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Substituent Effects on Nitrosation of 1,3-Diarylureas with Nitrosyl Chloride, Dinitrogen Trioxide, and Dinitrogen Tetroxide

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Twenty-eight *para*-substituted and eleven *ortho*-substituted 1,3-diarylureas were prepared. Their proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured to evaluate the acidity of the ureido protons in the *para*-substituted ureas, and to estimate the conformations of *ortho*-substituted molecules. The chemical shifts and acidities of two ureido protons were additively controlled by the two *para*-substituents in the 1,3-diarylureas. The sixteen *para*-substituted diarylureas were nitrosated with gaseous nitrosating reagents (dinitrogen trioxide, dinitrogen tetroxide or nitrosyl chloride) to give unstable isomeric mixtures of 1,3-diaryl-1-nitrosoureas [R^1–C_6H_4–N(NO)–CO–NH–C_6H_4–R^2] and 1,3-diaryl-3-nitrosoureas [R^1–C_6H_4–NH–CO–N(NO)–C_6H_4–R^2]. The isomer ratio of each nitrosated urea was correlated with the difference between the chemical shifts (d[NH]) of the two ureido protons in the ^{1}H-NMR spectrum of the starting urea. When d[NH] was below 0.25 ppm (with NOCl) or 0.45 ppm (with N_2O_3), good linearity was obtained (r(NOCl) = 0.943, n = 11; r(N_2O_3) = 0.869, n = 15). When d[NH] was over 0.25 ppm (NOCl) or 0.45 ppm (N_2O_3), the 1-nitrosated isomer [R^1–C_6H_4–N(NO)–CO–NH–C_6H_4–R^2] was the sole product. These principles could not be extended to dinitrogen tetroxide. Thirteen *para*-substituted diarylureas gave 1- or 3-nitrosated ureido derivatives as sole products and only four gave nitrosated isomeric mixtures.

The ^{1}H-NMR spectra of 5 types of *ortho*-substituted 1,3-diarylureas were measured for conformational analysis. Their conformations seem to be different from those of *para*-substituted diarylureas. Eleven *ortho*-substituted 1,3-diarylureas were nitrosated with nitrosyl chloride and dinitrogen tetroxide. In many cases, the nitroso group was predominantly introduced at the ureido nitrogen, which is less hindered sterically, and isomeric mixtures of 1- and 3-nitrosated ureas were obtained.

Keywords——nitrosation; dinitrogen trioxide; dinitrogen tetroxide; nitrosyl chloride; substituent effect; diarylurea; ^{1}H-NMR; substituent-induced chemical shift (SCS); conformation

In the course of our studies to prepare *N*-nitroso ureido derivatives having antitumor activity,[1] many disubstituted ureas were found to give isomeric mixtures of 1- and 3-nitrosated ureido derivatives. Regioselective nitrosation is important in connection with antitumor activities.[2] In the previous paper,[3] we have shown that the pH value of the reaction mixture is the principal factor controlling the regioselectivity of nitrosation of pyridylmethylureas. Other important factors have been identified by kinetic studies on the nitrosation of aniline derivatives;[4] they were electronic and steric factors of the substrates, as well as the ultimate form of the nitrosating reagent (which is related to the pH value of the medium). In order to estimate which nitrosated isomer, 1- or 3-nitrosated isomer, will be predominant, it would be interesting to examine the acidities of ureido protons and the conformation around the ureido group in starting materials. Generally proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy is useful for evaluating the acidities of amines and the shapes of molecules in solution.[5] In this paper, we describe the *para*- and *ortho*-substituent effects on the regioselectivity for nitrosation of diarylurea derivatives, and the correlation with chemical shifts of the two ureido protons in the ^{1}H-NMR spectra.

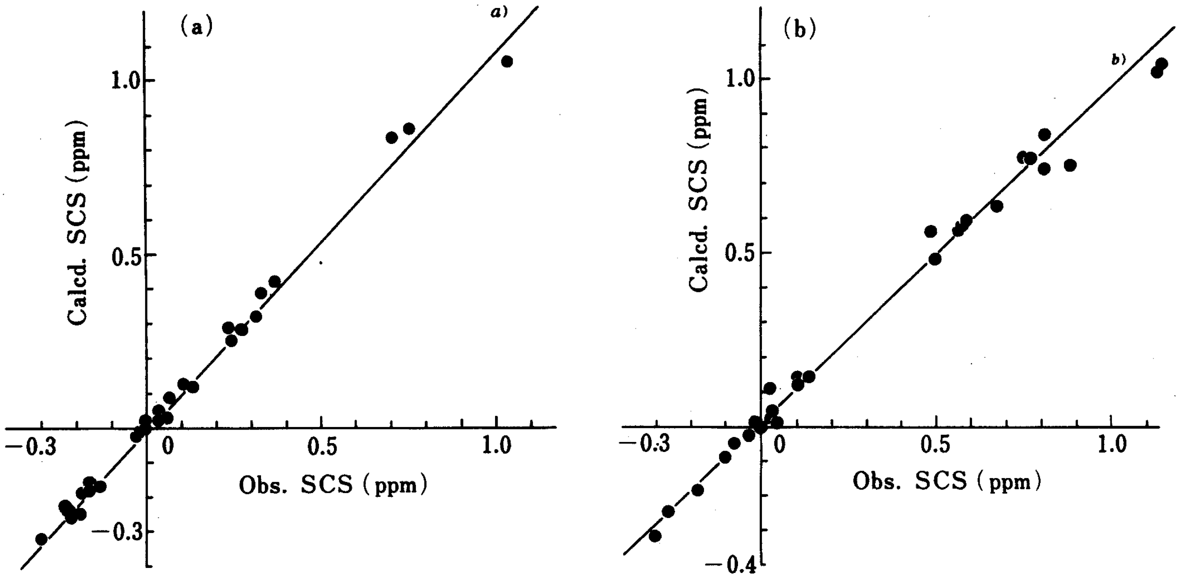


Fig. 1. Plots of Observed *vs.* Calculated SCS of NH^1 Protons (a) and NH^3 Protons (b) in *para*-Substituted 1,3-Diarylureas

a) $Y=-0.004+1.065X$ ($n=28$, $r=0.993$).
b) $Y=0.012+1.004X$ ($n=28$, $r=0.993$).

In the case of *para*-substituted diarylureas, the acidities of the two ureido protons can be relatively evaluated by correlating their ^{1}H-NMR chemical shifts with Hammett's values. However, the chemical shifts could not be directly correlated with them. In order to elucidate the effects of the *para*-substituents on the chemical shifts of both ureido protons, the observed substituent-induced chemical shift (SCS) and calculated SCS are summarized in Table I. The calculated SCS values were computed using empirical substituent constants (NH^1, NH^3: CH_3O, −0.23, −0.1; CH_3, −0.16, −0.03; H, 0, 0; F, −0.02, 0.04; Cl, −0.01, 0.14; CN, 0.25, 0.59; NO_2, 0.28, 0.77). As shown in Fig. 1, the results showed a high degree of linearity between observed SCS and calculated SCS ($r=0.993$, for both ureido protons NH^1 and NH^3). The averages of the errors are −0.003 (NH^1, S.D.=0.038) and −0.011 (NH^3, S.D.=0.035). From the results, it is concluded that the R^1 and R^2 substituent effects on both the N^1 and N^3 atoms are additive and control the chemical shifts of the ureido protons.

As a result of the additivity of the *para*-substitution effects, the chemical shifts of NH were not simply correlated with Hammett's constants. Thus, we attempted to correlate d[NH] (the difference of chemical shifts of the ureido protons in ^{1}H-NMR spectrum) with the combination of σ^1 (σ for the *para*-substituent of R^1) and σ^2 (σ for the *para*-substituent of R^2). As shown in Fig. 2, regression analysis yielded a good linear relationship ($r=0.9411$). This means that the relative acidities of NH^1 and NH^3 depend on combined electron-donating ability of the two *para*-substituents in the diarylurea derivatives.

Next, sixteen *para*-substituted 1,3-diarylureas (Ia—p) were nitrosated with nitrosyl chloride and dinitrogen trioxide. The results are shown in Table IV. With nitrosyl chloride, eight ureas (Ib—d, g, h, j, k, n) gave corresponding isomeric mixtures of 1- and 3-nitrosated ureas, and seven ureas (Ie, f, i, l, m, o, p) gave the corresponding 1-nitrosated ureas (II). With dinitrogen trioxide, thirteen ureas (Ib—d, g—p) afforded isomeric mixtures (II+III) and two ureas (Ie, f) gave 1-nitrosated derivatives as the sole products. We next examined the relation between the isomer ratio (Y=II/(II+III)) and d[NH]. When d[NH] is small enough [below 0.25 ppm (with NOCl) and 0.45 ppm (with N_2O_3)], *para*-substituted diarylureas (I) gave the corresponding isomeric mixtures of 1- and 3-nitrosated derivatives. Moreover, the amounts of the major products were proportional to d[NH] (Fig. 3) and a statistical treatment showed a

Table I. Chemical Shifts[a] and SCS[b] of Ureido Protons in Diarylureas

R^1	R^2	Chemical shift in ppm		Obs. SCS		Calcd SCS[c]		Error[d]		Compound[e] No. I (a—p)
		NH^1	NH^3	NH^1	NH^3	NH^1	NH^3	NH^1	NH^3	
CH_3O	CH_3O	8.31	8.31	−0.30	−0.30	−0.33	−0.33	0.03	0.03	
CH_3O	CH_3	8.40	8.53	−0.21	−0.26	−0.26	−0.26	0.05	0	a
CH_3O	H	8.38	8.51	−0.23	−0.10	−0.23	−0.10	0	0	b
CH_3O	F	8.42	8.54	−0.19	−0.07	−0.25	−0.05	0.06	−0.01	c
CH_3O	Cl	8.39	8.62	−0.22	0.01	−0.24	0.05	0.02	−0.03	d
CH_3O	CN	8.61	9.09	0	0.48	0.02	0.5	−0.02	−0.01	e
CH_3O	NO_2	8.65	9.24	0.04	0.63	0.05	0.68	−0.01	−0.04	f
CH_3	CH_3	8.43	8.43	−0.18	−0.18	−0.19	−0.19	0.01	0.01	
CH_3	H	8.45	8.58	−0.16	−0.03	−0.16	−0.03	0	0	q
CH_3	F	8.45	8.60	−0.16	−0.01	−0.18	0.01	0.02	−0.02	g
CH_3	Cl	8.48	8.64	−0.13	0.03	−0.17	0.11	0.04	−0.08	h
CH_3	CN	8.68	9.10	0.07	0.49	0.09	0.56	−0.02	−0.07	i
CH_3	NO_2	8.75	9.32	0.14	0.71	0.12	0.74	0.02	−0.03	r
H	H	8.61	8.61	0	0	0	0	0	0	
H	F	8.59	8.65	−0.02	0.04	−0.02	0.04	0	0	j
H	Cl	8.60	8.75	−0.01	0.14	−0.01	0.14	0	0	k
H	CN	8.86	9.20	0.25	0.59	0.25	0.59	0	0	l
H	NO_2	8.89	9.38	0.28	0.77	0.28	0.77	0	0	m
F	F	8.65	8.65	0.04	0.04	0.02	0.02	0.02	0.02	
F	Cl	8.67	8.72	0.06	0.11	0.03	0.12	0.03	−0.01	n
F	CN	8.85	9.18	0.24	0.57	0.29	0.56	−0.05	0.01	o
F	NO_2	8.93	9.40	0.32	0.79	0.32	0.75	0	0.04	s
Cl	Cl	8.72	8.72	0.11	0.11	0.13	0.13	−0.02	−0.02	
Cl	CN	8.94	9.20	0.33	0.59	0.39	0.58	−0.06	0.01	p
Cl	NO_2	8.98	9.38	0.37	0.77	0.42	0.76	−0.05	0.01	t
CN	CN	9.32	9.32	0.71	0.71	0.84	0.84	−0.13	−0.13	u
CN	NO_2	9.47	9.65	0.86	1.04	0.87	1.02	−0.01	0.02	v
NO_2	NO_2	9.65	9.65	1.04	1.04	1.05	1.05	−0.01	−0.01	
Average								−0.003	−0.014	
S.D.								0.037	0.035	

[a] δ ppm from tetramethylsilane. [b] $SCS_{NH1} = \delta_{R1} - \delta_H$; $SCS_{NH3} = \delta_{R2} - \delta_H$. $\delta_H = 8.61$ ppm (NH chemical shift of diphenylurea). [c] See the text. [d] Error $= SCS_{Obs.} - SCS_{Calcd}$. [e] The compounds which are not assigned compound numbers, have already been reported in reference 2.

good linearity between them. When d[NH] is large enough [over 0.25 ppm (with NOCl), and over 0.45 ppm (with N_2O_3)], a nitroso group is predominantly introduced at the nitrogen adjacent to the phenyl ring which bears a stronger electron-donating group, affording 1-nitrosated isomers (II) as sole products.

Thus, when dinitrogen trioxide and nitrosyl chloride are used, the relative reactivity of the two ureido nitrogens is determined by the *para*-substituents on the phenyl rings. Consequently the orientation of the nitroso group or the predominant isomer can be predicted from the chemical shifts of the ureido protons in diarylureas.

On nitrosation with dinitrogen tetroxide, *para*-substituted 1,3-diarylureas (If, h, i, l, m, o, p) gave the corresponding 1-nitrosated ureas (IIf, h, i, m, o, p). On similar nitrosation, however, 1,3-diarylureas (Ig, j, k, n) gave isomeric mixtures (IIg, j, k, n+IIIg, j, k, n) in the

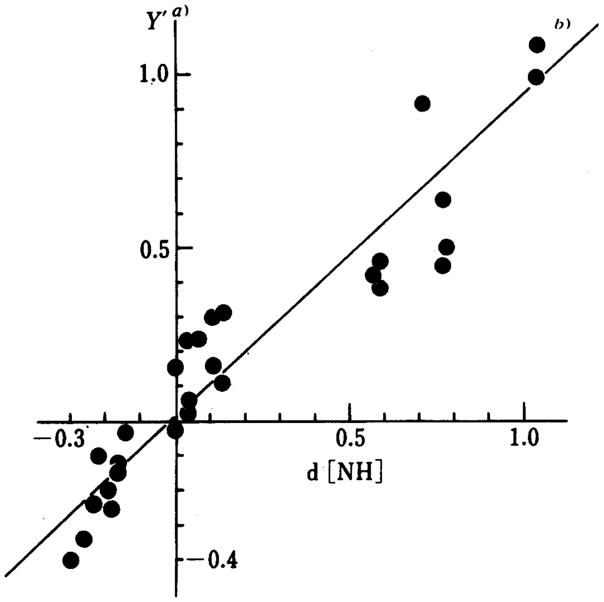


Fig. 2. Plots of d[NH] *vs.* a Linear Combination of the Hammett's Constants for *para*-Substituents: Results of Regression Analysis[a]

a) $Y'=-0.016+0.816\sigma^1+0.601\sigma^2$ ($\sigma^{1,2}$ denote the Hammett's substitution constants.[c]) ($r=0.941$; $F=96.86$ ($n=2$, 25; significant.))
b) $Y'=0.023+0.886\text{d[NH]}$.
c) N. Inamoto, "Shin Jikken Kagaku Kouza, Vol. 14-V," ed. by the Chemical Society of Japan, Maruzen, Tokyo, 1978, p. 2608.
d) Also see the foot notes of Table IV.

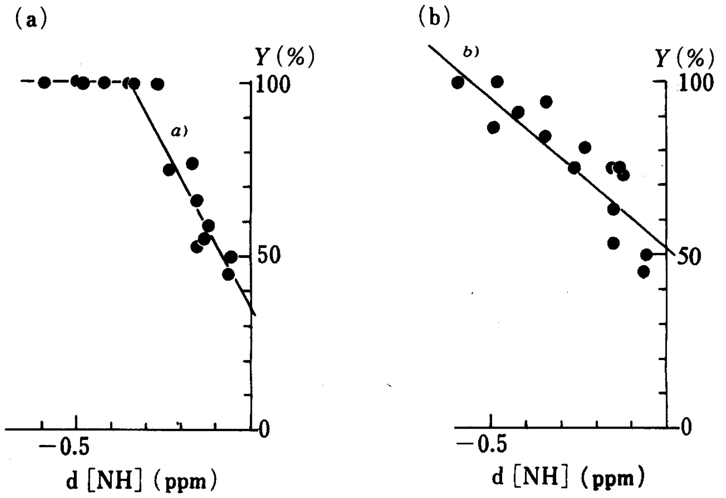


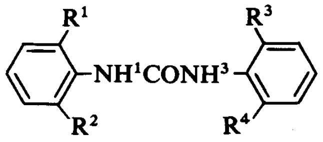
Fig. 3. Correlation between Y_{NOCl} and d[NH] (a), and Correlation between $Y_{\mathrm{N_2O_3}}$ and d[NH] (b)

a) $Y=34.53-202.07X$ ($n=11$, $r=0.943$).
b) $Y=52.79-89.18X$ ($n=15$, $r=0.869$).
Also see the footnotes of Table IV.

ratio of about 1 : 1. Thus, it is difficult to extend the results of nitrosation with nitrosyl chloride and dinitrogen trioxide to the case of dinitrogen tetroxide. Moreover, the nitrosation of 1-(4-methoxyphenyl)-3-arylureas (Ib—e), containing the most electron-donating group (CH_3O) in our experiments, gave exclusively the 3-nitrosated isomers (IIIb—e) instead of the 1-isomers expected from the former results. These results are contradictory. No simple explanation for the results can be offered at the present time, but it can be presumed that dinitrogen tetroxide interacts with the methoxy group in the ureas, reducing the reactivity of the nitrogen attached to the phenyl ring.[6] In any case, since dinitrogen tetroxide has very different properties from nitrosyl chloride and dinitrogen trioxide, it may be possible to develop a more regioselective nitrosation of *para*-substituted ureas.

Five types of *ortho*(*o*-mono, *o*,*o*′-di, *o*,*o*-di, *o*,*o*,*o*′-tri and *o*,*o*,*o*′,*o*′-tetra)-substituted diarylureas (IVa, b, VIIa, b, IVf, g, VIIIa, b, IVj, k) were prepared, and their ^{1}H-NMR spectra were measured in order to estimate the molecular shapes. The chemical shifts of the

Table II. ^{1}H-NMR Chemical Shifts of Ureido Protons in *ortho*-Substituted Diarylureas



Compound No.	R^1	R^2	R^3	R^4	Chemical shifts of NH protons (in ppm)
IVa	CH_3	H	H	H	7.88 8.98
IVb	CH_3CH_2	H	H	H	7.88 8.98
VIIa	CH_3	H	CH_3	H	8.21
VIIb	CH_3CH_2	H	CH_3CH_2	H	8.25
IVf	CH_3	CH_3	H	H	7.68 8.70
IVg	CH_3CH_2	CH_3CH_2	H	H	7.63 8.70
VIIIa	CH_3	CH_3	CH_3	H	7.92 8.15
VIIIb	CH_3CH_2	CH_3CH_2	CH_3CH_2	H	7.72 7.95
IVj	CH_3	CH_3	CH_3	CH_3	7.80
IVk	CH_3CH_2	CH_3CH_2	CH_3CH_2	CH_3CH_2	7.62

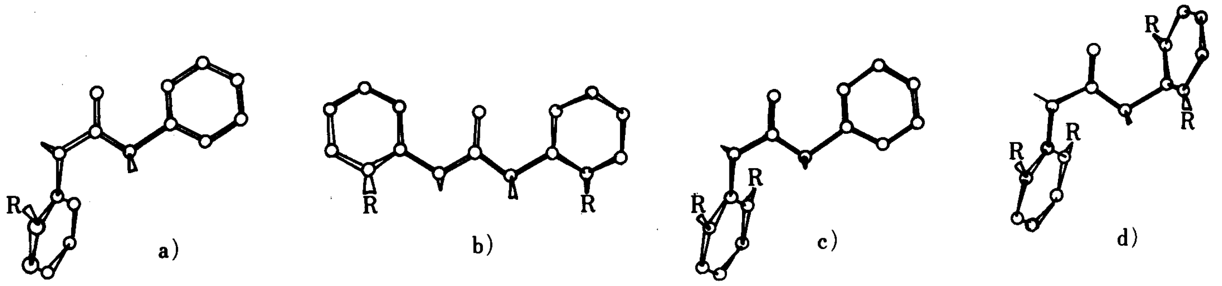
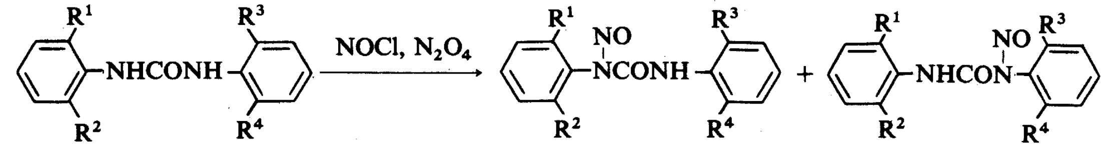


Fig. 4. Conformation of *ortho*-Substituted 1,3-Diarylureas

ureido protons are collected in Table II. The ^{1}H-NMR spectra of *ortho*-substituted 1,3-diarylureas (IVa, b, VIIIa, b, and IVf, g) exhibited the ureido proton signals at higher field than those of *para*-substituted urea derivatives: di(4-tolyl)urea, 8.43 ppm; 3-phenyl-1-(4-tolyl)-urea, 8.45 and 8.53 ppm). The ureido proton signals (NH^1) of compounds IVa,b, and IVf, g were observed at higher field (7.88, 7.88, 7.68 and 7.63 ppm, respectively) and the other ureido proton signals (NH^3) were at lower field (8.98, 8.98, 8.70 and 8.70 ppm, respectively), compared with those of *para*-substituted ureas. Based on the magnetic anisotropy effects of the aromatic rings on the two ureido protons, some of the most stable rotomers are estimated to be those shown in Fig. 4.

Eleven *ortho*-substituted 1,3-diarylureas were nitrosated with nitrosyl chloride and dinitrogen tetroxide to give *N*-nitrosated urea derivatives. In most cases, the nitroso group was introduced at a ureido nitrogen which was not sterically hindered, as shown in Table III. *ortho*-Monosubstituted ureas (IVa, b) gave 3-nitrosated derivatives (IVa, b) predominantly with both nitrosyl chloride and dinitrogen tetroxide. Symmetric *ortho*-disubstituted compounds (IVc—e) also afforded isomeric mixtures and the ratio of isomers reflected the relative bulk of the substituents. However, unsymmetric *ortho*-disubstitution did not always affect the nitrosation position. Compound IVf gave the 1-nitrosated isomer (Vf) predominantly though the N^1 atom seems to be more hindered than the other. *ortho*-Trisubstituted urea derivatives (IVh, i) gave VI(h, i) as expected from the illustration in Fig. 4d. *ortho*-Tetrasubstituted urea derivatives IVj, k were not nitrosated by nitrosyl chloride, but with dinitrogen tetroxide they

TABLE III. Isomer Ratio of *ortho*-Substituted 1,3-Diarylnitrosoureas



IVa—k Va—k VIa—k

Compound No.	R^1	R^2	R^3	R^4	Nitrosating reagent NOCl		N_2O_4	
					Isomer ratio			
IV					V	VI	V	VI
a	CH_3	H	H	H	39	61	21	71
b	CH_3CH_2	H	H	H	13	87	13	87
c	CH_3	H	Cl	H	57	43	77	23
d	C_6H_5	H	Cl	H	31	69	26	74
e	CH_3CH_2	H	Cl	H	39	61	42	58
f	CH_3	CH_3	H	H	81	19	50	50
g	CH_3CH_2	CH_3CH_2	H	H	0	100	0	100
h	CH_3	CH_3	CH_3O	H	0	100	0	100
i	CH_3	CH_3	Cl	H	8	92	6	94
j	CH_3	CH_3	CH_3	CH_3	(62% recovered)		(90% yield)	
k	CH_3CH_2	CH_3CH_2	CH_3CH_2	CH_3CH_2	(54% recovered)		(66% yield)	

yielded the corresponding nitrosoureas. This result means that the sizes of the nitrosating reagents are different from each other and/or the reaction mechanisms are not similar (one is an ionic reaction and the other is a radical reaction). Considering the special reactivity of dinitrogen tetroxide with *para*-substituted urea derivatives, the results suggest that the reaction mechanism of nitrosation with dinitrogen tetroxide is different from that with nitrosyl chloride and dinitrogen trioxide. Anyway, the nitrosation of *ortho*-substituted 1,3-diarylureas is controlled by steric factors.

Experimental[7]

Preparation of Diarylureas——The 1,3-diarylureas (Ia—p and IVa—k) were prepared by the reaction of the corresponding anilines and phenyl isocyanates or 1-methyl-1-nitroso-3-(substituted phenyl)urea derivatives. Some of them have already been synthesized and reported.[2] When the melting points of diarylureas were not identical with the reported ones, the products were subjected to elemental analysis. A typical preparation of 1,3-diarylureas (Ia—p) is described for the case of 1-(4-methoxyphenyl)-3-(4-tolyl)urea (Ia).

1-(4-Methoxyphenyl)-3-(4-tolyl)urea (Ia): A solution of 4-methoxyaniline (1.5 g, 0.01 mol) in benzene (50 ml) was added dropwise to a solution of 4-tolyl isocyanate (1.5 g, 0.01 mol) in benzene (100 ml) with stirring. The stirring was continued for 1.5 h. The solution was evaporated to dryness under reduced pressure and the residue was recrystallized from ethanol. Colorless needles, mp 243 °C (lit., mp 236 °C[8]). IR (Nujol): 1640 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.35, 8.40 (NH). *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.92. Found: C, 70.25; H, 6.38; N, 10.73.

1-(4-Methoxyphenyl)-3-phenylurea (Ib): Colorless needles from ethanol, mp 198 °C (lit., 186—190 °C,[8] mp 192 °C[9]). IR (Nujol): 1620 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.38, 8.52 (NH).

3-(4-Fluorophenyl)-1-(4-methoxyphenyl)urea (Ic): Colorless needles from ethanol, mp 230—240 °C (sublimate). IR (Nujol): 1630 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.42, 8.54 (NH). *Anal.* Calcd for $C_{14}H_{13}FN_2O_2$: C, 64.59; H, 5.04; N, 10.77. Found: C, 64.58; H, 5.04; N, 10.70.

3-(4-Chlorophenyl)-1-(4-methoxyphenyl)urea (Id): Colorless needles form ethanol, mp 250—255 °C (sublimate). IR (Nujol): 1630 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.39, 8.62 (NH). *Anal.* Calcd for $C_{14}H_{13}ClN_2O_2$: C, 71.35; H, 5.54; N, 11.94. Found: C, 71.35; H, 5.56; N, 11.95.

3-(4-Cyanophenyl)-1-(4-methoxyphenyl)urea (Ie): Pale yellow plates from ethanol, mp 248 °C. IR (Nujol): 1625 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.61, 9.09 (NH). *Anal.* Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.13; H, 5.09; N, 15.58.

1-(4-Methoxyphenyl)-3-(4-nitrophenyl)urea (If): Yellow needles from acetone, mp 234 °C (lit., mp 229 °C[10]). IR (Nujol): 1635 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.65, 9.24 (NH).

3-(4-Fluorophenyl)-1-(4-tolyl)urea (Ig): Colorless needles (from ethanol), mp 235—240 °C. IR (Nujol): 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.45, 8.64 (NH). *Anal.* Calcd for $C_{14}H_{13}FN_2O$: C, 68.82; H, 5.37; N, 11.48. Found: C, 67.99; H, 5.54; N, 11.77.

3-(4-Chlorophenyl)-1-(4-tolyl)urea (Ih): Colorless prisms, mp 267—270 °C (lit., 297—299 °C[11]). IR (Nujol): 1653 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.54, 8.71 (NH). *Anal.* Calcd for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 4.99; N, 10.48. Found: C, 64.47; H, 4.84; N, 10.64.

3-(4-Cyanophenyl)-1-(4-tolyl)urea (Ii): Pale yellow plates, mp 245—250 °C (sublimate). IR (Nujol): 1635 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.69, 9.10 (NH). *Anal.* Calcd for $C_{15}H_{13}N_3O$: C, 71.67; H, 5.21; N, 16.72. Found: C, 71.60; H, 5.40; N, 16.69.

1-(4-Fluorophenyl)-3-phenylurea (Ij): Colorless needles from ethanol, mp 245 °C (lit., mp 239 °C[12]). IR (Nujol): 1620 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.59, 8.65 (NH). *Anal.* Calcd for $C_{13}H_{11}FN_2O$: C, 67.80; H, 4.38; N, 12.17. Found: C, 67.51; H, 4.48; N, 12.18.

3-(4-Chlorophenyl)-1-phenylurea (Ik): Colorless needles from ethanol, mp 235—240 °C (sublimate) (lit., mp 237—238 °C,[13] mp 250—251 °C[14]). IR (Nujol): 1633 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.63, 8.74 (NH).

3-(4-Cyanophenyl)-1-phenylurea (Il): Pale yellow plates from ethanol, mp 210 °C (lit., mp 198.5 °C[15]). IR (Nujol): 1630 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.86, 9.20 (NH). *Anal.* Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.75; H, 4.77; N, 17.51.

3-(4-Nitrophenyl)-1-phenylurea (Im): Yellow needles from ethanol, mp 213—218 °C (lit., mp 225—227 °C,[16] 207 °C[17]). IR (Nujol): 1653 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.89, 9.38 (NH).

3-(4-Chlorophenyl)-1-(4-fluorophenyl)urea (In): Colorless needles from ethanol, mp 265—270 °C (sublimate). IR (Nujol): 1630 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.67, 8.73 (NH). *Anal.* Calcd for $C_{13}H_{10}FClN_2O$: C, 58.97; H, 3.81; N, 10.59. Found: C, 59.03; H, 3.77; N, 10.74.

3-(4-Cyanophenyl)-1-(4-fluorophenyl)urea (Io): Pale yellow plates, from ethanol, mp 241 °C. IR (Nujol): 1635 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.85, 9.18 (NH). *Anal.* Calcd for $C_{14}H_{10}FN_3O$: C, 65.86; H, 3.95; N, 16.47. Found: C, 65.72; H, 4.02; N, 16.26.

3-Phenyl-1-(4-tolyl)urea (Iq): mp 213 °C (lit., 218 °C[8]). 3-(4-Nitrophenyl)-1-(1-tolyl)urea (Ir): mp 277 °C (lit., 290 °C[17]). *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.09; H, 6.26; N, 12.41. 1-(4-Fluorophenyl)-3-(4-nitrophenyl)urea (Is): mp 250 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.52, 7.13, 7.69, 8.90 (ring protons). IR (Nujol): 1620 (C=O), 3150 (NH) cm^{-1}. *Anal.* Calcd for $C_{13}H_{10}FN_3O_3$: C, 56.73; H, 3.64; N, 15.27. Found: C, 56.79; H, 3.85; N, 15.39. 1-(4-Chlorophenyl)-3-(4-nitrophenyl)urea (It): >mp 300 °C (lit., 310 °C[17]). 1,3-Bis(4-cyanophenyl)urea (Iu): mp 275 °C (lit., 273 °C[15]). 1-(4-Cyanophenyl)-3-(4-nitrophenyl)urea (Iv): mp 290 °C (lit., 289—300 °C[18]).

1-(4-Chlorophenyl)-3-(4-cyanophenyl)urea (Ip): Pale yellow plates from ethanol, mp 261 °C. IR (Nujol): 1635 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.94, 9.20 (NH). *Anal.* Calcd for $C_{14}H_{10}ClN_3O$: C, 61.88; H, 3.68; N, 15.47. Found: C, 61.60; H, 3.78; N, 15.63.

1,3-Di(2-tolyl)urea (VIIa): mp 254 °C (lit., 256 °C[19]).

1,3-Bis(2-ethylphenyl)urea (VIIb): mp 231 °C. *Anal.* Calcd for $C_{17}H_{20}N_2O \cdot 2/3\ H_2O$: C, 72.77; H, 7.38; N, 9.98. Found: C, 72.72; H, 7.09; N, 9.98.

1-(2,6-Dimethylphenyl)-3-(2-tolyl)urea (VIIIa): mp 246 °C. IR (Nujol): 1632 (C=O), 3275 (NH). ^{13}C-NMR (DMSO-d_6) δ: 153.25. *Anal.* Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: 75.40; H, 7.15; N, 10.93.

1-(2,6-Diethylphenyl)-3-(2-ethylphenyl)urea (VIIIb): Colorless needles, mp 270 °C. IR (Nujol): 1622 (C=O), 3270 (NH). ^{13}C-NMR (DMSO-d_6) δ: 154.22 (C=O). *Anal.* Calcd for $C_{19}H_{24}N_2O \cdot 1/3H_2O$: C, 75.39; H, 8.15; N, 9.26. Found: 75.56; H, 8.04; N, 9.24.

3-Phenyl-1-(2-tolyl)urea (IVa): Colorless needles from ethanol, mp 207 °C. IR (Nujol): 1635 (C=O), 3280 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.98, 7.88 (NH). ^{13}C-NMR (DMSO-d_6) δ: 152.58. *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.54; H, 6.29; N, 12.35.

1-(2-Ethylphenyl)-3-phenylurea (IVb): Colorless needles from ethanol, mp 173 °C. IR (Nujol): 1624 (C=O), 3280 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.98, 7.88 (NH). ^{13}C-NMR (DMSO-d_6) δ: 152.52. *Anal.* Calcd for $C_{15}H_{16}N_2O$: C, 72.73; H, 6.62; N, 11.31. Found: C, 72.66; H, 6.43; N, 11.39.

3-(2-Chlorophenyl)-1-(2-tolyl)urea (IVc): Colorless needles from ethanol, mp 240 °C. IR (Nujol): 1638 (C=O), 3300 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.66, 8.63 (NH). ^{13}C-NMR (DMSO-d_6) δ: 152.50. *Anal.* Calcd for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 4.99; N, 10.64. Found: C, 64.45; H, 5.07; N, 10.62.

3-(2-Chlorophenyl)-1-(2-phenylphenyl)urea (IVd): Colorless needles from ethanol, mp 182 °C. IR (Nujol): 1640 (C=O), 3275—3325 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.64, 8.61 (NH). ^{13}C-NMR (DMSO-d_6) δ: 152.91. *Anal.* Calcd for $C_{19}H_{16}ClN_2O$: C, 70.80; H, 4.56; N, 8.70. Found: C, 70.68; H, 4.70; N, 8.64.

3-(2-Chlorophenyl)-1-(2-ethylphenyl)urea (IVe): Colorless needles from ethanol, mp 195 °C. IR (Nujol): 1636 (C=O), 3280 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.64, 8.61.(NH). ^{13}C-NMR (DMSO-d_6) δ: 152.69. *Anal.* Calcd for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.46; N, 10.20. Found: C, 65.55; H, 4.57; N, 10.17.

1-(2,6-Dimethylphenyl)-3-phenylurea (IVf): Colorless needles from ethanol, mp 246 °C. IR (Nujol): 1625 (C=O), 3275 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.68, 8.70 (NH). ^{13}C-NMR (DMSO-d_6) δ: 153.06. *Anal.* Calcd for $C_{15}H_{14}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.40; H, 7.15; N, 10.93.

1-(2,6-Diethylphenyl)-3-phenylurea (IVg): Colorless needles from ethanol, mp 231 °C. IR (Nujol): 1635 (C=O), 3270 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.63, 8.70 (NH). ^{13}C-NMR (DMSO-d_6) δ: 153.81. *Anal.* Calcd for $C_{17}H_{20}N_2O \cdot 2/3H_2O$: C, 72.77; H, 7.38; N, 9.98. Found: C, 72.72; H, 7.09; N, 9.98.

1-(2,6-Dimethylphenyl)-3-(2-methoxyphenyl)urea (IVh): Colorless needles from ethanol, mp 219 °C. IR (Nujol): 1640 (C=O), 3350 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.20, 8.36 (NH). ^{13}C-NMR (DMSO-d_6) δ: 152.84. *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.74; N, 10.36. Found: C, 71.03; H, 6.68; N, 10.33.

3-(2-Chlorophenyl)-1-(2,6-dimethylphenyl)urea (IVi): Colorless needles from ethanol, mp 256 °C. IR (Nujol): 1635 (C=O), 3275 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.27, 8.52 (NH). ^{13}C-NMR (DMSO-d_6) δ: 152.72. *Anal.* Calcd for $C_{15}H_{15}ClN_2O$: C, 65.55; H, 5.51; N, 10.20. Found: C, 65.48; H, 5.60; N, 10.11.

1,3-Bis(2,6-dimethylphenyl)urea (IVj): Colorless needles from ethanol, >mp 300 °C. IR (Nujol): 1620 (C=O), 3260 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.80 (NH). ^{13}C-NMR (DMSO-d_6) δ: 153.86. *Anal.* Calcd for $C_{17}H_{20}N_2O \cdot 1/3H_2O$: C, 74.45; H, 7.54; N, 10.22. Found: C, 74.54; H, 7.44; N, 10.41.

1,3-Bis(2,6-diethylphenyl)urea (IVk): Colorless needles from ethanol, >mp 300 °C. IR (Nujol): 1630 (C=O), 3280 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.62 (NH). ^{13}C-NMR (DMSO-d_6) δ: 154.91. *Anal.* Calcd for $C_{21}H_{28}N_2O$: C, 77.73; H, 8.70; N, 8.63. Found: C, 77.71; H, 8.68; N, 8.67.

Nitrosation of 1,3-Diarylureas(Ia—p and IVa—k) (A—C)——Each of sixteen *para*-substituted 1,3-diarylureas (Ia—p) was nitrosated in dimethylformamide at 0 °C with nitrosyl chloride, dinitrogen trioxide or dinitrogen tetroxide. Ia was too unstable for reproducible determination of the isomer ratio. Eleven *ortho*-substituted 1,3-diarylureas (IVa—k) were nitrosated in the same manner as *para*-substituted ureas with nitrosyl chloride and dinitrogen tetroxide. A typical experiment with 3-(4-chlorophenyl)-1-(4-methoxyphenyl)urea (Id) is described.

A. With Nitrosyl Chloride: A solution of nitrosyl chloride (500 mg, 6.7 mmol) in dimethylformamide (10 ml) was added dropwise to a solution of 3-(4-chlorophenyl)-1-(4-methoxyphenyl)urea (Id) (235 mg, 1 mmol) in dimethylformamide (1 ml) at below 0 °C, with stirring. The reaction mixture was further stirred at 0 °C for 2 h and diluted with ice-water (100 ml). The mixture was extracted with ether (200 ml, twice), the combined extracts were washed with cold water and dried over anhydrous sodium sulfate, and then the ether was evaporated off under reduced pressure. The residue was recrystallized from ether.

1-(4-Methoxyphenyl)-3-phenylnitrosourea (IIb+IIIb): Pale yellow fine crystals. Yield 68%. IR (Nujol): 1745 (C=O) cm^{-1}. ^{1}H-NMR (chloroform-d_1) δ: 12.05 (NH). 3-(4-Fluorophenyl)-1-(4-methoxyphenyl)nitrosourea (IIc+IIIc): Pale yellow fine crystals. Yield 38%. IR (Nujol): 1725 (C=O) cm^{-1}. ^{1}H-NMR (chloroform-d_1) δ: 11.83 (NH). 3-(4-Chlorophenyl)-1-(4-methoxyphenyl)nitrosourea (IId+IIId): Yellow fine crystals. Yield 78%. IR (Nujol): 1750 (C=O) cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 11.30 (NH). 3-(4-Cyanophenyl)-1-(4-methoxyphenyl)-1-nitrosourea (IIe): Yellow needles, mp 113 °C. Yield 87%. IR (Nujol): 1720 (C=O) cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 10.43 (NH). 1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-1-nitrosourea (IIf): Reddish yellow crystalline powder, mp 35—40 °C (dec.). IR (Nujol): 1720 (C=O) cm^{-1}. This compound was very unstable at room temperature; it exploded within a few minutes in the crystalline state. 3-(4-Fluorophenyl)-1-(4-tolyl)nitrosourea (IIg+IIIg): Pale yellow crystalline powder. Yield 85%. IR (Nujol): 1730 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 10.03 (NH). 3-(4-Chlorophenyl)-1-(4-tolyl)nitrosourea (IIh+IIIh): Pale yellow crystalline powder. Yield 87%. IR (Nujol): 1735 (C=O) cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 10.11 (NH). 3-(4-Cyanophenyl)-1-(4-tolyl)-1-nitrosourea (IIi): Pale yellow fine crystals, mp 69 °C (dec.). Yield 73%. IR (Nujol): 1730 (C=O) cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 10.30 (NH). 3-(4-Fluorophenyl)-1-phenylnitrosourea (IIj+IIIj): Pale yellow needles. Yield 81%. IR (Nujol): 1730 (C=O) cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 9.90 (NH). 3-(4-Chlorophenyl)-1-phenylnitrosourea (IIk+IIIk): Pale yellow fine crystals. Yield 63%. IR (Nujol): 1725 (C=O) cm^{-1}. This compound was unstable to obtain the NMR spectrum. 3-(4-Cyanophenyl)-1-phenyl-1-nitrosourea (IIl): Yellow fine prisms, mp 111 °C. Yield 73%. IR (Nujol): 1730 (C=O) cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 10.30 (NH). 3-(4-Nitrophenyl)-1-phenyl-1-nitrosourea (IIm): Reddish yellow crystalline powder, mp 45—48 °C. Yield 66%. IR (Nujol): 1740 (C=O) cm^{-1}. This compound was too unstable to obtain the NMR spectrum. 3-(4-Chlorophenyl)-1-(4-fluorophenyl)nitrosourea (IIn+IIIn): Pale yellow needles. Yield 76%. IR (Nujol): 1730 (C=O) cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 9.99 (NH). 3-(4-Cyanophenyl)-1-(4-fluorophenyl)-1-nitrosourea (IIo): Yellow prisms, mp 115 °C. Yield 72%. IR (Nujol): 1735 (C=O) cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 10.30 (NH). 1-(4-Chlorophenyl)-3-(4-cyanophenyl)-1-nitrosourea (IIp): Yellow needles, mp 82—83 °C. Yield 46%. IR (Nujol): 1725 (C=O) cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 10.33 (NH). 3-Phenyl-1-(2-tolyl)nitrosourea (Va+VIa): Yield 47%. IR (Nujol): 1735 (C=O), 3390 (NH) cm^{-1}. 1-(2-Ethylphenyl)-3-phenylnitrosourea (Vb+VIb): Yield 86%. IR (Nujol): 1700 (C=O), 3260 (NH) cm^{-1}. 3-(2-Chlorophenyl)-1-(2-tolyl)nitrosourea (Vc+VIc): Yield 86%. IR (Nujol): 1730 (C=O), 3360 (NH) cm^{-1}. 3-(2-Chlorophenyl)-1-(2-phenylphenyl)nitrosourea (Vd+VId): Yield 47%. IR (Nujol): 1730 (C=O), 3350 (NH) cm^{-1}. 3-(2-Chlorophenyl)-1-(2-ethylphenyl)nitrosourea (Ve+VIe): Yield 51%. IR (Nujol): 1730 (C=O), 3350 (NH) cm^{-1}. 1-(2,6-Dimethylphenyl)-3-phenylnitrosourea (Vf+VIf): Yield 76%. IR (Nujol): 1700 (C=O), 3300 (NH) cm^{-1}. 1-(2,6-Diethylphenyl)-3-phenylnitrosourea (Vg+VIg): Yield 74%. IR (Nujol): 1700 (C=O), 3330 (NH) cm^{-1}. 1-(2,6-Dimethylphenyl)-3-(2-methoxyphenyl)nitrosourea (Vh+VIh): Yield 96%, IR (Nujol): 1690 (C=O), 3250

(NH) cm^{-1}. 3-(2-Chlorophenyl)-1-(2,6-dimethylphenyl)nitrosourea (Vi + VIi): Yield 68%. IR (Nujol): 1700 (C=O), 3280 (NH) cm^{-1}.

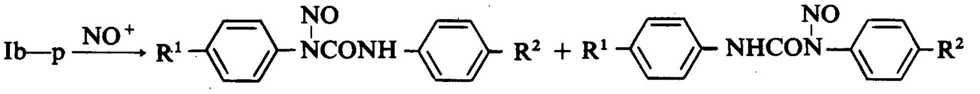
B. With Dinitrogen Trioxide: A solution of dinitrogen trioxide (500 mg, 6.6 mmol) in dimethylformamide (30 ml) was added dropwise to a solution of 3-(4-chlorophenyl)-1-(4-methoxyphenyl)urea (Id) (235 mg, 1 mmol) in dimethylformamide (5 ml) at below 0 °C, with stirring. The reaction mixture was further stirred at 0 °C for 2 h and diluted with ice water (100 ml). The mixture was extracted with ether (250 ml twice). The combined extracts were washed with cold water and dried over anhydrous sodium sulfate, and then the ether was evaporated off under reduced pressure. The residue was recrystallized from ether.

3-Phenyl-1-(4-methoxyphenyl)nitrosourea (IIb + IIIb): Yield 52%. 3-(4-Fluorophenyl)-1-(4-methoxyphenyl) nitrosourea (IIc + IIIc): Yield 64%. 3-(4-Chlorophenyl)-1-(4-methoxyphenyl)nitrosourea (IId + IIId): Yield 44%. 3-(4-Cyanophenyl)-1-(4-methoxyphenyl)-1-nitrosourea (IIe): Yield 43%. 1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-1-nitrosourea (IIf): Yield 38%. 3-(4-Fluorophenyl)-1-(4-tolyl)nitrosourea (IIg + IIIg): Yield 63%. 3-(4-Chlorophenyl)-1-(4-tolyl)nitorsourea (IIh + IIIh): Yield 83%. 3-(4-Cyanophenyl)-1-(4-tolyl)nitrosourea (IIi + IIIi): Yield 63%. 3-(4-Fluorophenyl)-phenylnitrosourea (IIj + IIIj): Yield 88%. 3-(4-Chlorophenyl)-1-phenylnitrosourea (IIk + IIIk): Yield 98% (wet). 3-(4-Cyanophenyl)-1-phenylnitrosourea (IIl + IIIl): Yield 51%. 3-(4-Nitrophenyl)-1-phenylnitrosourea (IIm + IIIm): Yield 63%. 3-(4-Chlorophenyl)-1-(4-fluorophenyl)nitrosourea (IIn + IIIn): Yield 65%. 3-(4-Cyanophenyl)-1-(4-fluorophenyl)nitrosourea (IIo + IIIo): Yield 48%. .1-(4-Chlorophenyl)-3-(4-cyanophenyl)nitrosourea (IIp + IIIp): Yield 74%.

C. With Dinitrogen Tetroxide: A solution of 3-(4-chlorophenyl)-1-(4-methoxyphenyl)urea (Id) (235 mg, 1 mmol) in dimethylformamide (5 ml) was cooled to 0 °C and stirred. Well chilled dinitrogen tetroxide (500 mg, 5.4 mmol) was added dropwise to the stirred solution at 0 °C. The reaction mixture was stirred for 2 h, then diluted with ice-water (100 ml), and extracted with ether (200 ml, twice). The combined extracts were washed with cold water, and dried over anhydrous sodium sulfate, then the ether was evaporated off under reduced pressure. The residue was recrystallized from ether.

1-(4-Methoxyphenyl)-3-phenyl-3-nitrosourea (IIIb): Pale yellow fine crystals, mp 111 °C. Yield 68%. 3-(4-Fluorophenyl)-1-(4-methoxyphenyl)-3-nitrosourea (IIIc): Pale yellow fine needles, mp 135 °C. Yield 38%. 3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-nitrosourea (IIId): Yellow fine needles. Yield 71%. 3-(4-Cyanophenyl)-1-(4-methoxyphenyl)-3-nitrosourea (IIIe): Orange yellow fine plates, mp, 112 °C. Yield 92%. 1-(4-Methoxyphenyl)-3-(4-

TABLE IV. The Isomer Ratio ($Y^{a)}$) of *para*-Substituted 1,3-Diaryl-1-nitrosoureas (IIa—p)



IIb—p IIIb—p

Compound No. II	1-Nitrosated isomer [IIb—p] ratio Y (%)			$d[NH]^{b)}$
	Y_{NOCl}	$Y_{N_2O_3}$	$Y_{N_2O_4}$	
b[c]	55	75	0[d]	−0.13
c	59	73	0	−0.12
d	76	81	0	−0.23
e	100	100	0	−0.48
f	100	100	100	−0.59
g	66	63	52	−0.15
h	76	75	76	−0.16
i	100	91	100	−0.42
j	45	45	46	−0.06
k	53	53	51	−0.15
l	100	84	100	−0.34
m	100	86	100	−0.49
n	50	50	50	−0.05
o	100	94	100	−0.33
p	100	75	100	−0.26

a) Y denotes the percentage of compound II in the nitrosated ureas (II and/or III). $Y = II/(II + III)$. The subscript of Y denotes the nitrosating reagent. *b)* $d[NH] = \delta_{R1} - \delta_{R2}$; δ_R: the chemical shift of ureido protons in diarylurea (Ib—p). *c)* The results for Ia were not reproducible. *d)* Upon the nitrosation with dinitrogen tetroxide, Ib—e gave IIIb—e exclusively.

nitrophenyl)-1-nitrosourea (IIf): Yield 40%. 3-(4-Fluorophenyl)-1-(4-tolyl)nitrosourea (IIg+IIIg): Yield 85%. 3-(4-Chlorophenyl)-1-(4-tolyl)-1-nitrosourea (IIh): Yield 90%. 3-(4-Cyanophenyl)-1-(4-tolyl)-1-nitrosourea (IIi): Yield 38%. 3-(4-Fluorophenyl)-1-phenylnitrosourea (IIj+IIIj): Yield 89%. 3-(4-Chlorophenyl)-1-phenylnitrosourea (IIk+IIIk): Yield 87% (wet). 3-(4-Cyanophenyl)-1-phenylnitrosourea (IIl+IIIl): Yield 50%. 3-(4-Nitrophenyl)-1-phenylnitrosourea (IIm+IIIm): Yield 56%. 3-(4-Chlorophenyl)-1-(4-fluorophenyl)nitrosourea (IIn+IIIn): Yield 85%. 3-(4-Cyanophenyl)-1-(4-fluorophenyl)nitrosourea (IIo+IIIo): Yield 78%. 1-(4-Chlorophenyl)-3-(4-cyanophenyl)nitrosourea (IIp+IIIp): Yield 41%. 3-Phenyl-1-(2-tolyl)nitrosourea (Va+VIa): Yield 31%. 1-(2-Ethylphenyl)-3-phenylnitrosourea (Vb+VIb): Yield 80%. 3-(2-Chlorophenyl)-1-(2-tolyl)nitrosourea (Vc+VIc): Yield 50%. 1-(2-Chlorophenyl)-3-(2-phenylphenyl)nitrosourea (Vd+VId): Yield 51%. 3-(2-Chlorophenyl)-1-(2-ethylphenyl)nitrosourea (Ve+VIe): Yield 43%. 1-(2,6-Dimethylphenyl)-3-phenylnitrosourea (Vf+VIf): Yield 69%. 1-(2,6-Diethylphenyl)-3-phenylnitrosourea (Vg+VIg): Yield 81%. 1-(2,6-Dimethylphenyl)-3-(2-methoxyphenyl)-nitrosourea (Vh+VIh): Yield 71%. 3-(2-Chlorophenyl)-1-(2,6-dimethylphenyl)nitrosourea (Vi=VIi): Yield 71%. 1,3-Bis(2,6-dimethylphenyl)nitrosourea (Vj=VIj): Pale yellow crystalline powder, mp 131 °C (dec.). Yield 90%. IR (Nujol): 1740 (C=O), 3360 (NH) cm^{-1}. 1,3-Bis(2,6-diethylphenyl)nitrosourea (Vk+VIk): Yellow crystalline powder, mp 120—125 °C (dec.). Yield 66%. IR (Nujol): 1720 (C=O), 3280 (NH) cm^{-1}.

Since the 1,3-diarylnitrosoureas were unstable, most of them could not be subjected to elemental analysis. They were then identified by means of infrared (IR) and ^{1}H-NMR spectroscopy, and derived to the corresponding 1-phenylazo-2-naphthols.

Even in the case of formation of a mixture of 1-nitroso and 3-nitroso isomers, only one carbonyl band in the IR spectrum of the nitrosated urea appeared in the range of 1725—1753 cm^{-1}, and also only one broad amide proton signal was observed in the region of 9.5—12.0 ppm in the ^{1}H-NMR spectra, except in the case of 1-(4-fluorophenyl)-3-phenylnitrosoureas (IIj+IIIj).

Determination Procedure for the Formation Ratio of 1,3-Diarylnitrosoureido Isomers (IIa—p, IIIa—p, Va—k, and VIa—k)——Since the nitrosated ureas are unstable, it is very difficult to separate them by using ordinary methods. 1,3-Diarylnitrosoureas were reacted with 2-naphthol and gave the corresponding 1-phenylazo-2-naphthols in reproducible yields. The conversion rates were generally similar among the nitrosoureas and the effects of substitution on the phenyl ring were within the range of experimental error.[2] Therefore, the formation ratio of azo-dye corresponds to the ratio of the parent 1,3-diarylnitrosoureido isomers.

A nitrosoarylurea (about 5 mg) was dissolved in ethanol (1 ml), then 0.1 M naphthol (1 ml) in ethanol and 1 N sodium hydroxide (1 ml) were added. The reaction mixture was allowed to stand for 5 min at room temperature. The resulting solution was subjected to thin layer chromatography (silica gel, activated for 1.5 h, at 110 °C) using 1,3,5-trimethylbenzene as the developing solvent. Each spot was scratched off and extracted with ether (10 ml, three times), and the extracts were evaporated to dryness. The residue was dissolved in benzene (5 ml). The absorption of the azo dye was measured at $\lambda_{\max}$ (480—520 nm). The ratio was calculated from calibration curves at $\lambda_{\max}$.

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References and Notes

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