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Thermal Decomposition of 1,3-Diaryl-1-nitrosoureas in Benzene

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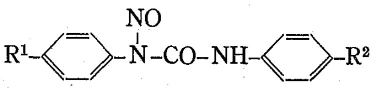
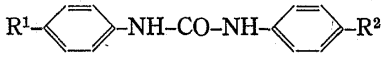
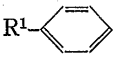
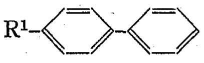
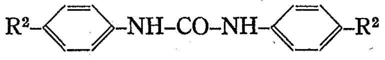
Thermal decomposition of several 1,3-diaryl-1-nitrosoureas (Ia—e) in benzene gave denitrosated 1,3-diarylureas (IIa—e), benzene derivatives (IIIa—e), biphenyls (IVa—e) and newly formed 1,3-diarylureas (Va—e).

Based on these results, pathways of the decomposition are proposed. Compounds Ia—e rearrange to the corresponding arylazo arylcarbamates (VIa—e), which decompose to give such intermediates as diazonium ions (VIIa—e), arylcarbamate anions (VIIIa—e) and aryl isocyanates (IXa—e). These intermediates further react with the solvent or other species to give the final products. The existence of these intermediates was confirmed by chemical and spectral studies.

Keywords——thermal decomposition; rearrangement; 1,3-diaryl-1-nitrosoureas; biphenyls; diazonium ions; aryl isocyanates

1-Alkyl-1-nitrosoureas [RN(NO)CONH$_2$] are well known as potent carcinogens and some of them have been used for studies of cancer in animal models.[1] On the other hand, some of the nitrosoureas having a 1-(2-chloroethyl)-1-nitrosoureido group [–NHCON(NO)CH$_2$CH$_2$Cl] are effective against some solid tumors, as well as leukemia.[2] Thus, many reports on the reactions of alkylnitrosoureas *in vitro* and *in vivo* have been published over the past ten years.[2] However, the chemical and biological activities of 1,3-diaryl-1-nitrosoureas [ArN(NO)CONHAr′] have not been clarified.

Table I. Yields (%) of the Products in the Thermal Decomposition of 1,3-Diphenyl-1-nitrosoureas in Benzene

						
	R^1	R^2	IIa—e Denitrosated ureas	IIIa—e Benzene der.	IVa—e Biphenyl der.	Va—e Reproduced ureas
Ia	H	H	12	—	28	42[a]
Ib	CH$_3$	CH$_3$	12	7	37	45[a]
Ic	Cl	Cl	19	6	22	35[a]
Id	CH$_3$	Cl	23	7	29	37
Ie	Cl	CH$_3$O	24	5	53	32

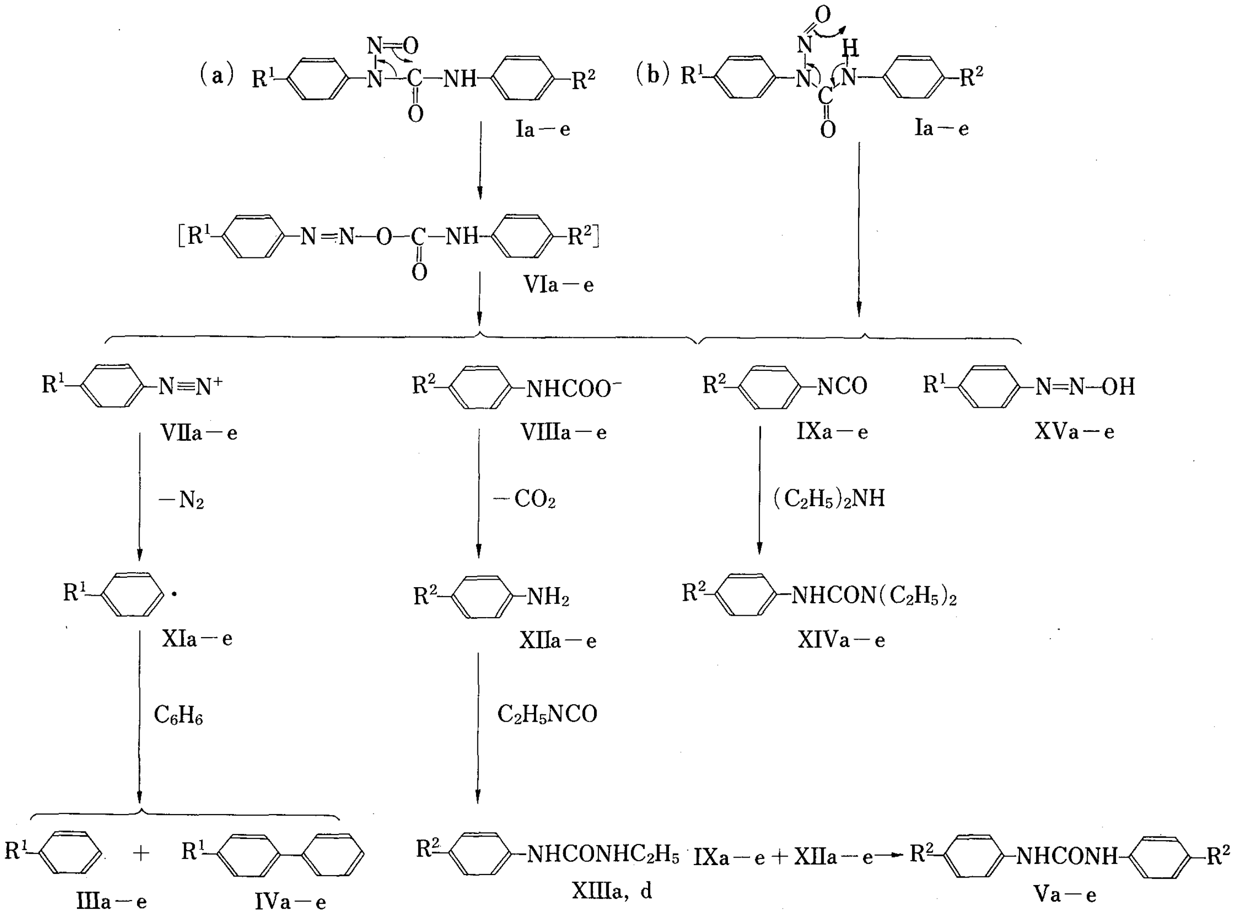
[a] The structures of the newly formed ureas (Va, b, c), which were slowly precipitated from the reaction mixtures, were the same as those of the denitrosated ureas (IIa, b, c) for the symmetric *N*-nitrosoureas (Ia, b, c).

This paper describes the thermal decomposition of 1,3-diaryl-1-nitrosoureas in benzene. The decomposition pathway is also discussed.

Symmetric (Ia, Ib, Ic) and unsymmetric 1,3-diaryl-1-nitrosoureas (Id, Ie) were prepared by the nitrosation of the corresponding 1,3-diarylureas with nitrosyl chloride or dinitrogen tetroxide in dimethylformamide.[3]

When 1,3-diaryl-1-nitrosoureas (Ia—e) were heated in benzene for 30 min, denitrosated ureas (IIa—e), benzene derivatives (IIIa—e), biphenyl derivatives (IVa—e) and newly formed ureas (Va—e) were obtained in the yields shown in Table I. Among these products, the newly formed ureas were obtained as precipitates when the filtrate separated from the denitrosated ureas was allowed to stand for a few days. The benzene derivatives were determined by means of gas chromatography, and the biphenyl derivatives were separated from the reaction mixture by means of column chromatography. In the case of the symmetric nitrosoureas (Ia, Ib, Ic), the newly formed ureas (Va, Vb, Vc) were the same as the denitrosated ureas (IIa, IIb, IIc). Thus, the products IIIa—e and IVa—e arose from the phenyl ring [$R^1C_6H_4N(NO)$] adjacent to the *N*-nitroso group, and the products Va—e arose from another phenyl ring [$-CONHC_6H_4R^2$].

These results suggest that 1,3-diaryl-1-nitrosoureas (Ia—e) first rearrange to the corresponding arylazo arylcarbamates (VIa—e), which decompose to diazonium cations (VIIa—e) and arylcarbamate anions (VIIIa—e) by the cleavage of the N–O bond and to aryl isocyanates (IXa—e) by cleavage of the O–CO bond (course a). Further, through course b, 1,3-diaryl-1-nitrosoureas (Ia—e) will decompose to produce aryl isocyanates (IXa—e) and aryldiazohydroxide (XVa—e) which then yield the diazonium cations (VIIa—e).



a: $R^1=R^2=H$, b: $R^1=R^2=CH_3$, c: $R^1=R^2=Cl$ d: $R^1=CH_3$, $R^2=Cl$, e: $R^1=Cl$, $R^2=OCH_3$

Chart 1

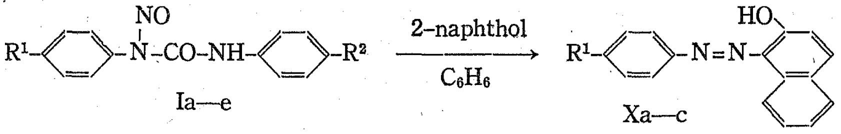
The proposed intermediacy of an arylazo arylcarbamate (VI) was substantiated by the following reactions of the compounds Ia—e. The intermediates (VIa—e) degrade further to give ion pairs (VIIa—e, VIIIa—e). The aryldiazonium ions (VIIa—e) give phenyl radicals (XIa—e) with evolution of molecular nitrogen and the radicals react with benzene itself to produce benzene derivatives (IIIa—e) by hydrogen abstraction reaction and biphenyl derivatives (IVa—e) by a coupling reaction of the radicals (XIa—e) with the produced benzene radical (Chart 1).

The arylcarbamate anions (VIIIa—e) produced from the diazo esters (VIa—e) immediately lose carbon dioxide to give the corresponding primary arylamines (XIIa—e). Practically, the treatment of Ia and Id with ethyl isocyanates in boiling benzene gave 1-ethyl-3-phenylureas, XIIIa in 41% yield and XIIId in 38% yield.

Formation of the aryl isocyanates (IXa—e) was spectroscopically and chemically confirmed as follows. Benzene solutions of the compounds Ia—e were heated for a short period and then concentrated. The infrared spectra of the solutions showed a strong peak at 1900 cm^{-1} due to a phenyl isocyanate. In fact, the reaction of Ia and Id with diethylamine in benzene gave 1,1-diethyl-3-phenylureas (XIVa, XIVd). These results indicate that the compounds IXa—e react with the compounds XIIa—e to give the newly formed ureas (Va—e) (Chart 1).

The decomposition of 1,3-diphenyl-1-nitrosourea (Ia) in alcohols was then examined. Solutions of Ia in methanol and in ethanol were refluxed. However, the main products were the denitrosated urea, in 71% yield in methanol, and in 66% yield in ethanol. Only the case of methanol was the formation of methyl phenylcarbamate [$C_6H_5NHCOOCH_3$] recognized by means of thin layer chromatography (TLC) of the reaction mixture.

Table II. The Yields of 1-Aryl-2-naphthols (Xa—e)



Compound No.	Ia	Ib	Ic	Id	Ie
R¹	H	CH_3	Cl	CH_3	Cl
R²	H	CH_3	Cl	Cl	CH_3O
Yields of Xa—e (%)	56	38	44	33	58

When solutions of the compounds Ia—e in benzene were refluxed in the presence of 2-naphthol, the corresponding 1-arylazo-2-naphthols (Xa—e) were produced in 33—58% yields as shown in Table II. In this case, formation of the biphenyls was not detectable by means of TLC of the reaction mixture. The reaction of the compounds Ia—e with 2-naphthol in alkaline ethanol also gave these 1-arylazo-2-naphthols in 55—65% yields. In alkaline ethanol, the compounds Ia—e decompose to give the diazonium ions, which react with 2-naphthol.[3] However, in benzene, it is not clear whether 2-naphthol reacts with the diazonium ions (VIIa—e) or directly with the rearranged intermediates (VIa—e).

In conclusion, the decomposition of 1,3-diaryl-1-nitrosoureas (Ia—e) in benzene starts with rearrangement to give reactive intermediates, arylazo arylcarbamates (IVa—e), which decompose to produce the final products. On the other hand, in alcohols, denitrosation is a main reaction pathway. The main route of the decomposition depends upon the nature of the solvent used.

Experimental

Melting points were taken on a Yanagimoto micromelting point apparatus and are uncorrected. The infrared spectra (IR) were measured with a JASCO-IR 102 spectrophotometer and the nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM 360A spectrometer with tetramethylsilane (TMS) as an internal standard. The visible spectra were obtained with a Shimadzu UV-200 spectrophotometer. Gas chromatographic analyses were performed on a Hitachi 063 gas chromatograph equipped with a flame-ionization detector using nitrogen gas. Samples were injected onto a 10% SE-30 column 1 m, which was heated at 60°C for benzene solutions.

Decomposition of 1,3-Diaryl-1-nitrosoureas (Ia—e) in Benzene——A typical experiment with 1,3-diphenyl-1-nitrosourea (Ia) is described. A solution of Ia (1.00 g, 4.2 mmol) yellow needles, mp 107°C,[3] in benzene (100 ml) was refluxed for 60 min. The reaction mixture was cooled to about 10°C and the precipitate was filtered off. This product was identical with 1,3-diphenylurea (IIa), mp 240°C (lit.,[4] mp 239.5 °C). Yield, 0.11 g (12%). The solution was allowed to stand for 2 d, then the solvent was removed under reduced pressure. The residue was treated with *n*-hexane, and the insoluble matter was filtered off. This product was identical with 1,3-diphenylurea (Va). Yield, 0.37 g (42%). The filtrate was poured onto a column of Kieselgel 60 (Merck), and the column was eluted with *n*-hexane–benzene (8: 2). The eluate was evaporated to dryness, and the viscous residue was recrystallized from ethanol to give biphenyl, mp 70°C. Yield, 0.18 g (28%). A sample for gas chromatography was prepared from the supernatant of the reaction mixture immediately after the reaction was finished.

Other compounds (Ib—e) were similarly treated in the same way as described above. 1,3-Di(4-tolyl)-1-nitrosourea (Ib), mp 105°C.[3] 1,3-Bis(4-chlorophenyl)-1-nitrosourea (Ic), mp 134°C.[3] 3-(4-Chlorophenyl)-1-(4-tolyl)-1-nitrosourea (Id), mp 119°C.[3] 3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-1-nitrosourea (Ie), mp 139°C.[3] 1,3-Di(4-tolyl)urea (IIb, Vb), mp 245—250°C (lit.,[5] mp 253°C). 1,3-Bis(4-chlorophenyl)urea (IIc, Vc, Vd), mp 255°C (sublimate) (lit.,[6] mp 285°C). 3-(4-Chlorophenyl)-1-(4-tolyl)urea (IId), mp 267°C (sublimate), (lit.,[7] 297—299°C). 1-(4-Chlorophenyl)-3-(4-methoxyphenyl)urea (IIe), mp 250—255°C.[3] 1,3-Bis(4-methoxyphenyl)urea (Ve), mp 245°C (lit.,[8] mp 232°C).

Decomposition of 1,3-Diaryl-1-nitrosoureas (Ia, Id) in Benzene in the Presence of Ethyl Isocyanate——A typical experiment with 1,3-diphenyl-1-nitrosourea (Ia) is described. Freshly prepared compound Ia (241 mg, 1 mmol) was refluxed for 1 h in benzene (200 ml) containing ethyl isocyanate (142 mg, 2 mmol). The reaction mixture was cooled to room temperature, and filtered to remove the insoluble denitrosated urea (IIa). The filtrate was concentrated, the concentrated solution was poured onto a column of Kieselgel 60 (Merck), and the column was eluted with *n*-hexane–benzene (9: 1), then with methanol. The eluate was concentrated to give 1-ethyl-3-phenylurea (XIIIa), mp 96°C (lit.,[9] mp 99°C). Yield, 78 mg (41%).

3-(4-Chlorophenyl)-1-(4-tolyl)-1-nitrosourea (Id) was treated as described above and 1-(4-chlorophenyl)-3-ethylurea (XIIId), mp 209°C (lit.,[10] mp 200°C) was obtained in 39% yield.

Trapping of Phenyl Isocyanates (IXa, IXd) produced by the Decomposition of 1,3-Diaryl-1-nitrosoureas (Ia, Id) in Benzene——A typical experiment with compound Ia is described. Compound Ia (241 mg, 1 mmol) was decomposed by the procedure described in the section, "Decomposition of 1,3-Diaryl-1-nitrosoureas in Benzene." As soon as gas evolution ceased, dimethylamine (146 mg, 2 mmol) was added to the reaction mixture. The solution was allowed to stand at room temperature for 1 d. The precipitate was filtered off. The filtrate was concentrated, the concentrated solution was poured onto a column of Kieselgel 60 (Merck), and the column was eluted with *n*-hexane, then with methanol. The eluate was concentrated to give 1,1-diethyl-3-phenylurea, (XIVa), mp 83—84°C (lit.,[11] mp 85°C). Yield, 137 mg (71%).

3-(4-Chlorophenyl)-1-(4-tolyl)-1-nitrosourea (Id) was treated as described for Ia, and 1-(4-chlorophenyl)-3,3-diethylurea (XIVd) mp 109—110°C (lit.,[12] mp 110°C), was obtained in 68% yield.

Decomposition of 1,3-Diaryl-1-nitrosourea (Ia) in Alcohols——A typical experiment with ethanol is described. A solution of compound Ia (241 mg, 1 mmol) in ethanol (50 ml), was refluxed for 30 min. The reaction mixture was evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to give the denitrosated urea (IIa), mp 240°C. Yield, 139 mg (66%). TLC of the reaction mixture was performed on Merck Kieselgel 60_{254} with *n*-hexane–ether (8: 2), and showed several spots whose *Rf* values did not coincide with that of ethyl phenylcarbamate, mp 49—51°C (lit.,[13] mp 52°C).

Compound Ia was similarly treated in methanol to afford denitrosated urea in 71% yield. TLC of the reaction mixture showed several spots and the *Rf* value of one coincided with that of methyl phenylcarbamate.

Decomposition of 1,3-Diaryl-1-nitrosoureas (Ia—e) in Benzene in the Presence of 2-Naphthol——A typical experiment with 1,3-diphenyl-1-nitrosourea (Ia) is described. A solution of freshly prepared compound Ia (241 mg, 1 mmol) and a two-fold excess of 2-naphthol (288 mg, 2 mmol) in benzene (50 ml) was refluxed for 2 h. The reaction mixture was cooled to room temperature, then the precipitate was filtered off. The filtrate was diluted with benzene to optimal concentration, and the absorbance was measured at 478 nm. The amount of each of the 1-arylazo-2-naphthols (Xa—e) was calculated from calibration curves prepared with the standard compounds. The melting points of the standards[14] were as follows. 1-Phenylazo-2-naphthol (Xa), mp 135°C. 1-(4-Tolylazo)-2-naphthol (Xb), mp 133°C. 1-(4-Chlorophenylazo)-2-naphthol (Xc), mp 165°C.

References and Notes

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