[Chem. Pharm. Bull. 29(5)1267—1273(1981)]

Rearrangement of 1-Substituted 3-(3-Pyridylmethyl)nitrosoureas to Their N-Nitroso Isomers in the Presence of Acids[1)]

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(Received October 29, 1980)

1-(2-Chloroethyl)- (IIa), 1-isopropyl- (IIb), 1-isobutyl- (IIc) and 1-cyclohexyl-1-nitroso-3-(3-pyridylmethyl)urea (IId) isomerized to the corresponding 3-nitroso isomers (IIIa—d) in formic acid. This type of rearrangement was also observed in acetic acid, 10% hydrochloric acid, 10% sulfuric acid, methanol saturated with hydrogen chloride, and thionyl chloride. However, 1-isopropyl- (IIIb) and 1-cyclohexyl-3-nitroso-3-(3-pyridylmethyl)urea (IIId), in which the N^1 substituents are bulky, hardly isomerized to the 1-nitrosoureas (IIb, d).

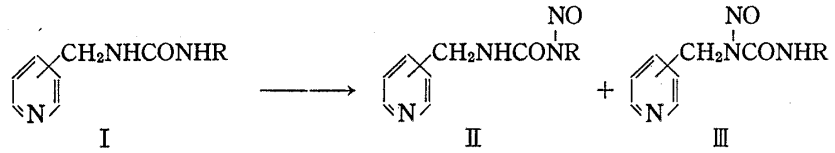
Transnitrosation of 1-(2-chloroethyl)-1-nitroso-3-(3-pyridylmethyl)urea (IIa) with 1-methyl-3-(2-pyridylmethyl)urea gave the denitrosated compound (Ia) and a newly nitrosated compound, 1-methyl-1-nitroso-3-(2-pyridylmethyl)urea (V).

It is suggested that this type of rearrangement is an acid-catalyzed, intermolecular rearrangement governed by the steric effect of the N^1 substituents.

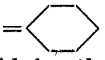
Keywords——nitrosoureas; pyridylmethylnitrosoureas; rearrangement; isomerization; transnitrosation; Fischer-Hepp rearrangement

There are a few examples of the rearrangement of N-nitroso compounds in the literature. The Fischer–Hepp rearrangement[2)] in an acid-catalyzed rearrangement, and, for instance, the nitroso group of N-methyl-N-nitrosoaniline migrates to the 4-position of the phenyl ring to produce 4-nitroso-N-methylaniline. The N-nitroso group of N-[(N-nitrosobenzylamino)methyl]-benzamide photochemically migrates to the benzyl carbon to produce N-(benzamidomethyl)-benzamidoxime.[3)] Johnston *et al.*[4)] obtained a mixture of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea and its 3-nitroso isomer by treating 1-(2-chloroethyl)-3-cyclohexylurea with aqueous sodium nitrite in formic acid. Since the treatment of the isomeric mixture with formic acid gave the 1-nitroso isomer in high yield, they suggested that the nitroso group of the 3-

Table I. Yields of the 1-Nitroso and 3-Nitroso Compounds in the Nitrosation of 1-Substituted 3-(3- or 4-Pyridylmethyl)ureas



I II III

Ureas	II Yield (%)	III Yield (%)
3-Pyridylmethyl derivatives		
Ia: R=CH_2CH_2Cl	59	29
Ib: R=$CH(CH_3)_2$	21	71
Ic: R=$CH_2CH(CH_3)_2$	59	9
Id: R= 	22	49
4-Pyridylmethyl derivatives		
Ie: R=$CH(CH_3)_2$	26	48

Preparation conditions : 1) nitrosation with $NaNO_2$ and 10% HCl; 2) extraction with $CHCl_3$ after neutralization; 3) separation by silica gel chromatography using $CHCl_3$.

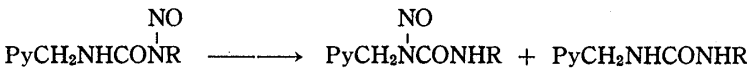
nitroso isomer in the mixture migrated to the N^1 nitrogen to produce the 1-nitroso isomer. However, this type of rearrangement in N-nitrosoureas requires further study.

This paper describes the rearrangement of 1-substituted 3-(3-pyridylmethyl)nitrosoureas and 1-substituted 3-(4-pyridylmethyl)nitrosoureas to their N-nitroso isomers.

We have prepared various types of N-nitrosoureas for screening as potential antitumor agents.[1,5] When 1-methyl-, 1-ethyl-, 1-phenyl-, and 1-(4-chlorophenyl)-3-(3-pyridylmethyl)-urea were nitrosated with sodium nitrite and hydrochloric acid, the corresponding 1-nitrosoureas were exclusively produced in more than 90% yields.[6] As shown in Table I, the similar nitrosation of 1-(2-chloroethyl)- (Ia), 1-isopropyl- (Ib), 1-isobutyl- (Ic) and 1-cyclohexyl-3-(3-pyridylmethyl)urea (Id) gave mixtures consisting of the 1-nitrosoureas (IIa—d) and their 3-nitroso isomers (IIIa—d), which were all separated by means of chromatography on a column of silica gel under ice-cooling with chloroform as an eluting solvent. 1-Isopropyl-3-(4-pyridylmethyl)urea (Ie) was similarly nitrosated to give the separable 1-nitroso and 3-nitroso isomers, IIe and IIIe. When the N^1 substituents were bulky isopropyl and cyclohexyl moieties, the 3-nitroso isomers were obtained in higher yields than the 1-nitroso isomers.

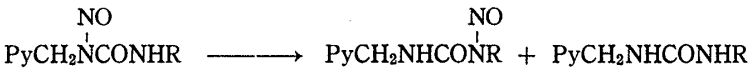
The infrared (IR) and proton nuclear magnetic resonance (NMR) data for these nitrosoureas were consistent with the assigned structures. The details of the spectral data are

Table II. Yields of the Rearrangement and Denitrosation Products of the 1-Nitrosoureas (II) and 3-Nitrosoureas (III) in Formic Acid-d_2



II III I

Nitrosoureas	Yields (%)	
	Rearrangement	Denitrosation
3-Pyridylmethyl derivatives		
IIa: R=CH_2CH_2Cl	38	28
IIb: R=$CH(CH_3)_2$	75	22
IIc: R=$CH_2CH(CH_3)_2$	25	15
IId: R= 	66	33
4-Pyridylmethyl derivatives		
IIe: R=$CH(CH_3)_2$	70	28



III II I

Nitrosoureas	Yields (%)	
	Rearrangement	Denitrosation
3-Pyridylmethyl derivatives		
IIIa: R=CH_2CH_2Cl	33	26
IIIb: R=$CH(CH_3)_2$	3	25
IIIc: R=$CH_2CH(CH_3)_2$	55	14
IIId: R= 	1	28
4-Pyridylmethyl derivatives		
IIIe: R=$CH(CH_3)_2$	2	26

Reaction conditions: 1) allowed to stand in a mixture of $CDCl_3$ and DCO_2D for 24 hr at room temperature; 2) determination by NMR spectroscopy.

The recovery of the starting nitrosoureas was calculated as 100% minus the yields of the rearranged isomer and the denitrosated product.

noted in the experimental section. For instance, the methylene of the 1-nitrosoureas [Py$\underline{CH_2}$-NHCON(NO)R] appeared as a doublet at 4.62—4.70 ppm, and that of the 3-nitrosoureas [Py$\underline{CH_2}$N(NO)CONHR] as a singlet at 4.99—5.05 ppm. On the other hand, the methylene of the starting ureas [Py$\underline{CH_2}$NHCONHR] appeared as a doublet at 4.20—4.30 ppm.

Treatment of each nitrosourea with formic acid resulted in the formation of a mixture of the corresponding 1-nitrosourea, 3-nitrosourea and denitrosated product. The yields of these isomers and denitrosated products were directly measured by means of NMR spectroscopy in formic acid-d_2. Each nitrosourea was dissolved in formic acid-d_2, the solution was allowed to stand for 24 hours at room temperature, and the yields of the rearranged and denitrosated compounds were determined by means of NMR spectroscopy without neutralization or extraction. Thus, as shown in Table II, compounds IIa, IIb, IId and IIe readily isomerized to the corresponding 3-nitroso isomers(IIIa,b,d,e). Though 1-isobutyl-3-nitroso-3-(3-pyridylmethyl)-urea (IIIc) readily isomerized to the 1-nitroso isomer (IIc), other 3-nitrosoureas (IIIb—e) hardly yielded any of the 1-nitroso isomers (IIb—e). It is suggested that this type of rearrangement is governed by the steric effect of the alkyl group attached to the N^1 nitrogen.

Table III. Yields of the Products in the Rearrangement of 1-(2-Chloroethyl)-1-nitroso-3-(3-pyridylmethyl)urea (IIa) in Various Media

IIa (mg)	Media	Reaction[a] conditions	Product (mg)	Yields (%)		
				Isomer (IIIa)	Recovery (IIa)	Denitrosated compound (Ia)
200	10% HCl 0.5 ml	rt 2d	183	28	49	16
200	10% H_2SO_4 0.5 ml	rt 2d	144	28	37	8
100	HCl in MeOH 0.5 ml	rt 2 hr	93	11	30	59
120	HCl in MeOH 1 ml	rt 2d	65	—	—	62
80	AcOH 0.5 ml	rt 2d	77	7	72	21
300	$SOCl_2$ 0.2 g	rt 2d	226	11	41	26
100	$SOCl_2$ 0.2 g	rt 18 hr	95	16	65	16
400	$POCl_3$(0.3 g) in $CHCl_3$ 5 ml	rt 2d	320	—	80	—
360	$POCl_3$ 0.7 g	40° 1 hr	270	—	75	—
120	HCO_2H 0.2 g	8—10° 1d	117	14	71	14
120	HCO_2H 0.2 g	40° 1d	114	34	34	30
120	HCO_2H (0.2 g) in $CHCl_3$ 0.4 ml	40° 1d	114	40	40	21
60	HCO_2H(50 mg) in $CDCl_3$ 0.5 ml	rt 2d		3	97	—

a) rt: room temperature, d: day.

This type of rearrangement was also observed in other acid media (Table III). When the 1-nitrosourea (IIa) was allowed to stand in 10% hydrochloric acid or 10% sulfuric acid at room temperature for 2 days, the 3-nitroso isomer (IIIa) was produced in 28% yield in each case. Treatment of IIa for 2 hours in methanol saturated with hydrogen chloride gave IIIa in 11% yield, together with the denitrosated compound (Ia) in 59% yield. However, similar treatment of IIa for 2 days gave only the denitrosated compound (Ia) in 62% yield. In acetic acid, IIa did not isomerize as fast as in formic acid, probably due to its weaker acidity. In thionyl chloride, IIa isomerized to IIIa in 16% yield after being allowed to stand for 18 hours. In phosphorus oxychloride, the rearrangement did not occur and the starting material was recovered. The rearrangement is not initiated by heat, since the nitrosourea (IIa) was recovered quantitatively when its benzene solution was refluxed for 4 hours.

As shown in Chart 1, treatment of IIa with 1-methyl-3-(2-pyridylmethyl)urea (IV) in formic acid gave the denitrosated compound (Ia) in 81% yield and a newly nitrosated compound, 1-methyl-1-nitroso-3-(2-pyridylmethyl)urea (V) in 73% yield. Furthermore, similar

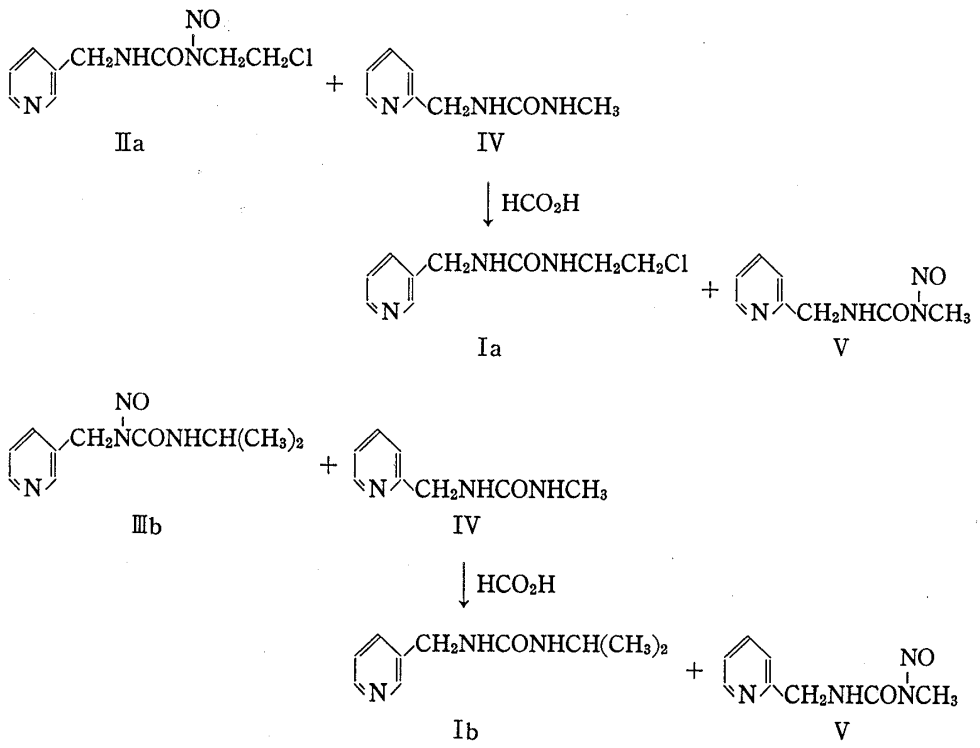


Chart 1

treatment of IIIb with IV also gave Ib and V, both in 70% yield. In addition, when an equimolar mixture of IIa and urea in formic acid was allowed to stand at room temperature, the denitrosated compound (Ia) was obtained in 78% yield. These reactions suggest that the rearrangement of 1-substituted 3-(3-or 4-pyridylmethyl)nitrosoureas is an acid-catalyzed, intermolecular rearrangement.

This type of rearrangement seems to be similar to the Fischer–Hepp rearrangement,[2] in which an N-nitroso group departs as nitrosyl chloride or nitrous acid, followed by ring nitrosation. However, an intramolecular mechanism has been proposed for the Fischer–Hepp rearrangement.[7,8] At this stage, it can be assumed that the reaction of the N-nitrosoureas with formic acid produces nitroso formate, and this nitroso formate nitrosates the denitrosated ureas to produce their N-nitroso isomers.

Experimental

All melting points are uncorrected. IR spectra were measured on a JASCO A-102 spectrophotometer and UV spectra on a Shimadzu UV-200 spectrophotometer. NMR spectra were measured on a Varian EM 360A spectrometer with tetramethylsilane as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; sh, shoulder; Py, pyridine ring.

1-Substituted 3-(3- or 4-Pyridylmethyl)urea (Ia—e)——1-(2-Chloroethyl)-3-(3-pyridylmethyl)urea (Ia), 1-cyclohexyl-3-(3-pyridylmethyl)urea (Id) and their nitrosoureas (IIa, IIIa, IId, IIId) were prepared according to our previous paper.[5]

1-Isopropyl-3-(3-pyridylmethyl)urea (Ib): Isopropyl isocyanate (8.5 g, 0.1 mol) was added dropwise to an ice-cooled solution of 10.8 g (0.1 mol) of 3-pyridylmethylamine in 100 ml of ether, and the mixture was stirred for 2 hr. The resulting crystals were filtered off, washed with ether, and dried. Colorless needles (from a mixture of $CHCl_3$ and ether), mp 107—108°. Yield, 16.6 g (86.0%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 3365, 1660 (NHCONH). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 257 (3.44), 262.5 (3.46), 270 (sh). NMR ($CDCl_3$) ppm: 1.03 (6H, d, J=7 Hz, $CH(\underline{CH_3})_2$), 3.75 (1H, m, $\underline{CH}(CH_3)_2$), 4.20 (2H, d, J=7 Hz, $Py\underline{CH_2}$), 5.50 (1H, d, J=7 Hz, NH), 6.15 (1H, t, J=7 Hz, NH), 7.14 (1H, dd, J=8 and 5 Hz, C^5–H), 7.48 (1H, dt, J=8 and 2 Hz, C^4–H), *ca.* 8.4 (2H, C^2–H and C^6–H). *Anal.* Calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.75. Found: C, 62.22; H, 7.96; N, 21.55.

1-Isobutyl-3-(3-pyridylmethyl)urea (Ic): Isobutylamine (3.0 g, 0.04 mol) was added dropwise to a suspension of 8.0 g (0.04 mol) of 1-methyl-1-nitroso-3-(3-pyridylmethyl)urea[1] in 20 ml of water in an ice-

bath, and the mixture was stirred for 4 hr at room temperature. The resulting crystals were filtered off, and recrystallized from a mixture of $CHCl_3$ and ether. Colorless leaflets, mp 97°. Yield, 4.6 g (53.9%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 3370, 1660 (NHCONH). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 262.5 (3.43), 257 (3.41), 270 (sh). NMR ($CDCl_3$) ppm: 0.85 (6H, d, J=7 Hz, $CH_2CH(\underline{CH_3})_2$), 1.60 (1H, m, $CH_2\underline{CH}(CH_3)_2$), 2.92 (2H, t, J=7 Hz, $\underline{CH_2}CH(CH_3)_2$), 4.30 (2H, d, J=7 Hz, Py$\underline{CH_2}$), 5.35 (1H, br t, NH), 5.75 (1H, br t, NH), 7.15 (1H, dd, J=8 and 5 Hz, C^5–H), 7.59 (1H, dt, J=8 and 2 Hz, C^4–H), *ca.* 8.4 (2H, C^2–H and C^6–H). *Anal.* Calcd for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.58; H, 8.12; N, 20.54.

1-Isopropyl-3-(4-pyridylmethyl)urea (Ie): This compound was prepared as in the case of Ib. Colorless flakes (from a mixture of CH_2Cl_2 and ether), mp 120—121°. Yield, 92.6%. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 3370, 1660 (NHCONH). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 252.5 (sh), 257.5 (3.32), 264 (sh). NMR ($CDCl_3$) ppm: 1.03 (6H, d, J=7 Hz, $CH(\underline{CH_3})_2$), 3.78 (1H, m, $\underline{CH}(CH_3)_2$), 4.20 (2H, d, J=7 Hz, Py$\underline{CH_2}$), 5.42 (1H, d, J=7 Hz, NH), 6.05 (1H, t, J=7 Hz, NH), 7.05 (2H, d, J=6.5 Hz, C^3–H and C^5–H), 8.42 (2H, d, J=6.5 Hz, C^2–H and C^6–H). *Anal.* Calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.75. Found: C, 61.91; H, 8.16; N, 21.55.

Nitrosation of 1-Isopropyl-3-(3-pyridylmethyl)urea (Ib)——A solution of 3.1 g (0.045 mol) of sodium nitrite in 10 ml of water was added dropwise to a solution of 5.8 g (0.03 mol) of Ib in 30 ml of 10% HCl at −5—0° with stirring, and the mixture was further stirred for 1 hr. The reaction mixture was neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and the solvent was distilled off under reduced pressure. An oily residue (6.7 g) was obtained. This oily product (1.2 g) was dissolved in $CHCl_3$, and chromatographed on a column of silica gel under ice-water cooling. The first fraction eluted with $CHCl_3$ gave 0.85 g (70.8%) of hygroscopic 1-isopropyl-3-nitroso-3-(3-pyridylmethyl)urea (IIIb), mp 49° (dec.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 1720 (NHCO), 1475 (NO). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 251 (3.74), 255 (3.74), 263 (sh), 384 (sh), 396.5 (1.92), 414 (1.86). NMR ($CDCl_3$) ppm: 1.30 (6H, d, J=7 Hz, $CH(\underline{CH_3})_2$), 4.23 (1H, m, $\underline{CH}(CH_3)_2$), 5.00 (2H, s, Py$\underline{CH_2}$), 6.8 (1H, br, NH), 7.2—8.5 (4H, pyridine ring-H). *Anal.* Calcd for $C_{10}H_{14}N_4O_2 \cdot 1/5H_2O$: C, 53.18; H, 6.43; N, 24.81. Found: C, 53.14; H, 6.32; N, 25.20. The second fraction eluted with the same solvent gave 0.25 g (20.8%) of 1-isopropyl-1-nitroso-3-(3-pyridylmethyl)urea (IIb). Pale yellow flakes, mp 58—59° (dec.) (from ether). The analytical data of this unstable compound did not coincide strictly with the calculated values. However, the following spectral data supported the assigned structure. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 1718 (NHCO), 1475 (NO). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 251 (sh), 256 (3.84), 262 (sh), 393 (sh), 405 (1.93), 414 (1.91). NMR ($CDCl_3$) ppm: 1.30 (6H, d, J=7 Hz, $CH(\underline{CH_3})_2$), 4.64 (2H, d, J=6.5 Hz, Py$\underline{CH_2}$), 5.03 (1H, m, J=7 Hz, $\underline{CH}(CH_3)_2$), 7.30 (1H, dd, J=8 and 5 Hz, C^5–H), 7.5 (1H, br, NH), 7.75 (1H, dt, J=8 and 2 Hz, C^4–H), *ca.* 8.6 (2H, C^2–H and C^6–H). *Anal.* Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.47; H, 6.34; N, 25.99.

Nitrosation of 1-Isobutyl-3-(3-pyridylmethyl)urea (Ic)——A solution of 2.3 g (0.03 mol) of sodium nitrite in 10 ml of water was added dropwise to a solution of 4.14 g (0.02 mol) of Ic in 20 ml of 10% HCl at −5—0° with stirring, and the reaction mixture was treated as in the case of Ib. The residue (4.7 g), consisting of 83% of the 1-nitrosourea and 17% of the 3-nitrosourea, was chromatographed on silica gel with $CHCl_3$ as an eluting solvent under the condition of ice-water cooling. The first fraction gave 1-isobutyl-3-nitroso-3-(3-pyridylmethyl)urea (IIIc), 0.42 g (8.9%) as an oily product. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 1720 (NHCO), 1470 (NO). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 251 (3.75), 255 (3.75), 263 (sh), 385 (sh), 397 (1.88), 414 (1.81). NMR ($CDCl_3$) ppm: 0.98 (6H, d, J=7 Hz, $CH_2CH(\underline{CH_3})_2$), 1.90 (1H, m, J=7 Hz, $CH_2\underline{CH}(CH_3)_2$), 3.34 (2H, t, J=7 Hz, $\underline{CH_2}CH(CH_3)_2$), 5.05 (2H, s, Py$\underline{CH_2}$), *ca.* 7.4 (1H, br, NH), 7.40 (1H, dd, J=8 and 5 Hz, C^5–H), 7.80 (1H, dt, J=8 and 1.5 Hz, C^4–H), *ca.* 8.6 (2H, C^2–H and C^6–H). The second fraction gave 1-isobutyl-1-nitroso-3-(3-pyridylmethyl)urea (IIc), yellow needles (from ether), mp 100° (dec.). Yield, 2.76 g (58.5%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 1720 (NHCO), 1475 (NO). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 251 (sh), 256 (3.92), 262 (sh), 386 (sh), 398.5 (2.03), 416 (1.97). NMR ($CDCl_3$) ppm: 0.82 (6H, d, J=7 Hz, $CH_2CH(\underline{CH_3})_2$), 1.90 (1H, m, J=7 Hz, $CH_2\underline{CH}(CH_3)_2$), 3.70 (2H, d, J=7 Hz, $\underline{CH_2}CH(CH_3)_2$), 4.70 (2H, d, J=6.5 Hz, Py$\underline{CH_2}$), 6.9 (1H, br, NH), 7.38 (1H, dd, J=8 and 5 Hz, C^5–H), 7.85 (1H, dt, J=8 and 1.5 Hz, C^4–H), *ca.* 8.7 (2H, C^2–H and C^6–H). *Anal.* Calcd for $C_{11}H_{16}N_4O_2$: C, 55.91; H, 6.83; N, 23.72. Found: C, 55.82; H, 6.97; N, 23.67.

Nitrosation of 1-Isopropyl-3-(4-pyridylmethyl)urea (Ie)——A solution of 2.3 g (0.03 mol) of sodium nitrite in 10 ml of water was added dropwise to a solution of 4.0 g (0.02 mol) of Ie in 20 ml of 10% HCl at −5—0° with stirring, and the mixture was further stirred for 1 hr. The reaction mixture was neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and the solvent was evaporated off under reduced pressure. The residue was recrystallized from a mixture of acetone and ether, then from acetone. 1-Isopropyl-1-nitroso-3-(4-pyridylmethyl)urea (IIe), yellow prisms, mp 76° (dec.), was obtained. Yield, 1.2 g (26.1%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 1720 (NHCO), 1478 (NO). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 251 (3.95), 258 (sh), 389 (sh), 400.5 (1.95), 414 (1.94). NMR ($CDCl_3$) ppm: 1.30 (6H, d, J=7 Hz, $CH(\underline{CH_3})_2$), 4.62 (2H, d, J=6.5 Hz, Py$\underline{CH_2}$), 5.00 (1H, m, J=7 Hz, $\underline{CH}(CH_3)_2$), 7.21 (2H, dd, J=6 and 1.5 Hz, C^3–H and C^5–H), 7.8 (1H, br, NH), 8.50 (2H, dd, J=6 and 1.5 Hz, C^2–H and C^6–H). *Anal.* Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.81; H, 6.75; N, 25.28. The mother liquor was evaporated to dryness, and the residue was recrystallized from ether. 1-Isopropyl-3-nitroso-3-(4-pyridylmethyl)urea (IIIe), pale yellow needles, mp 81° (dec.), was obtained. Yield, 2.2 g (47.8%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410, 1718 (NHCO), 1472 (NO). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 245.5 (3.82), 258 (sh), 384 (sh), 396 (1.92), 413.5 (1.86). NMR ($CDCl_3$) ppm: 1.30 (6H, d, J=7 Hz, $CH(\underline{CH_3})_2$), 4.20 (1H, m, $\underline{CH}(CH_3)_2$), 4.99 (2H, s, Py$\underline{CH_2}$), 6.85 (1H, br, NH),

7.14 (2H, dd, $J=6$ and 1.5 Hz, C^3–H and C^5–H), 8.52 (2H, dd, $J=6$ and 1.5 Hz, C^2–H and C^6–H). *Anal.* Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.87; H, 6.48; N, 25.24.

Nitrosation of 1-(2-Chloroethyl)-3-(3-pyridylmethyl)urea (Ia) in Formic Acid and Change of the Isomer Ratio——Sodium nitrite (2.1 g, 0.03 mol) was added in small portions to a solution of 4.2 g (0.02 mol) of Ia in 25 ml of 99% formic acid at −5—0° with stirring, and the mixture was further stirred. Next, 100 ml of $CHCl_3$, then a suspension of 60 g of $NaHCO_3$ in 200 ml of water were added, and the mixture was stirred. The $CHCl_3$ layer was separated, and the aqueous layer was further extracted with two 50 ml portions of $CHCl_3$. The combined $CHCl_3$ layer was washed with 50 ml of water, dried over anhyd. Na_2SO_4, and the solvent was evaporated off under reduced pressure. The residue was dissolved in $CDCl_3$, and the isomer ratio was determined by means of NMR spectroscopy. When the reaction mixture described above was allowed to stand for 15 min, 1 hr and 1 day, the isomer ratios of IIa to IIIa were 1.78, 1.72 and 1.25, respectively. This result suggested a transnitrosation.

Identification of the Products in the Rearrangement of 1-(2-Chloroethyl)-1-nitroso-3-(3-pyridylmethyl)-urea (IIa) and Its 3-Nitroso Isomer (IIIa) in Formic Acid——1-(2-Chloroethyl)-1-nitroso-3-(3-pyridylmethyl)-urea (IIa): A solution of 600 mg (0.0025 mol) of IIa in 2 ml of 99% formic acid was allowed to stand for 3 days at room temperature. The reaction mixture was poured into ice-water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The solvent was distilled off under reduced pressure, and the residue was extracted with ether. The insoluble part of the residue was the denitrosated compound (Ia). Yield, 77 mg (14.6%). The ether later was evaporated to dryness under reduced pressure, and the residue was chromatographed on a column of silica gel using $CHCl_3$. The first fraction gave 205 mg (34.2%) of the rearranged compound (IIIa), and from the second fraction 160 mg (26.7%) of IIa was obtained.

1-(2-Chloroethyl)-3-nitroso-3-(3-pyridylmethyl)urea (IIIa): A solution of 600 mg (0.0025 mol) of IIIa in 2 ml of 99% formic acid was treated as described in the case of IIa. The rearranged compound (IIa), the denitrosated compound (Ia) and IIIa were obtained in yields of 176 mg (29.3%), 84 mg (15.9%) and 195 mg (33.3%), respectively.

Direct Measurement of the Yields of the Products in the Rearrangement of 1-Substituted 3-(3- or 4-Pyridylmethyl)nitrosourea (IIa—e, IIIa—e) in Formic Acid-d_2——A solution of 0.0025 mol of a nitrosourea (IIa—e, IIIa—e) in a mixture of 0.1 ml of $CDCl_3$ and 0.4 ml of 99% formic acid-d_2 was allowed to stand for 24 hr at room temperature. The quantities of the 1-nitrosoureas, the 3-nitrosoureas and the denitrosated compounds were determined from the NMR spectrum of the appropriate nitrosourea. Their yields are listed in Table II.

Rearrangement of 1-(2-Chloroethyl)-1-nitroso-3-(3-pyridylmethyl)urea (IIa) in Various Media——A solution of IIa in various media was treated according to the conditions shown in Table III. The reaction mixture was poured into ice-water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The solvent was distilled off under reduced pressure, the residue was dissolved in $CDCl_3$, and the isomer ratio was determined by means of NMR spectroscopy.

Reaction of the Nitrosoureas (IIa, IIIb) with Urea or 1-Methyl-3-(2-pyridylmethyl)urea (IV) in Formic Acid——The Reaction of IIa with Urea: A solution of 73 mg (0.0003 mol) of IIa and 18 mg (0.0003 mol) of urea in 1 ml of 99% formic acid was allowed to stand for 2 days at room temperature. The reaction mixture was treated in the usual way as described above. The product was 1-(2-chloroethyl)-3-(3-pyridylmethyl)urea (Ia),[5] colorless granules, mp 86°. Yield, 50 mg (77.8%).

The Reaction of IIa with IV: A solution of 243 mg (0.001 mol) of IIa and 165 mg (0.001 mol) of IV (mp 122°) in 1 ml of 99% formic acid was allowed to stand for 2 days at room temperature, and the reaction mixture was treated in the usual way as described above. It was 0.5 g of an oily product, which contained a newly nitrosated compound, 1-methyl-1-nitroso-3-(2-pyridylmethyl)urea (V), 1-(2-chloroethyl)-3-nitroso-3-(3-pyridylmethyl)urea (IIIa) and the denitrosated compound (Ia) in 73%, 2% and 81% yields, respectively. The starting materials, IV (27%) and IIa (17%), were also partially recovered. They were all determined by means of NMR spectroscopy.

The Reaction of IIIb with IV: A solution of 150 mg (0.0007 mol) of 1-isopropyl-3-nitroso-3-(3-pyridylmethyl)urea (IIIb) and 120 mg (0.0007 mol) of IV in 1 ml of 99% formic acid was allowed to stand for 3 days at room temperature, and the reaction mixture was treated as described above. The product (250 mg) consisted of the nitrosated compound (V), the denitrosated compound (Ib) (both 70%), and the starting materials, IIIb and IV (both 30%).

References and Notes

1) S. Kamiya, M. Miyahara, S. Sueyoshi, I. Suzuki, and S. Odashima, *Chem. Pharm. Bull.*, **26**, 3884 (1978).
2) O. Fischer and E. Hepp, *Ber.*, **19**, 2991 (1886); H.J. Shine, "Aromatic Rearrangements," Elsevier Publishing Co. 1968, p. 231; F. Müller, "Methodender Organischen Chemie," Vol. 10, in Houben-Weyl, 1971, p. 1051.
3) H. Yamashita, K. Ito, and M. Sekiya, *Chem. Pharm. Bull.*, **26**, 2249 (1978).
4) T.P. Johnston, G.S. McCalb, P.S. Opliger, and J.A. Montgomery, *J. Med. Chem.*, **9**, 892 (1966).

5) S. Kamiya, *Chem. Pharm. Bull.*, **25**, 1121 (1977).
6) S. Kamiya, *Chem. Pharm. Bull.*, **23**, 2744 (1975).
7) G. Steel and D.L.H. Williams, *Chem. Comm.*, **1969**, 975.
8) T.I. Aslapovskaya, E. Yu. Belyaev, B.P. Kumarev, and B.A. Porai-Koshits, *Reakts. Sposobnost Org. Soedin.*, **1968**, 456 [*C.A.*, **70**, 19368 *t* (1969)].