[Chem. Pharm. Bull. 19(6)1293—1294(1971)]

UDC 547.831.6.04 : 547.466.04

S-(1-Oxido-4-quinolyl)-DL-methionine Salt, a Product from the Reaction of 4-Nitroquinoline 1-Oxide and DL-Methionine[1]

It is known that the nitro group of 4-nitroquinoline 1-oxide (4-NQO), a potent carcinogen found by Ochiai, *et al.*[2] and Nakahara, *et al.*,[3] undergoes substitution by various nucleophilic agents.[4] As for substitution by sulfur-containing nucleophile, 4-NQO has been reported to react with thiols, such as cysteine and thioglycolic acid, to give sulfides.[5] The present communication is concerned with a sulfonium salt formed by the reaction of 4-NQO with DL-methionine under physiological conditions. We have isolated S-(1-oxido-4-quinolyl)-DL-methionine reineckate (I). The reaction involved presents a new pattern of nucleophilic substitution to 4-NQO, and the fact that this carcinogenic compound reacts under mild conditions with methionine, whose optically active form makes an important supply source of methyl group in the biological transmethylation reaction, may be, we believe, of considerable significance in relation to its biological activity. Along with I, we obtained S-(1-oxido-4-quinolyl)-DL-homocysteine (II) by reacting 4-NQO with DL-homocysteine.

Processes through which I and II were obtained are summarized in Chart 1.

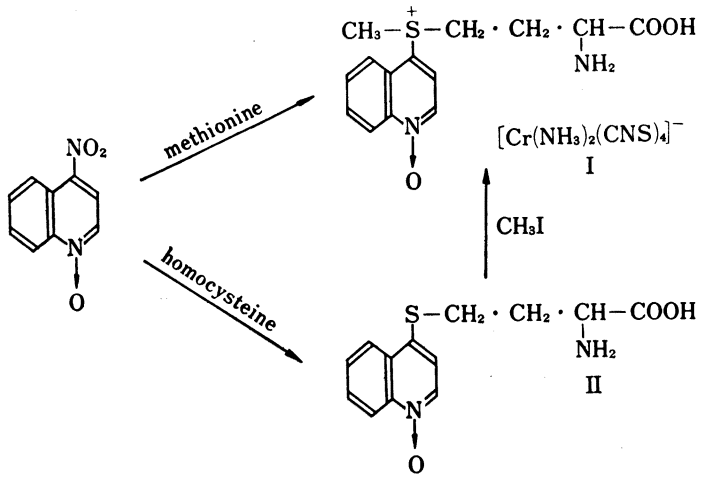

Chart 1

A mixture of 4-NQO and DL-methionine in 50% alcohol, adjusted to pH 7.2 with sodium hydroxide, was stirred for 2 weeks at 37°. Then the reaction mixture, which was now positive to nitrite ion test, was extracted with chloroform to remove unchanged 4-NQO. The aqueous layer was evaporated *in vacuo* at room temperature and the concentrated solution was acidified to pH 2.0 with 0.1 N hydrochloric acid. Precipitation of the reaction product from the acid solution with Reinecke salt, followed by purification with dry acetone, afforded pink microcrystals of I, mp 210° (decomp.). Ninhydrin reaction, positive. UV $\lambda_{max}^{H_2O}$ (log ε): 231

1) This constitutes Part XLV of a series entitled "Electronic Properties of N-Heteroaromatics." Part XLIV: T. Okano, A. Takadate, and K. Uekama, *Gann*, **61**, 541 (1970).
2) E. Ochiai, M. Ishikawa, and Z. Sai, *Yakugaku Zasshi*, **63**, 280 (1943).
3) W. Nakahara, F. Fukuoka, and T. Sugimura, *Gann*, **48**, 129 (1957).
4) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Company, Amsterdam, 1967, pp. 367—382.
5) T. Okabayashi, *Yakugaku Zasshi*, **73**, 946 (1953); M. Hamana and S. Kumadaki, *ibid.*, **88**, 665 (1968); T. Okamoto and M. Ito, *Chem. Pharm. Bull.* (Tokyo), **11**, 785 (1962).

(2.97), 317 (2.48), 330 (2.45). Fluorescence maxima (H_2O, excitation at 320 mμ) mμ: 345, 453. PPC: *Rf* 0.69 (BuOH–AcOH–H_2O (1:1:1)). *Anal.* Calcd. for $C_{14}H_{17}O_3N_2S \cdot C_4H_6N_6S_4Cr \cdot H_2O$: C, 34.82; H, 4.22; N, 18.05. Found: C, 35.07; H, 4.34; N, 17.90.

I was synthesized by way of another process. A 50% alcoholic mixture of 4-NQO and DL-homocysteine hydrochloride was stirred for 5 hr at room temperature. Throughout the incubation time, pH of the reaction mixture was maintained at 2.0 by frequent addition of aqueous sodium hydroxide. Liberation of nitrite ion was observed. Insoluble matter, DL-homocystine which had been formed during the incubation, was then filtered off from the mixture. The filtrate was evaporated to dryness at room temperature and the residue recrystallized from ethanol–water mixture to give light yellow needles of II, mp 121—121.5° (decomp.). Ninhydrin reaction, positive. UV $\lambda_{max}^{H_2O}$ mμ (log ε): 231 (2.81), 275 (2.47), 335 (2.62). *Anal.* Calcd. for $C_{13}H_{14}O_3N_2S$: C, 56.18; H, 5.24; N, 10.02. Found: C, 56.10; H, 5.07; N, 10.07. II was dissolved in acetic acid and was methylated with methyl iodide. The acetic acid was then evaporated at reduced pressure and the residue dissolved in 0.1 N hydrochloric acid. Precipitation of the methylated product from the acid solution with Reinecke salt, followed by purification with dry acetone, afforded pink microcrystals of I, mp 210° (decomp.). Ninhydrin reaction, positive. UV $\lambda_{max}^{H_2O}$ mμ (log ε): 231 (2.97), 317 (2.48), 330 (2.45). Fluorescence maxima (H_2O, excitation at 320 mμ): 345, 453. PPC: *Rf* 0.68 (BuOH–AcOH–H_2O(1:1:1)). *Anal.* Calcd. for $C_{14}H_{17}O_3N_2S \cdot C_4H_6N_6S_4Cr \cdot H_2O$: C, 34.82; H, 4.22; N, 18.05. Found: C, 35.08; H, 4.19; N, 18.21.

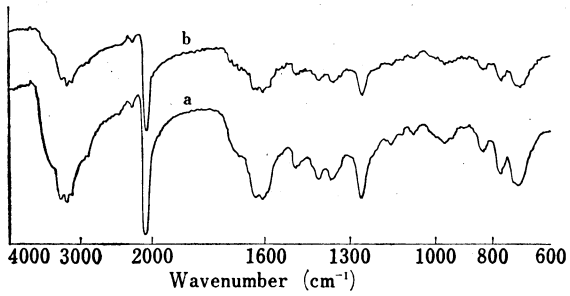

Fig. 1. Infrared Spectra of S-(1-Oxido-4-quinolyl)-DL-methionine Reineckate (I) in KBr

samples: a, from the reaction of 4-NQO and methionine
b, obtained *via* the homocysteine derivative II

The infrared spectra, shown in Fig. 1, of the reineckate obtained from the reaction of 4-NQO with DL-methionine and that obtained *via* II were identical with each other.

The work is under continuation and further results will be presented in the near future.

Acknowledgement This work was supported by a Grant-in-Aid for Cancer Research from the Ministry of Education, to which authors' thanks are due.

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Received March 29, 1971