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Nitrosation of 1-(2-Chloroethyl)- and 1-Cyclohexyl-3-(3-pyridyl)methylureas[1]

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The nitrosation of 1-(2-chloroehtyl)- and 1-cyclohexyl-3-(3-pyridyl)methylureas with sodium nitrite and hydrochloric acid, gave a mixture consisting of the corresponding 1- and 3-nitroso derivatives. These isomers were successfully separated by fractional crystallization using diethyl ether. Their structures were confirmed by means of nuclear magnetic resonance spectroscopy and chemical reaction.

Keywords——N-nitrosation; nitrosourea derivatives; 1-(2-chloroethyl)-1-nitroso-3-(3-pyridyl)methylurea; 1-(2-chloroethyl)-3-nitroso-3-(3-pyridyl)methylurea; 1-cyclohexyl-1-nitroso-3-(3-pyridyl)methylurea; 1-cyclohexyl-3-nitroso-3-(3-pyridyl)methylurea; separation of N-nitroso isomers

In the preceding paper,[1] the present author reported that the nitrosation of 1-alkyl- and 1-aryl-3-(3-pyridyl)methylureas gave only the corresponding 1-nitroso derivatives in over 95% yields.

This paper describes the nitrosation of some 1-substituted-3-(3-pyridyl)methylureas to produce two structural isomers.

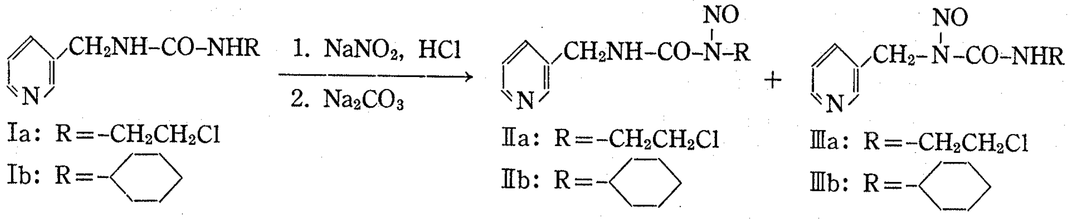

Chart 1

The ureas, 1-(2-chloroethyl)-3-(3-pyridyl)methylurea (Ia) and 1-cyclohexyl-3-(3-pyridyl)-methylurea (Ib) were prepared by the reaction of 3-pyridylmethylamine with 2-chloroethyl and cyclohexyl isocyanates, in diethyl ether.

Compound (Ia) was nitrosated with sodium nitrite and hydrochloric acid under ice-cooling, and the nuclear magnetic resonance(NMR) spectrum of the crude crystals showed that this nitrosation produced two structural isomers. From the NMR integral ratios, the composition of the crude crystals was roughly estimated to be 71% of the 1-nitroso isomer, 1-(2-chloroethyl)-1-nitroso-3-(3-pyridyl)methylurea (IIa), and 29% of the 3-nitroso isomer, 1-(2-chloroethyl)-3-nitroso-3-(3-pyridyl)methylurea (IIIa). Subsequently, since IIa was less soluble than IIIa in diethyl ether, the two isomers were successfully separated by fractional crystallization using diethyl ether to give IIa, mp 92—93° (decomp.), and IIIa, mp 88—89° (decomp.). The structures of IIa and IIIa were confirmed by means of NMR spectroscopy and chemical reaction.

As shown in Fig. 1, the NMR spectrum of IIa in deuterochloroform shows a doublet due to $\underline{CH}_2NHCON(NO)$ at 5.39τ, which changed to a singlet on deuteration with deuterium

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[1] This work was presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan (April, 1976, Nagoya). The preceding paper: S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), 23, 2744 (1975).

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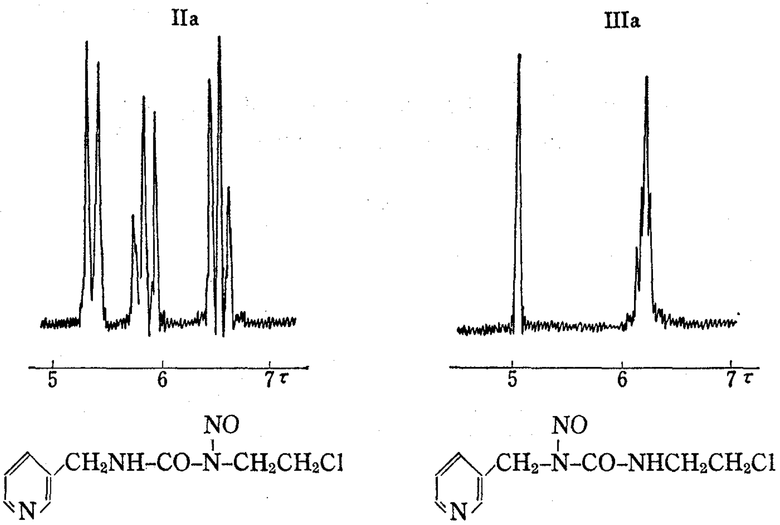

IIa IIIa

Fig. 1. NMR Spectra of 1-(2-Chloroethyl)-1-nitroso-3-(3-pyridyl)-methylurea (IIa) and 1-(2-Chloroethyl)-3-nitroso-3-(3-pyridyl)-methylurea (IIIa) in Deuterochloroform

oxide, and a pair of triplet due to $N(NO)\underline{CH_2}\underline{CH_2}Cl$ at 5.89 and 6.56 τ. On the other hand, that of IIIa showed a singlet due to $\underline{CH_2}N(NO)CONH$ at 5.06 τ and a multiplet due to $NH\underline{CH_2}\underline{CH_2}Cl$ at 6.28 τ. This clear difference in the NMR signals for $NHCON(NO)CH_2CH_2Cl$ and $N(NO)CONHCH_2CH_2Cl$ groups, was also observable in those of the related N-(2-chloroethyl)-N-nitroso derivatives.[3,4]

Compound (Ib) was similarly nitrosated, and the crude crystals consisting of the 1-nitroso isomer (IIb) (30%) and the 3-nitroso isomer (IIIb) (70%), were obtained. The mixture was also successfully separated by fractional crystallization using diethyl ether.

The reaction of IIIa with benzylamine gave 1-(2-chloroethyl)-3-benzylurea ($C_6H_5CH_2$-$NHCONHCH_2CH_2Cl$), and this type of reaction was an additional proof for the structure of IIIa.

This successful isolation of the structural isomers produced by the nitrosation of Ia and Ib, is the first example in the nitrosation of 1,3-disubstituted ureas reported.

Antitumor activity of these nitroso compounds for AH-13 and L-1210 cells are testing, and the results will be reported in a separate paper.

Experimental[5]

1-(2-Chloroethyl)-3-(3-pyridyl)methylurea (Ia) and 1-Cyclohexyl-3-(3-pyridyl)methylurea (Ib)——1-(2-Chloroethyl)-3-(3-pyridyl)methylurea (Ia): Pale yellow leaflets (from a mixture of chloroform and diethyl ether), mp 96—97° (decomp.) (lit.,[6] mp 96°). Yield, 97%. 1-Cyclohexyl-3-(3-pyridyl)methylurea (Ib): To an ice-cooled mixture of 2.16 g (0.02 mole) of 3-pyridylmethylamine in 50 ml of diethyl ether was added dropwise 2.50 g (0.02 mole) of cyclohexyl isocyanate, and the reaction mixture was stirred for 30 min. The crystals separated were filtered, washed with diethyl ether, and dried. Colorless needles (from a mixture of ethanol and diisopropyl ether), mp 146—147°. Yield, 4.47 g (96%). IR (cm^{-1}, nujol): 3300, 1620 (NHCO-NH). *Anal.* Calcd. for $C_{13}H_{19}ON_3$: C, 66.92; H, 8.21; N, 18.01. Found: C, 67.04; H, 8.14; N, 17.92.

Nitrosation of 1-(2-Chloroethyl)-3-(3-pyridyl)methylurea (Ia)——To a solution of 8.54 g (0.04 mole) of Ia in 40 ml of 10% hydrochloric acid was added dropwise a solution of 4.14 g (0.06 mole) of sodium nitrite

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[3] S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 2498 (1972).

[4] T.P. Johnston, G.S. McCaleb, P.S. Opliger, and J.A. Momtgomery, *J. Med. Chem.*, **9**, 892 (1966).

[5] All melting points are uncorrected. Infrared (IR) spectra were measured on a JASCO Model-S spectrophotometer. NMR spectra were measured on a Japan Electron Optics JNMC-60H spectrometer, and tetramethylsilane was used as an internal standard for deuterochloroform.

[6] H. Nakao, M. Fukushima, F. Shimizu, and M. Arakawa, *Yakugaku Zasshi*, **94**, 1032 (1974).

in 10 ml of water under ice-cooling, and the reaction mixture was stirred for 30 min. The reaction mixture was neutralized with a 10% sodium carbonate solution, the crystals separated were extracted with chloroform, and the chloroform layer was dried over anhyd. sodium sulfate. After evaporation of the chloroform, the residue was recrystallized from diethyl ether, and the crystals separated mainly consisted of 1-(2-chloroethyl)-1-nitroso-3-(3-pyridyl)methylurea (IIa). The crystals obtained from the filtrate mainly consisted of 1-(2-chloroethyl)-3-nitroso-3-(3-pyridyl)methylurea (IIIa). These crude IIa and IIIa parts were recrystallized from diethyl ether several times. IIa: Pale orange pillars, mp 92—93° (decomp.) (lit.,[6] mp 87°). Yield, 4.58 g (54%). IR (cm^{-1}, nujol): 3180, 1730, 1535 (NHCON(NO)). *Anal.* Calcd. for $C_9H_{11}O_2N_4Cl$: C, 44.54; H, 4.57; N, 23.09. Found: C, 44.88; H, 4.66; N, 23.39. IIIa: Pale orange pillars, mp 88—89° (decomp.). Yield, 1.76 g (21%). IR (cm^{-1}, nujol): 3160, 1720, 1520 (N(NO)CONH). *Anal.* Calcd. for $C_9H_{11}O_2N_4Cl$: C, 44.54; H, 4.57; N, 23.09. Found: C, 44.53; H, 4.59; N, 23.38.

Nitrosation of 1-Cyclohexyl-3-(3-pyridyl)methylurea (Ib)——To an ice-cooled solution of 2.80 g (0.012 mole) of Ib in 20 ml of 10% hydrochloric acid with stirring was added dropwise a solution of 1.38 g (0.02 mole) of sodium nitrite in 5 ml of water, and the reaction mixture was stirred for 30 min. The reaction mixture was neutralized with a 10% sodium carbonate solution, the crystals separated were extracted with chloroform, and the chloroform layer was dried over anhyd. sodium sulfate. The chloroform was distilled off under reduced pressure, and the residue was recrystallized from diethyl ether to give the yellow crystals which mainly consisted of 1-cyclohexyl-1-nitroso-3-(3-pyridyl)methylurea (IIb). The filtrate was concentrated under reduced pressure to give the pale yellow pillars which mainly consisted of 1-cyclohexyl-3-nitroso-3-(3-pyridyl)methylurea (IIIb). These IIb and IIIb parts were respectively recrystallized from diethyl ether several times. IIb: Yellow pillars, mp 78° (decomp.). Yield, 0.70 g (22%). IR (cm^{-1}, nujol): 3180, 1710, 1520 (N(NO)CONH). NMR (τ, $CDCl_3$): 5.40 (d, $\underline{CH_2}$NH). *Anal.* Calcd. for $C_{13}H_{18}O_2N_4$: C, 59.52; H, 6.92; N, 21.36. Found: C, 59.59; H, 6.90; N, 21.61. IIIb: Pale yellow pillars, mp 91—92° (decomp). Yield, 1.54 g (49%). IR (cm^{-1}, nujol): 3180, 1710, 1520 (N(NO)CONH). NMR (τ, $CDCl_3$): 5.02 (s, $\underline{CH_2}$N(NO)). *Anal.* Calcd. for $C_{13}H_{18}O_2N_4$: C, 59.52; H, 6.92; N, 21.36. Found: C, 59.56; H, 6.86; N, 21.50.

The Reaction of 1-(2-Chloroethyl)-3-nitroso-3-(3-pyridyl)methylurea (IIIa) with Benzylamine——A solution of 0.24 g (0.001 mole) of IIIa in a 50% aqueous ethanol was mixed with 0.11 g (0.001 mole) of benzylamine, and the mixture was allowed to stand for two days. The reaction mixture was concentrated under reduced pressure, the separated crystals were filtered, and recrystallized from aqueous ethanol to give colorless needles, mp 112°. The IR spectrum of this compound in nujol was identical with that of the authentic 1-(2-chloroethyl)-3-benzylurea, which was synthesized by the reaction of 2-chloroethyl isocyanate and benzylamine in diethyl ether. Yield, 0.085 g (40%). NMR (τ, $CDCl_3$): 6.70 (m, NH$\underline{CH_2}\underline{CH_2}$Cl), 5.92 (d, $\underline{CH_2}$NH), 6.0 (broad signal, $\underline{NH}$CO$\underline{NH}$). *Anal.* Calcd. for $C_{10}H_{13}ON_2Cl$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.75; H, 6.23; N, 12.83.