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Nitrosation of 1-Substituted 3-(2-Pyridylmethyl)ureas and Related Compounds[1)]

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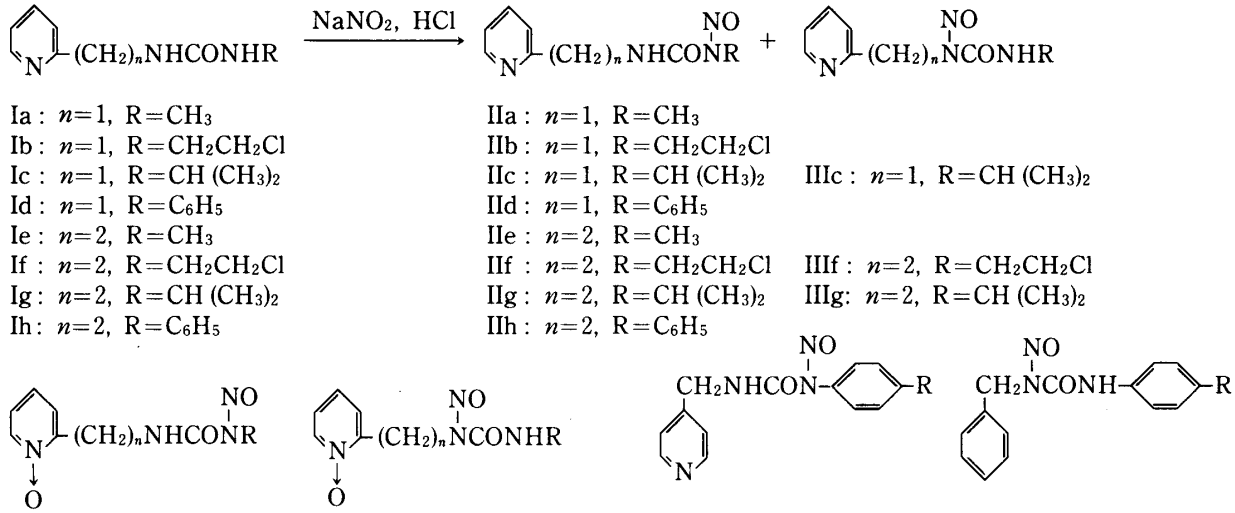
Nitrosation of 1-methyl- (Ia), 1-(2-chloroethyl)- (Ib) and 1-phenyl-3-(2-pyridylmethyl)-urea (Id) with hydrochloric acid and sodium nitrite gave exclusively the corresponding 1-nitrosoureas (IIa, b, d). However, nitrosation of the 1-isopropylurea (Ic) gave a mixture of the 1-nitrosourea (IIc) and the 3-nitrosourea (IIIc). Similar results were also obtained in the nitrosation of 1-substituted 3-(2-pyridylethyl)ureas (Ie—h).

The reaction of the nitrosoureas and *m*-chloroperbenzoic acid in chloroform gave the *N*-oxides (IVa—f, Vc, f, g), which were more stable than the nitrosoureas.

Keywords——nitrosourea; 1-substituted 3-(2-pyridylmethyl)nitrosourea; 1-substituted 3-(2-pyridylethyl)nitrosourea; nitrosation; antitumor activity

We previously reported the antitumor activity of 1-substituted 3-(3-pyridylmethyl)-nitrosourea derivatives[2,3)] and the 1,3-migration of the nitroso group in these compounds.[1)] Deriving heterocyclic antitumor nitrosoureas to their *N*-oxides or salts makes them more stable and is advantageous for clinical use. This paper describes the nitrosation of 1-substituted 3-(2-pyridylmethyl)ureas and related compounds.



Ia: n=1, R=CH_3
Ib: n=1, R=CH_2CH_2Cl
Ic: n=1, R=$CH(CH_3)_2$
Id: n=1, R=C_6H_5
Ie: n=2, R=CH_3
If: n=2, R=CH_2CH_2Cl
Ig: n=2, R=$CH(CH_3)_2$
Ih: n=2, R=C_6H_5

IIa: n=1, R=CH_3
IIb: n=1, R=CH_2CH_2Cl
IIc: n=1, R=$CH(CH_3)_2$
IId: n=1, R=C_6H_5
IIe: n=2, R=CH_3
IIf: n=2, R=CH_2CH_2Cl
IIg: n=2, R=$CH(CH_3)_2$
IIh: n=2, R=C_6H_5

IIIc: n=1, R=$CH(CH_3)_2$
IIIf: n=2, R=CH_2CH_2Cl
IIIg: n=2, R=$CH(CH_3)_2$

IVa: n=1, R=CH_3
IVb: n=1, R=CH_2CH_2Cl
IVc: n=1, R=$CH(CH_3)_2$
IVe: n=2, R=CH_3
IVf: n=2, R=CH_2CH_2Cl

Vc: n=1, R=$CH(CH_3)_2$
Vf: n=2, R=CH_2CH_2Cl
Vg: n=2, R=$CH(CH_3)_2$

VIa: R=H
VIb: R=Cl

VIIa: R=H
VIIb: R=CH_3

Chart 1

All 2-pyridylmethylureas (Ia—d) and 2-pyridylethylureas (Ie—h) were prepared by the reaction of 2-pyridylmethylamine or 2-pyridylethylamine with an appropriate isocyanate in ether. As shown in Chart 1, the nitrosation of 1-methyl- (Ia), 1-(2-chloroethyl)- (Ib) and 1-phenyl-3-(2-pyridylmethyl)urea (Id) with sodium nitrite and 10% hydrochloric acid gave exclusively the corresponding 1-nitrosoureas (IIa, b, d). The nitrosated nitrogens were

determined from the methylene signals [Py$\underline{CH_2}$N(NO)CONHR, Py$\underline{CH_2}$NHCON(NO)R], singlet or doublet, in the nuclear magnetic resonance (NMR) spectra, as noted in the experimental section. However, the similar nitrosation of 1-isopropyl-3-(2-pyridylmethyl)urea (Ic) gave an approximately 1: 2 mixture of the 1-nitrosourea (IIc) and the 3-nitrosourea (IIIc), which was determined by measuring the NMR integral ratio of the methylene protons of the isomers in the reaction mixture. When the 1: 1 mixture consisting of IIc and IIIc was allowed to stand for 7.5 h in formic acid-d_2 at 23°C, the ratio changed to 1: 4, accompanied by denitrosation. This was due to a 1,3-migration of the N^1 nitroso group to the N^3 nitrogen to produce the 3-nitroso isomer. Recrystallization from ether gave the pure 3-nitroso isomer (IIIc).

Though these heterocyclic nitrosourea derivatives had to be stored in a refrigerator because of their poor stability, their *N*-oxides were stable at room temperature. Treatment of IIa and IIb with *m*-chloroperbenzoic acid in chloroform gave the *N*-oxides (IVa, IVb). The similar *N*-oxidation of the 1: 2 mixture consisting IIc and IIIc mentioned above also gave a mixture of their *N*-oxides (IVc, Vc), which could be separated by fractional crystallization. Since the existence of an *N*-nitroso group in these *N*-oxides was confirmed by their diazo-coupling reaction using sulfanilic acid and *N*-(2-naphthyl)ethylenediamine, they were not *N*-nitroureas but *N*-nitrosourea *N*-oxides.

In the nitrosation of 1-substituted 3-(2-pyridylethyl)ureas (Ie—h), the 1-methylurea (Ie) and the 1-phenylurea (Ih) gave exclusively the corresponding 1-nitrosoureas (IIe, IIh). However, the 1-(2-chloroethyl)urea (If) and the 1-isopropylurea (Ig) produced a mixture of the 1-nitrosourea (IIf) and the 3-nitroso isomer (IIIf) in a ratio of 5: 1, and a mixture of the 1-nitrosourea (IIg) and the 3-nitrosourea (IIIg) in a ratio of 1: 2, respectively. The former mixture was similarly treated with *m*-chloroperbenzoic acid, and the reaction mixture (consisting of the 1-nitrosourea *N*-oxide and the 3-nitrosourea *N*-oxide) was fractionally recrystallized from acetone to give stable 1-(2-chloroethyl)-1-nitroso-3-(2-pyridylethyl)urea *N*-oxide (IVf) in 43% yield and the unstable 3-nitroso isomer (Vf) in 16% yield. Fractional crystallization of the 1: 2 mixture consisting of IIg and IIIg gave only the pure 3-nitroso isomer (IIIg), which formed the *N*-oxide (Vg) on treatment with *m*-chloroperbenzoic acid.

The nitrosation of 1-phenyl- and 1-(4-chlorophenyl)-3-(4-pyridylmethyl)urea also gave exclusively the 1-nitrosoureas (VIa, b) as observed in the cases of Id and Ih (Chart 1). However, the nitrosation of 1-phenyl- and 1-(4-tolyl)-3-benzylurea, in which a pyridine ring having a strong inductive effect is replaced by a phenyl ring, gave not the 1-nitrosoureas but the 3-nitrosoureas (VIIa, b) exclusively.

The isomer ratios observed in the nitrosation of these 1,3-disubstituted ureas suggest that this type of nitrosation is governed by steric and inductive effects of the substituents on the N^1 and N^3 nitrogens, and when a bulky substituent is present, an isomeric mixture consisting of N^1-nitrosourea and N^3-nitrosourea is produced.

Some of the nitrosourea *N*-oxides were tested for activity against rat ascites hepatoma AH 13 and mouse lymphoid leukemia L 1210.[3,4] Compounds IVa and IVe (having a 1-methyl-1-nitrosoureido group) were active against both tumors. Compounds IVb and IVf [having a 1-(2-chloroethyl)-1-nitrosoureido group] were highly active against both tumors. It is interesting that compound Vc (having a nitroso group attached to the nitrogen adjacent to the pyridylmethyl group) was weakly active against L 1210.[4]

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured on a JASCO A-102 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; Py, pyridine nucleus

1-Substituted 3-(2-Pyridylmethyl)urea (Ia—d) and 3-(2-Pyridylethyl)ureas (Ie—h)——These compounds were prepared by the method reported in our previous paper.[2]

1-Methyl-3-(2-pyridylmethyl)urea (Ia): Colorless leaflets (from a mixture of ethanol and *n*-hexane), mp 122—123°C. Yield, 79%. *Anal.* Calcd for $C_8H_{11}N_3O$: C, 58.16; H, 6.71; N, 25.44. Found: C, 57.87; H, 6.60; N, 25.28.

1-(2-Chloroethyl)-3-(2-pyridylmethyl)urea (Ib): Colorless needles (from a mixture of chloroform and cyclohexane), mp 116°C.[5]

1-Isopropyl-3-(2-pyridylmethyl)urea (Ic): Colorless leaflets (from a mixture of chloroform and ether), mp 137—138°C. Yield, 93%. *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-Phenyl-3-(2-pyridylmethyl)urea (Id): Colorless leaflets (from acetone), mp 138—140°C. Yield, 94%. *Anal.* Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.61; H, 5.72; N, 18.18.

1-Methyl-3-(2-pyridylethyl)urea (Ie): Colorless, hygroscopic leaflets (from a mixture of ethanol and *n*-hexane), mp 81°C. Yield, 90%. NMR ($CDCl_3$) δ: 2.62 (d, $J=5$ Hz, CH_3), 2.82 (t, $J=6$ Hz, $PyCH_2$), 3.50 (q, $J=4$ Hz, $\underline{CH_2}NH$). Picrate: Orange pillars (from ethanol), mp 162—163°C. *Anal.* Calcd for $C_9H_{13}N_3O\cdot C_6H_3N_3O_7$: C, 44.12; H, 3.95; N, 20.58. Found: C, 44.53; H, 3.70; N, 20.44.

1-(2-Chloroethyl)-3-(2-pyridylethyl)urea (If): Colorless granules (from a mixture of chloroform and diisopropyl ether), mp 108—109°C. Yield, 95%. *Anal.* Calcd for $C_{10}H_{14}ClN_3O$: C, 52.75; H, 6.20; N, 18.45. Found: C, 52.63; H, 6.19; N, 18.24.

1-Isopropyl-3-(2-pyridylethyl)urea (Ig): Colorless needles (from a mixture of chloroform and ether), mp 78—79°C. Yield, 78%. *Anal.* Calcd for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.65; H, 8.34; N, 19.72.

1-Phenyl-3-(2-pyridylethyl)urea (Ih): Colorless granules (from a mixture of chloroform and *n*-hexane), mp 127°C. Yield, 94%. *Anal.* Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.31; H, 6.17; N, 17.40.

Nitrosation of 1-Substituted 3-(2-Pyridylmethyl)ureas (Ia—d) and 3-(2-Pyridylethyl)ureas (Ie—f)——1-Methyl-1-nitroso-3-(2-pyridylmethyl)urea (IIa): A solution of sodium nitrite (16.5 g, 0.1 mol) in 25 ml of water was added to a solution of 16.7 g (0.1 mol) of Ia in 30 ml of 10% hydrochloric acid with stirring under ice-cooling. After neutralization, the separated crystals were filtered and washed with ice-water. Pale yellow granules (from ether), mp 78—81°C (dec.). Yield, 15.7 g (71%). IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO). NMR ($CDCl_3$) δ: 3.20 (s, CH_3), 4.68 (d, $J=6$ Hz, $PyCH_2$). *Anal.* Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.31; H, 5.08; N, 28.56.

1-Methyl-1-nitroso-3-(2-pyridylmethyl)urea *N*-Oxide (IVa): *m*-Chloroperbenzoic acid [80% purity, 2.38 g (0.01 mol)] was added to a solution of 1.94 g (0.01 mol) of IIa in 50 ml of chloroform under ice-cooling with stirring, and the mixture was allowed to stand overnight at room temperature. The reaction mixture was extracted with 5% sodium carbonate twice, washed with water, and dried over anhyd. sodium sulfate. The solvent was evaporated off under reduced pressure, and the residue was recrystallized from acetone to give yellow–orange pillars, mp 124°C (dec.). Yield, 0.61 g (29%). NMR ($CDCl_3$) δ: 3.12 (s, CH_3), 4.80 (d, $J=5$ Hz, $PyCH_2$). *Anal.* Calcd for $C_8H_{10}N_2O_4$: C, 45.71; H, 4.79; N, 26.65. Found: C, 45.72; H, 4.79; N, 26.17.

1-(2-Chloroethyl)-1-nitroso-3-(2-pyridylmethyl)urea (IIb): Pale yellow, fine needles (from ether), mp 67—68°C (dec.). [lit.,[5] mp 70°C (dec.)]. Yield, 64%.

1-(2-Chloroethyl)-i-nitroso-3-(2-pyridylmethyl)urea *N*-Oxide (IVb): This compound was prepared in the same way as IVa. Yellow pillars (from a mixture of acetone and diisopropyl ether), mp 135—137°C (dec.). Yield, 81%. NMR ($CDCl_3$) δ: 4.80 (d, $J=3$ Hz, $PyCH_2$), 5.88, 6.53 (a pair of triplets, $J=6$ Hz, $N(NO)\underline{CH_2}\underline{CH_2}Cl$). *Anal.* Calcd for $C_9H_{11}ClN_4O_3$: C, 41.79; H, 4.29; N, 21.66. Found: C, 41.92; H, 4.15; N, 22.19. Tosylate: Pale yellow leaflets (from ethanol), mp 130—132°C (dec.). *Anal.* Calcd for $C_9H_{11}N_4O_3\cdot C_7H_8O_3S$: C, 44.89; H, 4.48; N, 13.15. Found: C, 44.60; H, 4.45; N, 13.00.

1-Isopropyl-3-nitroso-3-(2-pyridylmethyl)urea (IIIc) and 1-Isopropyl-3-nitroso-3-(2-pyridylmethyl)urea *N*-Oxide (Vc): A solution of 2.1 g (0.03 mol) of sodium nitrite in 5 ml of water was added dropwise to a solution of 4.0 g (0.02 mol) of Ic in 20 ml of 10% hydrochloric acid with stirring under ice-cooling. The reaction mixture was further stirred for 1 h, then neutralized with sodium bicarbonate, and extracted with chloroform. The chloroform layer was dried over anhyd. sodium sulfate, and the solvent was evaporated off under reduced pressure. When the residue was recrystallized from a mixture of chloroform and ether, the starting material (Ic) was recovered. Recovery, 0.55 g (14%). The mother liquor was concentrated under reduced pressure, and the residue was recrystallized from ether to give IIIc. Yellow prisms, mp 84—85°C (dec.). Yield, 1.0 g (22%). IR ν_{max}^{Nujol} cm^{-1}: 3330, 1695 (NHCO). NMR ($CDCl_3$) δ: 1.30 (d, $J=7$ Hz, $CH(\underline{CH_3})_2$), 5.13 (s, $PyCH_2$), 6.9 (br, NH). *Anal.* Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.89; H, 6.29; N, 25.12. The 1-nitroso isomer (IIc) was not isolated because of its instability. NMR ($CDCl_3$) δ: 1.32 (d, $J=7$ Hz, $CH(\underline{CH_3})_2$), 4.71 (d, $J=5.5$ Hz, $PyCH_2$).

The residue consisting of IIc and IIIc, prepared in the manner noted above, was dissolved in 100 ml of chloroform, 4.5 g (0.022 mol) of *m*-chloroperbenzoic acid (purity: 85%) was added under ice-cooling, and a further 150 ml of chloroform was added. The reaction mixture was allowed to stand overnight at room temperature, and washed with sat. sodium carbonate solution until the aqueous layer was alkaline. The chloroform layer was dried over anhyd. sodium sulfate and the solvent was distilled off. The residue was

washed with *n*-hexane, and recrystallized from a mixture of ether and benzene. The first crop was the *m*-chlorobenzoate of 1-isopropyl-3-nitroso-3-(2-pyridylmethyl)urea *N*-oxide (Vc), mp 122°C (dec.). Yield, 2.2 g (27%). IR ν_{max}^{Nujol} cm^{-1}: 3240, 1718 (NHCO), 1285 (N→O). NMR ($CDCl_3$) δ: 1.30 (d, J=6 Hz, $CH(\underline{CH_3})_2$), 5.25 (s, $PyCH_2$), 9.5 (br, NH). *Anal.* Calcd for $C_{10}H_{14}N_4O_3 \cdot C_7H_5ClO_2$: C, 51.71; H, 4.85; N, 14.19. Found: C, 51.20; H, 4.99; N, 14.12.

The mother liquor separated from the first crop was concentrated under reduced pressure, the residue (2.7 g) was dissolved in chloroform, and the solution was chromatographed on a silica gel column. Elution with methylene dichloride gave the 1-nitroso isomer (IVc) as an unstable semi-solid. NMR ($CDCl_3$) δ: 1.25 (d, J=6 Hz, $CH(\underline{CH_3})_2$), 4.60 (d, J=5 Hz, $PyCH_2$).

Deoxygenation of 1-Isopropyl-3-nitroso-3-(2-pyridylmethyl)urea *N*-Oxide (Vc): A solution of the *m*-chlorobenzoate of Vc (0.10 g) and phosphorus trichloride in 5 ml of methylene dichloride was refluxed for 10 min. The reaction mixture was mixed with ice-water, neutralized with sodium bicarbonate, and extracted with methylene dichloride. The methylene dichloride layer was passed through a silica gel column, and the column was eluted with the same solvent. The eluate was concentrated under reduced pressure, and the NMR signals of the semi-solid residue coincided with those of authentic IIIc. Yield, 50 mg (89%).

Measurement of the Change of the Isomer Ratio in Formic Acid-d_2: An approximately 1: 1 mixture containing IIc and IIIc in a mixture of 0.1 ml of $CDCl_3$ and 0.35 ml of 99% formic acid-d_2 was allowed to stand at 23°C. The quantities of the 1-nitrosourea (IIc), the 3-isomer (IIIc) and the denitrosated compound (Ic) were determined from the NMR spectrum. After 7.5 h, IIc was reduced by 66% and IIIc was increased by 39% relative to the starting quantities. Thus, Ic was produced in 14% yield. The signals in formic acid-d_2 were as follows.

IIc: NMR (CD_2O) δ: 1.28 (d, J=7 Hz, $CH(\underline{CH_3})_2$), 5.15 (s, $PyCH_2$).

IIIc: NMR (CD_2O) δ: 1.33 (d, J=7 Hz, $CH(\underline{CH_3})_2$), 4.25 (m, $\underline{CH}(CH_3)_2$), 5.49 (s, $PyCH_2$).

1-Nitroso-1-phenyl-3-(2-pyridylmethyl)urea (IId): Pale yellow leaflets (from acetone), mp 104°C (dec.). Yield, 82%. NMR ($CDCl_3$) δ: 4.85 (d, J=3 Hz, $PyCH_2$). *Anal.* Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.72; H, 4.70; N, 21.81. The nitrosated nitrogen N^1 was also identified by the reaction of IId with 2-naphthol to give 1-phenylazo-2-naphthol, mp 132—133°C.

1-Methyl-1-nitroso-3-(2-pyridylethyl)urea (IIe): Pale yellow needles (from ether), mp 87—88°C (dec.). Yield, 86%. NMR ($CDCl_3$) δ: 3.10 (s, CH_3), 6.90 (t, J=5 Hz, $PyCH_2$), 6.10 (q, J=4 Hz, $\underline{CH_2}NH$), 7.9 (br, NH). *Anal.* Calcd for $C_9H_{12}N_4O_2$: C, 51.91; H, 5.81; N, 26.91. Found: C, 52.15; H, 5.95; N, 26.98.

1-Methyl-1-nitroso-3-(2-pyridylethyl)urea *N*-Oxide (IVe): Pale yellow needles (from ether), mp 128°C (dec.). Yield, 76%. *Anal.* Calcd for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.16; H, 5.28; N, 25.17.

1-(2-Chloroethyl)-1-nitroso-3-(2-pyridylethyl)urea *N*-Oxide (IVf): A solution of 3.45 g (0.05 mol) of sodium nitrite in 10 ml of water was added dropwise to a solution of 6.83 g (0.03 mol) of If with stirring under ice-cooling. The reaction mixture was neutralized with sodium bicarbonate, and extracted with chloroform, then the chloroform layer was dried over anhyd. sodium sulfate. The chloroform was distilled off under reduced pressure. The residue was a mixture of IIf [NMR($CDCl_3$) δ: 3.42 (m, $PyCH_2\underline{CH_2}$)] and IIIf [NMR ($CDCl_3$) δ: 3.82 (t, J=6 Hz, $PyCH_2\underline{CH_2}$)] in a ratio of 5: 1. The mixture was similarly treated with *m*-chloroperbenzoic acid to form the *N*-oxides. The reaction mixture was similarly treated, and the product mixture (consisting of IVf and Vf) was recrystallized from acetone. The first crop was the 1-nitroso isomer (IVf), pale yellow needles, mp 128°C (dec.). Yield, 3.21 g (43%). NMR ($CDCl_3$) δ: 3.48, 4.17 (a pair of triplet, J=6 Hz, $\underline{CH_2}\underline{CH_2}Cl$), 3.33 (m, $PyCH_2\underline{CH_2}$), 3.86 (t, J=6 Hz, $Py\underline{CH_2}CH_2$). *Anal.* Calcd for $C_{10}H_{13}ClN_4O_3$: C, 44.04; H, 4.80; N, 20.55. Found: C, 44.29; H, 4.70; N, 20.82. The mother liquor separated from the first crop was concentrated under reduced pressure, and the separated crystals were recrystallized from acetone without heating three times. The unstable 3-nitroso isomer (Vf) thus obtained, yellow pillars, mp 81°C (dec.), was still contaminated with the 1-nitroso isomer (IVf) in a ratio of 7: 1 [NMR($CDCl_3$) δ: 3.68, 4.02 (a pair of triplets, J=6 Hz, $Py\underline{CH_2}\underline{CH_2}$)]. Yield, 1.19 (16%).

1-Isopropyl-3-nitroso-3-(2-pyridylethyl)urea (IIIg): A solution of 6.0 g (0.09 mol) of sodium nitrite in 10 ml of water was added dropwise to a solution of 8.3 g (0.04 mol) of Ig in 50 ml of 10% hydrochloric acid under ice-cooling, and the reaction mixture was stirred for 1 h. The reaction mixture was neutralized with sodium bicarbonate, and extracted with chloroform, then the chloroform layer was dried over anhyd. sodium sulfate. Evaporation of the chloroform under reduced pressure gave a residue consisting of IIg and IIIg in a ratio of 1: 2, and the residue was recrystallized from ether to give pure IIIg, yellow prisms, mp 63°C. Yield, 5.3 g (56%). IR ν_{max}^{Nujol} cm^{-1}: 3170, 1708 (NHCO). NMR ($CDCl_3$) δ: 1.28 (d, J=6 Hz, $CH(\underline{CH_3})_2$), 2.90, 4.24 (a pair of triplet, J=6 Hz, $Py\underline{CH_2}\underline{CH_2}$), 3.9—4.4 (m, J=6 Hz, $\underline{CH}(CH_3)_2$), 6.75 (br, NH). *Anal.* Calcd for $C_{11}H_{16}N_4O_2$: C, 55.91; H, 6.83; N, 23.72. Found: C, 55.62; H, 7.05; N, 23.83. The mother liquor separated from the first crop was concentrated under reduced pressure, the solution was poured in a silica gel column, and the column was washed with ether. The solvent was distilled off under reduced pressure, and the NMR spectrum of the residue revealed that the residue was an approximately 1: 9 mixture of IIIg and IIg [NMR($CDCl_3$) δ: 1.28 (d, J=6 Hz, $CH(\underline{CH_3})_2$), 3.10 (t, J=6 Hz, $Py\underline{CH_2}CH_2$), 3.89 (q, J=6 Hz, $PyCH_2\underline{CH_2}$), 4.97 (m, J=6 Hz, $\underline{CH}(CH_3)_2$)].

1-Nitroso-1-phenyl-3-(2-pyridylethyl)urea (IIh): Pale yellow needles (from a mixture of acetone and

n-hexane), mp 90°C (dec.). Yield, 91%. IR ν_{max}^{Nujol} cm^{-1}: 3136, 1710 (NHCO). NMR ($CDCl_3$) δ: 3.13 (t, J=6 Hz, $PyCH_2$), 3.93 (q, J=4 Hz, $\underline{CH_2}NH$), 8.1 (br, NH). *Anal.* Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.08; H, 5.28; N, 20.31.

Nitrosation of 1-Aryl-3-(4-pyridylmethyl)ureas and 1-(4-Tolyl)-3-benzylurea——1-Phenyl- and 1-(4-chlorophenyl)-3-(4-pyridylmethyl)urea were nitrosated in the same way as described for the nitrosation of Ia.

1-Phenyl-3-(4-pyridylmethyl)urea: Colorless needles (from acetone), mp 138—139°C. *Anal.* Calcd for $C_{12}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.72; H, 5.55; N, 18.54.

1-Nitroso-1-phenyl-3-(4-pyridylmethyl)urea (VIa): Pale yellow granules (from acetone), mp 114°C (dec.). Yield, 94%. NMR ($CDCl_3$) δ: 4.62 (d, J=5 Hz, $PyCH_2$), 2.35 (br, NH). *Anal.* Calcd for $C_{12}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.92; H, 4.55; N, 21.98.

1-(4-Chlorophenyl)-3-(4-pyridylmethyl)urea: Colorless needles (from acetone), mp 174°C. Yield, 57%. *Anal.* Calcd for $C_{12}H_{12}ClN_3O$: C, 59.66; H, 4.62; N, 16.06. Found: C, 59.76; H, 4.56; N, 15.93.

1-(4-Chlorophenyl)-1-nitroso-3-(4-pyridylmethyl)urea (VIb): Pale yellow powder (recrystallized from ethanol without heating), mp 111—112°C (dec.). Yield, 90%. NMR ($CDCl_3$) δ: 4.64 (d, J=5 Hz, $PyCH_2$). *Anal.* Calcd for $C_{12}H_{11}ClN_4O_2$: C, 53.71; H, 3.81; N, 19.27. Found: C, 53.92; H, 3.81; N, 18.89.

3-Benzyl-3-nitroso-1-phenylurea (VIIa): A solution of 0.69 g (0.01 mol) of sodium nitrite in 4 ml of water was added dropwise to a solution of 1.13 g (0.005 mol) of 1-phenyl-3-benzylurea (mp 168°C; prepared by the reaction of phenyl isocyanate and benzylamine in ether) in 60 ml of formic acid. The reaction mixture was treated with 100 ml of water, and stirred for 10 min. The separated pale yellow needles were filtered off, washed with ice-water, and dried under reduced pressure. Pale yellow, fine needles (from ether), mp 97—98°C (dec.). Yield, 0.62 g (81%). NMR ($CDCl_3$) δ: 5.50 (s, $PyCH_2$), 8.84 (br, NH). *Anal.* Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.47; H, 5.01; N, 16.18. This nitrosourea decomposed to give benzaldehyde at its melting point.

3-Benzyl-3-nitroso-1-(4-tolyl)urea (VIIb): Nitrous fumes were passed for 20 min into a cold solution of 1.20 g (0.005 mol) of 3-benzyl-1-(4-tolyl)urea (mp 184°C) in acetic acid. The reaction mixture was then poured into ice-water, and the separated crystals were filtered off and washed with water. Yellow needles (from diisopropyl ether), mp 109—110°C (dec.). Yield, 1.02 g (73%). NMR ($CDCl_3$) δ: 2.36 (s, CH_2), 5.07 (s, NH). *Anal.* Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 67.16; H, 5.62; N, 15.70.

References and Notes

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