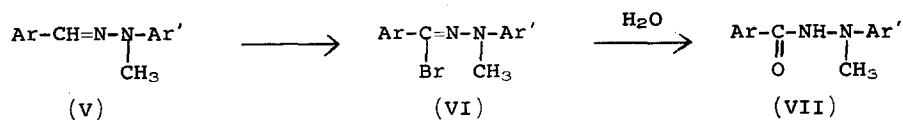
Either a tautomeric or geometric change in the hydrazone as the slow step could be responsible for the observed independence of bromine concentration in the brominations we reported for compounds (V). However the former possibility can be eliminated since isomerism to ene-hydrazine or azomethanes cannot take place with the substrates (V). Moreover, very recently, Simon and co-workers (4) found that for benzylidene *p*-nitrophenylhydrazone, where such tautomerism is possible, no exchange between methine hydrogen and H^3 -labelled 70% aqueous acetic acid occurred at 78.3° . The prebromination change we are observing therefore is a geometric isomerism.

Ultraviolet and n.m.r. (5) studies show that *N,N*-disubstituted hydrazones of type (V) exist primarily in configuration (VA) with the RNAr'



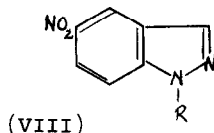
group on the same (syn) side of the azomethine bond as the methine hydrogen. The anti isomer (VB) although observable spectroscopically (i.e. present in 5% concentration) in solution when R = H has not been detected when R = CH₃ (C). Our data can be interpreted however by the existence of a small concentration of this isomer (VB) in solution which then brominates (probably for steric reasons) at a far greater rate than the syn. form. Such a geometric change (VA→VB) would be expected (6) to correspond to the substituent effects we have observed.

The bromination of compounds (V) had been qualitatively examined previously, the products of which reactions were either unworkable (7a) or involved substitution in either the arylidene (7b, c) or arylhydrazine (7b) rings. We have confirmed that arylidene p- substitution (e.g. the formation of p-bromobenzylidene-N-methyl-N-(p-nitrophenyl)hydrazine) does occur in 23% yield when benzylidene-N-methyl-N-(p-nitrophenyl)hydrazine is stirred as a slurry in glacial acetic acid at room temperature with one equivalent of bromine. A small quantity (6%) of the desired hydrazidic halide (VI) was also obtained together with N-(p-nitrophenyl)-N-methyl-C-phenyl hydrazide (29%) (VII) and unreacted hydrazone (22%). Modification of the reaction conditions with knowledge of the kinetic data improved the results. Thus, the N-alkylhydrazones (V) were first dissolved in the minimum quantity of warm glacial acetic acid, then the solution was treated with one molar equivalent of bromine, the bromine being added drop-wise with stirring. As the mixture cooled, the desired hydrazidic bromide (VI) precipitated (average bromination times 5 minutes). This procedure yielded the hydrazidic bromides (VI, Ar = C₆H₅) m.p. 123-129°, yield 50%; (VI, Ar = p-Br-C₆H₅) m.p. 175-176° yield 52% ; (VI, Ar = p-CH₃C₆H₅) m.p. 136-137°, yield 40% and (VI, Ar = p-ClC₆H₅) m.p. 173-174°, yield 30%. The structures of these hydrazidic bromides are consistent with analytical and spectral data and with the ready conversion in aqueous solvent mixtures of compounds (VI) to the hydrazides (VII).



The mechanism we have suggested above for the bromination of N,N-disubstituted hydrazones requires that the reaction with the anti isomer (Vb), if it were available, would be dependent on the bromine concentration. Using 5-nitroindazole (VIII, R = H) and 1-methyl-5-nitroindazole (VIII,

R = CH₃) as models for (Vb) we have found that this is, in fact, the case. Thus, in 95 : 5 water : methanol as solvent containing 0.1 m. KBr (in which these reactions were more conveniently measured by the electrometric method), the rates of bromination of the indazole (VIII, R = H and R = CH₃) were 78.7 and 4.43 1.mole sec. respectively.



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