1,3-Nitroso Rearrangement and Transnitrosation of 1-Aryl-3-benzyl-1-nitrosoureas Which Decompose to Liberate Nitrosyl Radical under Mild Conditions¹⁾

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Thermolysis of 1-aryl-3-benzyl-1-nitrosoureas (1c, d) was carried out in CCl_4 at 33°C under an atmosphere of air or argon. Decomposition of 1c, d under aerobic conditions gave mainly benzyl isocyanate (4b) via a diazoester intermediate, whereas under anaerobic conditions, decomposition gave 1-aryl-3-benzyl-3-nitrosoureas (5c, d) as 1,3-shifted products, and 3-benzyl-1-(4-substituted 2-nitrophenyl)-3-nitrosoureas (8c, d) as transnitrosated products via N–NO bond cleavage. 3-Benzyl-1-(4-substituted 2-nitrophenyl)ureas (6c, d) were also produced by N–NO bond cleavage. The 1,3-nitroso shift and transnitrosation under these conditions were assumed to involve a nitrosyl radical fission pathway. The nitrosated nitro compounds (8c, d) were also obtained together with 6c, d by nitration of the ureas (7c, d) with a mixture of fuming nitric acid and acetic acid. The *N*-nitrosourea (1c) acted as a nitrosating agent on 3-methyl-1-(4-tolyl)urea (7a) to convert it into nitrosoureas (1a and 5a).

From our results, we presumed that the *O*-nitrosoisourea (11) or its isomer (12) was an intermediate in the 1,3-nitroso shift and also an ultimate nitrosating agent in the transnitrosation reaction.

Keywords nitrosourea; *O*-nitrosoisourea; nitrosyl radical; 1,3-nitroso shift; transnitrosation; radical reaction; diazoester rearrangement; Chapman rearrangement

Many reports on *N*-nitrosoureas have dealt with the biological activities of aliphatic *N*-nitrosoureas such as 1,3-dialkylnitrosoureas.^{2,3)} While studying the preparation of aryl-1-nitrosoureas (1). We also examined the decomposition of 3,3-dialkyl-1-aryl-1-nitrosoureas (2)⁵⁾ under mild conditions.

composition of 3,3-dialkyl-1-aryl-1-nitrosoureas (2)⁵⁾ under mild conditions.

As shown in Chart 1, 1-aryl-3-methyl-1-nitrosoureas (1a, b) in carbon tetrachloride at 33°C decomposed to give aryl diazohydroxides (3a, b), methyl isocyanate (4a), 1-aryl-3-methyl-3-nitrosoureas (5a, b), 3-methyl-1-(4-substituted 2-nitrophenyl)ureas (6a, b) and 1-aryl-3-methylureas (7a, b). The possibility of producing aryl diazohydroxides (3) and alkyl isocyanates (4) in the decomposition of 1-aryl-1-nitrosoureas (1) was described in our previous paper.¹⁾ The antitumor activities of 1-aryl-3-methyl-3-nitrosoureas (5) have been investigated by Yano *et al.*⁶⁾

The decomposition mechanism and the biological properties of *N*-aryl-*N*-nitroso type ureas (1) are not known in detail. The thermolysis of *N*-nitrosoureas (1a, b) was considered^{1,5)} to proceed by both a diazoester rearrangement and an N–NO bond cleavage. Aryl diazohydroxides (3a, b) and methyl isocyanate (4a) were produced via the corresponding diazoester intermediate.¹⁾ Other compounds (6–8) were also produced from the N–NO bond cleavage.^{5,7,8)} The 3-nitrosoureas (5a, b) were formed from the 1-nitrosoureas (1a, b) by thermal 1,3-rearrangement of the nitroso group.¹⁾

It is known^{1,9,10)} that the disubstituted 1-nitrosoarenes isomerize to the corresponding 3-nitrosoarenes in the presence of acids. Despite the absence of acids, 1-aryl-3-methyl-1-nitrosoureas (1a, b) isomerized to the corresponding 3-nitrosoureas (5a, b). Migration of a nitroso group is formally similar to the isomerization of 1a under acidic conditions. However, the mechanism of the 1,3-nitroso

shift reaction in an aprotic solvent such as carbon tetrachloride may differ from that seen under the acidic conditions.

We studied the thermolysis of 1-aryl-3-benzyl-1-nitrosoureas (**1c–e**). The decomposition of 3-benzyl-1-(4-tolyl or 4-methoxyphenyl)-1-nitrosoureas (**1c,d**) under an atmosphere of argon, which is also described in this paper, also gave 3-benzyl-1-(4-substituted 2-nitrophenyl)-3-nitrosoureas (**8c,d**) as new products. The 3-nitrosoureas (**8**) are the eventual transnitrosated products of **6** arising from **1**. The mechanisms of the formation of the 3-nitrosoureas (**5, 8**) in the decomposition of **1** are not well known; it is not clear whether nitrosyl radical liberation is involved or not. We wish to report here on the decomposition mechanism of 1-aryl-1-nitrosoureas (**1c–e**) in connection with a Fisher–Hepp rearrangement¹¹) in an acid-catalyzed reaction.

Results and Discussion

1-Nitrosoureas (**1**) and their 3-nitroso isomers (**5**), with 1-(4-tolyl), 1-(4-methoxyphenyl) and 1-(2-tolyl) substituents, were prepared by nitrosation of the corresponding ureas (**7**) using a method described in a previous paper.¹⁾ Their analytical and spectral data are shown in Tables I and II.

When the 4-substituted phenyl derivatives of *N*-nitrosoureas (**1c,d**) were dissolved in carbon tetrachloride and allowed to stand at 33 °C for 6 h under aerobic conditions or under an atmosphere of argon, they decomposed to give products (**4b, 5c,d–8c,d**) as shown in Chart 1. These products were identified by comparison with authentic samples. Their yields were determined by high-performance liquid chromatography (HPLC) with the aid of an internal standard, and are shown in Table III. The

isocyanates (**4**) were preferentially formed in air. In contrast, the 1,3-nitroso-shifted products (**5**) and the transnitrosated compounds (**8**) were preferred in argon. The yields of nitro compounds (**6**) were somewhat better in air.

A detailed examination of the thermolysis of 4-substituted phenylnitrosoureas (**1**) using HPLC was performed with **1c**. Time courses of product yields are displayed in Fig. 1, with first-order rate plots for the decomposition of **1c**. The rate constant under aerobic conditions was $4.85 \times 10^{-5} \text{ s}^{-1}$, and a major product was benzyl isocyanate (**4b**) (40% yield) obtained *via* a diazoester rearrangement.¹²⁾

When **1c** was dissolved in carbon tetrachloride and the solution was permitted to stand overnight at room temperature, the infrared (IR) spectrum of the resulting decomposition mixture showed a strong $\text{N}=\text{C}=\text{O}$ group absorption at 2250 cm^{-1} . The 1,3-rearranged compound (**5c**) was found in an 8% yield in air. Formation of the transnitrosated compound (**8c**) could not be detected. On the other hand, the first-order plot in argon was curved and appeared to be composed of two linear components. The rate constant for the initial stage was $5.27 \times 10^{-5} \text{ s}^{-1}$, and was close to the value of the rate constant under aerobic conditions. The second stage had a rate constant of $3.36 \times 10^{-4} \text{ s}^{-1}$. In the second stage, the main products were the 1,3-nitroso-shifted compound (**5c**) (55% yield) with the transnitrosated compound (**8c**) (3% yield). The isocyanate (**4b**) was not observed. In the decomposition of nitrosourea (**1c**), the nitro compound (**6c**) and the denitrosated compound (**7c**) were minor products, and their yields were less than 12% under both air and argon. In spite of the argon atmosphere, the nitro compound (**6c**) derived by oxidation was always

TABLE I. Physicochemical Properties and Analytical Data of 1-Aryl-3-benzylureas

Compd.	Yield ^{a)} (%)	mp (°C) ^{b)}	Formula	Analysis (%) Calcd (Found)			N ¹ H N ³ H	IR ^{c)} $\nu \text{ cm}^{-1}$ Ring CO
				C	H	N		
1c	10	85.5–86.5 ^{e)}	$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$	66.90 (66.65)	5.61 5.65	15.61 15.64	— 3430	1600w 1720
1d	10	90.5–91.5 ^{e)}	$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3$	63.15 (63.24)	5.30 5.56	14.73 14.36	— 3430	1605m 1715
1e	12	91–92 ^{e)}	$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$	66.90 (66.73)	5.61 5.61	15.61 15.48	— 3430	1605w 1725
5c	80	100–101 ^{e)}	$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$	66.90 (66.79)	5.61 5.61	15.61 15.69	3390 —	1590s 1725
5d	65	95–96 ^{e)}	$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3$	63.15 (62.95)	5.30 5.31	14.73 14.86	3400 —	1595s 1720
5e	70	77.5–78.5 ^{e)}	$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$	66.96 (67.02)	5.61 5.69	15.61 15.72	3410 —	1585s 1720
6c	70	176–177	$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3$	63.15 (63.09)	5.30 5.31	14.73 14.69	3340 3440	1575s 1690
6d	65	193.5–194.5	$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_4$	59.79 (59.28)	5.02 4.94	13.95 13.97	3300 3440	1575m 1685
7c	97	168–169	$\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$	74.97 (74.84)	6.71 6.78	11.66 11.63	3025 ^{d)} 3300 ^{d)}	1610sh 1615
7d	98	166.5–167.5	$\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2$	70.39 (70.19)	6.29 6.33	10.93 10.88	3060 ^{d)} 3300 ^{d)}	1605s 1620
7e	88	134.5–135.5	$\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$	74.97 (74.86)	6.71 6.81	11.66 11.57	3025 ^{d)} 3310 ^{d)}	1605m 1625
8c	13 (80)	96–97	$\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_4$	57.32 (57.12)	4.49 4.44	17.83 17.89	3280 —	1575s 1725
8d	12 (85)	100–101	$\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_5$	54.54 (54.07)	4.27 4.26	16.96 16.75	3300 —	1580s 1730

a) Isolated yields. Yields from **6** are given in parentheses. b) Compounds **1** and **5** were recrystallized from a mixture of *n*-hexane and ether, and **6–8** were from acetone. c) Compounds **7** were measured in Nujol mull and others in CHCl_3 . Abbreviation: s, strong; w, weak; m, moderate; sh, shoulder. d) Two NH stretching bands were indistinguishable. The bands at 3300 cm^{-1} were strong and broad. e) Decomposition points.

TABLE II. ^{13}C -NMR Chemical Shifts (ppm)^{a)} of *N*-Nitrosoureas (**1**, **5**, **8**), Nitro Compounds (**6**) and Ureas (**7**)

1: X=NO, Z=H 5: X=H, Z=NO 7: X=Z=H 6: X=Z=H 8: X=H, Z=NO

Compd.	Y	C-1 C-1'	C-2 C-2'	C-3 C-3'	C-4 C-4'	C-5 C-5'	C-6 C-6'	CO	CH ₂	Me	OMe
1c	4-Me	129.4 137.3	127.6 127.9	130.0 128.8	140.2 127.8	130.0 128.8	127.6 127.9	153.4		21.3	
1d	4-OMe	124.3 137.4	129.1 128.0	114.6 128.8	110.3 127.8	114.6 128.8	129.1 128.0	153.5	44.6		55.4
1e	2-Me	131.9 137.5	136.2 127.8	130.3 128.7	127.7 128.0	130.9 128.7	126.9 127.8	153.1	44.7	17.4	
5c	4-Me	134.1 ^{b)} 134.5	120.4 128.6	129.8 128.8	134.8 ^{b)} 127.9	129.8 128.8	120.4 128.6	150.6	44.5	20.9	
5d	4-OMe	129.7 134.6	122.2 128.6	114.5 128.7	157.1 127.9	114.5 128.7	122.2 128.6	150.8	42.8		55.5
5e	2-Me	129.4 134.5 ^{b)}	134.8 ^{b)} 128.6	130.7 128.8	125.6 127.9	127.0 128.6	122.6 128.7	150.8	42.9	17.6	
6c	4-Me	131.6 135.6	138.3 127.7	125.3 128.8	134.6 127.6	136.9 128.8	121.6 127.7	154.2		20.3	
6d	4-OMe	130.9 136.2	138.3 127.7	108.0 128.8	153.9 127.6	123.4 128.8	124.2 127.7	154.3	44.7		55.9
7c	4-Me	134.4 ^{b)} 139.0	122.5 127.5	130.0 128.7	135.6 ^{b)} 127.4	130.0 128.7	122.5 127.5	155.1	44.5	20.8	
7d	4-OMe	130.8 139.1	125.2 127.5	114.8 128.7	157.4 127.4	114.8 128.7	125.2 127.5	156.6	44.4		55.6
7e	2-Me	133.0 139.1	136.0 127.5 ^{b)}	131.1 128.7 ^{b)}	126.3 127.4 ^{b)}	127.6 ^{b)} 128.7 ^{b)}	125.9 127.5 ^{b)}	156.4	44.5	17.8	
8c	4-Me	131.4 134.3 ^{b)}	137.2 128.7 ^{c)}	125.9 128.7 ^{c)}	134.4 ^{b)} 128.0	136.7 128.7 ^{c)}	121.9 128.7 ^{c)}	151.1	42.8	20.6	
8d	4-OMe	127.2 134.4	138.1 128.6	109.2 128.7	155.6 128.0	123.2 128.7	123.6 128.6	151.1	42.8		56.0

a) Measured in CDCl_3 with TMS as an internal standard. Measured at -10°C for **1c–d** and at room temperature for other compounds. b) Assignments may be reversed. c) Overlapping.

TABLE III. Yields of Decomposition Products of Nitrosoureas (**1**) in CCl_4 at 33°C

Conditions	Compd.	Products (%) ^{a)}				
		4	5	6	7 ^{c)}	8 ^{c)}
Air ^{b)}	1c	40	5	8	12	—
	1d	31	8	29	11	—
Argon ^{b)}	1c	—	55	6	3	3
	1d	—	34	15	15	0.2

a) Determined by HPLC. b) The extent of decomposition of **1** was 60% in air and 80% in argon. c) Final yields.

observed, presumably due to air contamination caused by small leaks in the reaction system.

The formation of the 1,3-shifted compound (**5c**), the oxidized product (**6c**), and the transnitrosated compound (**8c**) via a pathway of N–NO bond cleavage proceed more smoothly under argon than under aerobic conditions. The slow decomposition in the first stage under argon proceeds in a similar manner under aerobic conditions because of a small amount of oxygen in the reaction system. Formation of the nitro compounds (**6**) as oxidation products consumed oxygen in the reaction system. Consequently, more rapid decomposition during the second, oxygen-free stage gave the 3-nitroso isomer (**5**) via the N–NO bond cleavage.

Benzyl isocyanate (**4b**) was preferentially formed in air, and was not observed in argon. Currently, it is not clear

Fig. 1. Relationship between $\ln C$ (C : Concentration of **1c**) and Time for the Decomposition of 3-Benzyl-1-(4-tolyl)-1-nitrosourea (**1c**) in CCl_4 at 33°C , and Percent Yields of Benzyl Isocyanate (**4b**), 3-Benzyl-1-(4-tolyl)-3-nitrosourea (**5c**), and 3-Benzyl-1-(2-nitro-4-tolyl)urea (**6c**) vs. Time as Determined by HPLC

Air: **1c**, $\blacktriangle$; **4b**, $\bullet$; **5c**, ∇ ; **6c**, $\blacksquare$. Argon: **1c**, $\triangle$; **5c**, ∇ ; **6c**, $\square$.

why the formation of benzyl isocyanate (**4b**) via a diazoester intermediate (**9**) is favored in the presence of oxygen. However, the following mechanism is suggested to account for the decomposition of compound **1** (Chart 2). Thermal cleavage of the N–NO bond generates a nitrosyl (NO) and a

Chart 2

ureidyl radical (10). Recombination of these two partially regenerates the starting nitrosoarene (1) or yields *O*-nitrosoisourea (11) through a resonance hybrid of the ureidyl radical (10A–C). The *O*-nitrosoisourea (11), or its proton-transformed isomer (12), is thought to be an intermediate in the decomposition of 1 to give the 3-nitrosoarene (5).

It is widely known that *O*-alkylimidates undergo Chapman rearrangement^{13,14} to *N*-alkylamides by a thermodynamically controlled process. Therefore, the resulting intermediate (10) reverts to the parent nitrosoarene (1), or after the proton has shifted, the intermediate (12) rearranges to the thermodynamically stable 3-nitrosoarene (5) by an analogous Chapman rearrangement. When oxygen is present in the reaction system, a nitrosyl radical is oxidized to a nitro radical (NO₂). The nitro radical reacts with the ureidyl radical to form the nitro compound (6). In addition, oxygen also reacts with the ureidyl radical to give a ureidyl-oxygen radical (13), followed by a nitrosyl radical to give an adduct (14). Formation of these oxygen adducts (13, 14) competes with formation of *O*-nitroso intermediates (11, 12). Oxygen prevents the 1,3-nitroso transfer via an *O*-nitroso intermediate and reduces the yield of the 3-nitrosoarene (5).

In the decomposition of 3-benzyl-1-(4-methoxyphenyl)-1-nitrosoarene (1d), the rate constant was $k = 3.80 \times 10^{-5} \text{ s}^{-1}$ in air. Furthermore, $k = 5.43 \times 10^{-5} \text{ s}^{-1}$ in the first stage, and $k = 1.08 \times 10^{-4} \text{ s}^{-1}$ in the second stage in argon. The nitro compound (6d) was formed in good yield compared with the 4-tolyl derivative (1c). This is significant since the ureidyl radical (because of the contribution of 10C due to a resonance effect of the *p*-MeO group) is likely to produce the nitro compound (6d).

The Fisher–Hepp rearrangement involves transformation from *N*-nitroso to *C*-nitroso compounds under acidic conditions, for example, from *N*-nitroso-*N*-methylaniline to *N*-methyl-4-nitrosoaniline in hydrochloric acid.¹¹ It is believed that the attacking entity is nitrosyl chloride.^{15,16}

In our study, the conversion of compound 1 to 3-alkyl-1-(2-nitroso-4-tolyl)ureas (15) failed under our experimental conditions. The 1,3-nitroso rearrangement via an *O*-nitroso intermediate (11) occurs preferentially because *O*-nitrosation is more rapid than phenyl-*C*-nitrosation. In this regard, the nitrophenyl compound (6) is believed to be produced by air oxidation of a nitrosyl radical,⁸ and not by oxidation of the *C*-nitroso compound (15). In general, oxidation of the *C*-nitroso (15) to the *C*-nitro compound (6) requires an oxidizing agent such as K₂Cr₂O₇¹⁷ or NO⁺¹⁸ under acidic conditions.

The transnitrosated products (8) were finally obtained in 0.2–3% yields only under an atmosphere of argon. It is worth noting that thermal transnitrosation of *N*-nitroso compounds took place in the absence of acids, because this is rarely seen, except with *N*-nitrosodiphenylamine,¹⁹ *N*-nitrosocarbazole²⁰ and 3-isopropyl-1-(4-tolyl)-1-nitrosoarene.¹ Usually, the presence of acids and nucleophilic reagents in the reaction accelerates the transfer of a nitroso group of *N*-nitrosoarenes to secondary amines.²¹ However, the compounds (8c,d) are believed to be derived by the reaction of the nitro compounds (6c,d) with 1c,d.

In our case, the intermediate (11 or 12) acted as a nitrosating agent, and nitrosated the resulting nitro compounds (6c,d) to give 3-nitrosoarenes (8c,d). Formation of 8 via the *O*-nitrosoisourea (11) is also inhibited by the

Chart 3

Fig. 2. Transnitrosation of 3-Benzyl-1-(4-tolyl)-1-nitroso-urea (1c) to 3-Methyl-1-(4-tolyl)-urea (7a)

Yields of the products, 3-methyl-1-(4-tolyl)-1-nitroso-urea (1a) and 3-methyl-1-(4-tolyl)-3-nitroso-urea (5a), were determined by HPLC. Air: 1a, ●; 5a, ▲. Argon: 5a, △.

presence of oxygen. Thus, the *O*-nitroso intermediate (11 or 12) nitrosates other ureas similarly to the nitro compounds (6).

In order to clarify further the transnitrosation process, we performed transnitrosation using the *N*-nitroso-urea (1c) and 3-methyl-1-(4-tolyl)urea (7a) in carbon tetrachloride at 33 °C under aerobic or anaerobic conditions (Chart 3). The formation curve of the transnitrosated products is shown in Fig. 2. Both transnitrosated products, 3-methyl-1-(4-tolyl)-1-nitroso-urea (1a) (3% yield) and 3-methyl-1-(4-tolyl)-3-nitroso-urea (5a) (17% yield), were formed under aerobic conditions. Compound 5a (22% yield) was produced faster in argon than in air. This may be attributed to competition between formation of the *O*-nitrosoisourea intermediate (11) and the radical species (13). Perhaps, the *O*-nitrosoisourea (11 or 12) nitrosates the urea (7a) through the interaction shown in Chart 3. The transnitrosated product, 1-nitroso-urea (1a) was not observed in argon. This shows that the compound (1a) is also converted into its isomer (5a) via a 1,3-nitroso shift in the same manner as the isomerization from 1c to 5c in argon.

Thermolysis of 3-benzyl-(2-tolyl)-1-nitroso-urea (1e) was very slow at 33 °C (in air, $k = 3.47 \times 10^{-6} \text{ s}^{-1}$; in argon, $k = 4.91 \times 10^{-6} \text{ s}^{-1}$), and its kinetic behavior in argon was linear, different from the decomposition of the 4-tolyl derivative (1c).

Benzyl isocyanate (4b), related to a diazoester rearrangement, was observed by IR spectroscopy. The corresponding nitro compound and the denitrosated product (7e) of N-NO bond cleavage were rarely observed. The cause

seems to be the difference in degree of twisting about the phenyl- N^1 bond in the aryl- $\text{N}^1(\text{NO})\text{CON}^3(\text{alkyl})_2$ moiety between the 4-tolyl derivative (1c) and the 2-tolyl derivative (1e) as described previously.⁴⁾ The twisting (1e) deactivates N-NO bond cleavage, and activates a diazoester rearrangement.

We found during the preparation of the authentic samples of the nitro compounds (6) that nitration of the ureas (7) in a mixture of fuming nitric and acetic acid at room temperature gave the nitrosated nitro compounds (8) in about 13% yield, together with the nitro compounds (6) in about 70% yield. In spite of the nitrative conditions, nitrosation occurred. This is due to reaction of N_2O_4 contained in fuming nitric acid with the nitro compounds (6) produced by nitration, because N_2O_4 is known to have the ability to nitrosate.²²⁾ Currently, we are attempting to detect the presence of an *O*-nitrosoisourea intermediate, and hope to publish our results in the near future.

Experimental

All melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with a JASCO A-102 spectrophotometer. High-performance liquid chromatography (HPLC) was performed on a JASCO 880-PU chromatograph with a ultraviolet (UV) detector (JASCO 875-UV) operating at 254 nm, using a TSK-Gel LS 310K column (4 × 300 mm i.d., Toyo Soda) with *n*-hexane-ethyl acetate (80:20 and 87:13, v/v) as a mobile phase. Peak areas were determined with a Shimadzu C-R3A Chromatopac. The internal standard employed was 4-methyl-2-nitroacetanilide. Proton nuclear magnetic resonance (^1H -NMR) spectra were measured with a Varian EM 360-A spectrometer and carbon-13 nuclear magnetic resonance (^{13}C -NMR) spectra were measured with a JEOL FX-200 spectrometer, with tetramethylsilane (TMS) as an internal standard. The abbreviations are as follows: s, singlet; d, doublet; br, broad.

1-Aryl-3-benzylureas (7c–e) Aryl isocyanate (aryl = 4-tolyl, 4-methoxyphenyl, 2-tolyl) (75 mmol) was added dropwise to an ice-cooled solution of benzylamine (75 mmol) in 100 ml of ether, and the mixture was allowed to stand at room temperature with stirring for 3 h. The resulting crystals were filtered off, and recrystallized from acetone. Yield, 88–98%. ^1H -NMR (DMSO- d_6) δ : 1c: 2.22 (3H, s, CH_3), 4.30 (2H, d, $J = 7 \text{ Hz}$, CH_2), ca. 6.5 (1H, br, NH), 6.97, 7.26 (4H, d, $J = 9 \text{ Hz}$, tolyl- $\text{H}^{2,3}$), 7.30 (5H, s, phenyl-H), ca. 8.4 (1H, br, NH). The spectral and analytical data of the ureas (7) are listed in Tables I and II.

***N*-Nitroso-ureas (1c–e, 5c–e)** *N*-Nitroso-ureas (1, 5) were prepared by nitrosation of the ureas (7) in CHCl_3 at 5 °C using isoamyl nitrite as described in a previous paper.¹⁾ A typical method is described below for 1c and 5c. Isoamyl nitrite (0.06 mol) was added dropwise to a suspension of 3-benzyl-1-(4-tolyl)urea (7c) (0.04 mol) in CHCl_3 (200 ml) at 0–5 °C and the mixture was stirred for 10 h. The unreacted urea was filtered off and the filtrate was evaporated under reduced pressure in an ice-water bath. The residue was chromatographed on a column of silica gel with a mixture of *n*-hexane and ether (7:3) under cooling. The first and the second fractions gave the 3-nitroso-urea (5c) and the 1-nitroso isomer (1c) in 80% and 10% yields, respectively. ^1H -NMR (CDCl_3) δ : 1c: 2.37 (3H, s, CH_3), 4.70 (2H,

d, $J=7$ Hz, CH_2), 6.84, 7.26 (4H, dd, $J=9$ Hz, tolyl- $\text{H}^{2,3}$), 7.38 (5H, s, phenyl-H), ca. 7.3 (1H, br, NH). **5c**: 2.35 (3H, s, CH_3), 5.05 (2H, s, CH_2), 7.20, 7.45 (4H, d, $J=9$ Hz, tolyl- $\text{H}^{2,3}$), 7.30 (5H, s, phenyl-H), ca. 8.75 (1H, br, NH).

Nitrosation of the ureas (**7d,e**) was carried out according to the method described for **7c**. When the urea (**7e**) was nitrosated, the 1-nitrosourea (**1e**) and its 3-nitroso isomer (**5e**) were obtained 71% and 12% yields, respectively. In the case of **7d**, the first fraction gave the 3-nitrosourea (**5d**) (65% yield). The second fraction was a mixture containing the desired *N*-nitrosourea (**1d**) and the nitro compound (**6d**). To separate **1d** and **2d** by column chromatography was difficult. The mixture was crystallized in a freezer, and pale yellow crystals of **1d** and yellow crystals of **6d** were separated by the use of tweezers. **1d**: Yield, 10%. The physicochemical, analytical and spectral data are listed in Tables I and II.

3-Benzyl-1-(4-substituted 2-nitrophenyl)ureas (6c,d) and 3-Benzyl-1-(4-substituted 2-nitrophenyl)-3-nitrosoureas (8c,d) A typical experiment is described. Fuming nitric acid ($d=1.52$, 1.5 ml) was added to a suspension of 3-benzyl-1-(4-tolyl)urea (**7c**) (1.2 g, 5 mmol) in acetic acid (10 ml) at 5–10°C with stirring, and the mixture was stirred for 3 h at room temperature. The reaction mixture was poured into crushed ice and extracted with CHCl_3 . The CHCl_3 layer was washed with saturated NaHCO_3 solution and with water, and was filtered through a silicon-treated filter paper (1 ps phase separators, Whatman Ltd.). The solvent was evaporated off in an ice-water bath. The residue was chromatographed on a column of silica gel with CHCl_3 as an eluting solvent. The first fraction gave 0.2 g (12.7%) of 3-benzyl-1-(2-nitro-4-tolyl)-3-nitrosourea (**8c**), which was identical with an authentic sample produced by the nitrosation of **6c**. The second fraction gave 1.0 g (69.9%) of 3-benzyl-1-(2-nitro-4-tolyl)urea (**6c**). $^1\text{H-NMR}$ (CDCl_3) δ : **6c**: 2.35 (3H, s, CH_3), 4.48 (2H, d, $J=7$ Hz, CH_2), ca. 5.7 (1H, br, NH), 7.38, 7.96 (2H, dd, $J=9$, 2 Hz, tolyl- $\text{H}^{3,5}$), 8.55 (1H, d, $J=9$ Hz, tolyl- $\text{H}^{1,6}$), 7.34 (5H, s, phenyl-H), ca. 9.7 (1H, br, NH).

3-Benzyl-1-(4-methoxyphenyl)urea (**7d**) gave 3-benzyl-1-(2-nitro-4-methoxyphenyl)-3-nitrosourea (**8d**) from the first fraction and 3-benzyl-1-(4-methoxy-2-nitrophenyl)urea (**6d**) from the next fraction. The yields of **6d** and **8d** were 65% and 12%, respectively. Their physicochemical, analytical and spectral data are listed in Tables I and II.

The Nitrosation of 6c,d with Isoamyl Nitrite Isoamyl nitrite (0.7 g, 6.0 mmol) was added dropwise to a suspension of 3-benzyl-1-(2-nitro-4-tolyl)urea (**6c**) (1.43 g, 5.0 mmol) in CHCl_3 (50 ml) at 0–5°C and stirred for 10 h. The unreacted **6c** was filtered off and the filtrate was evaporated to dryness under reduced pressure in an ice-water bath. The residue was chromatographed on a column of silica gel with CHCl_3 as an eluting solvent. The eluate gave 0.126 g (80%) of 3-benzyl-1-(2-nitro-4-tolyl) urea (**8c**). Yellow crystals. $^1\text{H-NMR}$ (CDCl_3) δ : **8c**: 2.44 (3H, s, CH_3), 5.10 (2H, s, CH_2), 7.55, 8.10 (2H, dd, $J=9$, 2 Hz, tolyl- $\text{H}^{3,5}$), 8.78 (1H, d, $J=9$ Hz, tolyl- $\text{H}^{1,6}$), 7.3 (5H, s, phenyl-H), ca. 7.3 (1H, br, NH).

3-Benzyl-1-(2-nitro-4-methoxyphenyl)urea (**6d**) gave 3-benzyl-1-(2-nitro-4-methoxyphenyl)-1-nitrosourea (**8d**) in a similar manner. Yield, 85%. The physicochemical, analytical and spectral data are listed in Tables I and II.

Decomposition of *N*-Nitrosoureas (1c,d) The *N*-nitrosoureas (**1c,d**) (0.035 mmol) were dissolved in CCl_4 (exactly 10 ml) containing 4-methyl-2-nitroacetanilide⁴⁾ as an internal standard. The solutions were kept at $33\pm0.5^\circ\text{C}$ for 6 h under an atmosphere of argon or air. The decomposition products were determined by the HPLC method. These results are shown in Fig. 1 and Table III. A similar experiment was performed on **1e**, but no product was observed.

Transnitrosation of *N*-Nitrosourea (1c) to the Urea (7a) 3-Benzyl-1-(4-tolyl)-1-nitrosourea (**1c**) (9.4 mg, 0.035 mmol) was added to a suspen-

sion of 3-methyl-1-(4-tolyl)urea (**7a**) (5.74 mg, 0.035 mmol) in CCl_4 solution (10 ml) containing an internal standard. The solution was kept at $33\pm0.5^\circ\text{C}$ for 6 h under an atmosphere of argon or air. The yields of 3-methyl-1-(4-tolyl)-1-nitrosourea (**1a**) and 3-methyl-1-(4-tolyl)-3-nitrosourea (**5a**) were also determined by the HPLC method. The results are shown in Fig. 2 and Chart 3.

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