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Reductive Cleavage of Sulfur-containing Carbamates with Raney Nickel

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Sulfur-containing carbamates, which are used in a number of pesticides and herbicides, were examined for their reductive cleavage with Raney nickel. Three types of the carbamates, S-*p*-chlorobenzyl N,N-diethylthiolocarbamate (I), S-benzyl N,N-diethyldithiocarbamate (II), and methyl N-phenylthiocarbamate (III), were respectively reacted with Raney nickel in ethanol to afford the corresponding reduction products as follows:

I→N,N-diethylformamide, toluene, and hydrogen chloride; II→N,N-diethylmethylamine and toluene; III→N-ethylcyclohexylamine, N-methyl-N-ethylcyclohexylamine, and N,N-diethylcyclohexylamine.

Formation of some of the reduction products indicated an effective participation of ethanol in the process of reduction of the carbamates. Most of the products were adsorbed more or less on Raney nickel, resulting in their unsatisfactory recovery.

Introduction

Studies on the reductive cleavage of sulfur-containing organophosphorus compounds with Raney Nickel and its applicability for analysis of organophosphorus pesticides were reported in our previous paper.[2] Carbamates containing a sulfur atom are used in a number of pesticides and herbicides. In continuation of the preceding work, we have been interested in the reactivity of sulfur-containing carbamates to Raney nickel and its use as an analytical tool.

The present paper reports the reductive cleavage of three types of sulfur-containing carbamate, thiocarbamate, thiolocarbamate, and dithiocarbamate, with Raney nickel and examination on the analytical use of this reaction.

Experimental

Reagent and Solvent——Raney nickel (W-2) was prepared by the known method[3] and stored in absolute EtOH at 0—5°. S-*p*-Chlorobenzyl N,N-diethylthiolocarbamate (I), bp 126—129°/0.008 Torr, and S-benzyl N,N-diethyldithiocarbamate (II), bp 191—193°/8 Torr were purified by distillation of commercial products.[4] Methyl N-phenylthiocarbamate (III), mp 88.0°, was prepared from phenyl isothiocyanate and methanol.[5] N,N-Diethylmethylamine was obtained by methylation of diethylamine with formate-formaldehyde.[6] Other solvents and reagents, which were all special reagent grade, were used without further purification.

Analytical Methods——Identification of reaction products by thin-layer chromatography (TLC) was carried out on different chromatographic media. Avicel SF thin-layer (20×10 cm, 0.25 mm thick) preactivated at 70° for 30 min was developed with Solvent 1, 1N HCOOH–*n*-PrOH (2: 8). Polyamide B-10 thin-layer (20×10 cm, 0.25 mm thick) preactivated at 60° for 60 min was developed with Solvent 2, acetone–H_2O (4: 6). Silica gel H thin-layer (20×10 cm, 0.25 mm thick) preactivated at 105° for 60 min was developed with Solvent 2. After drying in air, the ascendingly developed thin-layer plate was saturated with I_2 vapor to visualize most of organic compounds. Primary and tertiary amino compounds were detected by the

1) Location: *Shirokane, 5-9-1, Minato-ku, Tokyo.*
2) K. Nagasawa, T. Yamada, and A. Ogamo, *Chem. Pharm. Bull.* (Tokyo), **19**, 2373 (1971).
3) R. Mozingo, "Org. Syntheses," Collected Vol. 3, ed. by E.C. Horring, John Wiley & Sons, Inc., New York, London, 1955, p. 181
4) S-*p*-Chlorobenzyl N,N-diethylthiolocarbamate (I) and S-benzyl N,N-diethyldithiocarbamate (II) are called commercially "Saturn" and "Cabac," respectively.
5) K. Nagasawa, H. Yoshidome, and F. Kamata, *J. Chromatogr.*, **52**, 453 (1970).
6) H.T. Clarke, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

Ninhydrin reagent[7] and the Dragendorff reagent,[8] respectively. Secondary amino compounds were positive to both reagents. Carbamates, with or without sulfur atom, were detected by the Bromofluorescein reagent.[8]

Gas chromatography (GC) was made with a Hitachi Perkin-Elmer F6-D gas chromatograph equipped with a hydrogen flame ionization detector, employing a 2 m × 3 mm glass column packed with one of the following: (1) 10% SE-30 on Chromosorb W (80—100 mesh) for toluene, (2) polyethylene glycol 20M on Chromosorb WAW (60—80 mesh) for N,N-diethylformamide, and (3) Chromosorb 103 (80—100 mesh) for amines. For the quantitative analysis of toluene, N,N-diethylmethylamine, and N,N-diethylformamide by GC, ethylbenzene, N,N,N′,N′-tetramethylethylenediamine, and hexadecane were respectively used as an internal standard.

Measurement of mass spectra was made with a JEOL JMS-01 SG mass spectrometer. GC-mass analysis was carried out with a Shimadzu LKB-9000 GC–MS employing a 1 m × 3 mm column packed with Chromosorb 103 or with a JASCO Finnigan 3100 GC–MS employing a 2 m × 2 mm column packed with Chromosorb 103.

Procedure for the Reaction of Sulfur-containing Carbamates with Raney Nickel——To a flask containing 50 mg of one of the carbamates, anhyd. EtOH (10 ml) and Raney nickel (3 ml by wet volume) were added. The flask was provided with a condenser equipped with a trap containing EtOH, and the flask was heated for 1 hr at 83±2° under stirring. When cooled, the reaction mixture was centrifuged (3000 rpm, 10 min) and the precipitate was washed with EtOH (10 ml × 2). The supernatant, washings, and ethanol in the trap were combined, and added with EtOH to make the volume 50 ml. The solution obtained was submitted to TLC, GC, and ultraviolet (UV) analyses.

For isolation or identification of a minor component of the reaction products, this procedure was suitably scaled up and operated.

Determination of Chloride Ions Liberated from S-*p*-Chlorobenzyl N,N-Diethylthiolocarbamate (I)——An accurately weighed I (*ca.* 100 mg) was reacted with Raney nickel (6 ml by wet volume) according to the procedure described above. After separated from Raney nickel by centrifugation, the supernatant and washings were combined and added with 1N NaOH. The slightly alkaline solution obtained was evaporated to dryness and the solid residue was dissolved in water to make the volume 50 ml. A 10 ml aliquot of this solution was submitted to Mohr's chloride determination.[9]

Results and Discussion

Characterization of the Reaction Products of S-*p*-Chlorobenzyl N,N-Diethylthiolocarbamate (I) with Raney Nickel

TLC analysis on the test solution prepared by the procedure just described indicated the formation of N,N-diethylformamide as expected. Spots developed on different chromatographic media had the same *Rf* values as those of the authentic samples (Table I). Identification was also made by GC, and the yield of N,N-diethylformamide was 86.7%. Toluene, a

Table I. Chromatographic Data of the Reaction Products of S-*p*-Chlorobenzyl N,N-Diethylthiolocarbamate with Raney Nickel

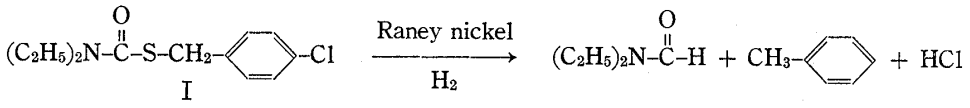
	Thin-layer chromatography *Rf* on the layer of			Gas chromatography	
	Polyamide B-10	Kiesel gel H	Avicel SF	Retention time (min)	Recovery (%)
Reaction product 1	0.73	0.81	0.90	6.8[a]	86.7
Reaction product 2	—	—	—	1.95[b]	66.2
N,N-Diethylformamide	0.73	0.81	0.90	6.8[a]	74.3[c]
Toluene	—	—	—	1.95[b]	56.3[c]

a) column: polyethylene glycol 20M/Chromosorb WAW; column temp.: 135°; carrier gas: N_2 1.5 kg/cm²
b) column: 10% SE-30/Chromosorb W; column temp.: 90°; carrier gas: N_2 2.0 kg/cm²
c) Each 50 mg of N,N-diethylformamide or toluene was reacted with Raney nickel in ethanol according to the procedure described in the text. After the reaction at 83 ± 2° for 1 hr, the amount of N,N-diethylformamide or toluene recovered was determined by GC.

7) R. Consden, A.H. Gordon, and A.J.P. Martin, *Biochem. J.*, **38**, 224 (1944).
8) E. Stahl(ed.), "Thin-Layer Chromatography," Springer-Verlag, Berlin, Heidelberg, New York, 1969, p. 874, 859.
9) F. Mohr, *Ann. Chem.*, **97**, 335 (1856).

sole reduction product from *p*-chlorobenzylthio moiety in I, was detected by UV spectrometry and GC, and its yield was 66.2%. Chloride ions liberated from *p*-chlorobenzyl group in I was determined by the Mohr's method to afford 99.5% recovery.

These results indicated that I was cleaved by reduction with Raney nickel as follows:



Recovery of chloride ion was quantitative but those of N,N-diethylformamide and toluene were not. The results shown in Table I indicate that low recovery of the latter two compounds is due to their adsorption on Raney nickel and not due to formation of other reduction products.

Characterization of the Reaction Products of S-Benzyl N,N-Diethyldithiocarbamate (II) with Raney Nickel

TLC examination on the test solution prepared from II showed two spots positive to the Ninhydrin reagent, *Rf* values of which agreed with those of N,N-diethylmethylamine and triethylamine (Table II). GC analysis also indicated the formation of these amines together

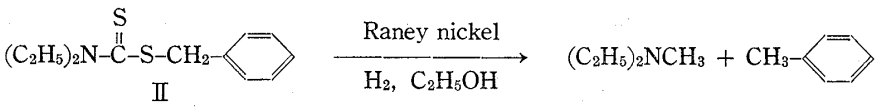
Table II. Chromatographic Data of the Reaction Products of S-Benzyl N,N-Diethyldithiocarbamate with Raney Nickel

	Thin-layer chromatography *Rf* on Avicel SF layer	Gas chromatography	
		Retention time(min)	Recovery(%)
Reaction product 1	0.58	2.50[a]	66.5
Reaction product 2	0.65	3.88[a]	1
Reaction product 3	—	1.95[b]	75.1
N,N-Diethylmethylamine	0.58	2.50[a]	52.5[c]
Triethylamine	0.65	3.88[a]	—
Toluene	—	1.95[b]	56.3[d]

a) column: Chromosorb 103; column temp.: 200°; carrier gas: N_2 2.0 kg/cm²
b) See the footnote *b*) in Table I.
c) N,N-Diethylmethylamine (50 mg) was reacted with Raney nickel in ethanol according to the procedure described in the text. After the reaction at 83±2° for 1 hr, the amount of N,N-diethylmethylamine recovered was determined by GC.
d) See the footnote *c*) in Table I.

with toluene. As can be seen in Table II, triethylamine is a minor component of the reduction products. Although data are not shown here, it was confirmed by GC that a minute amount of N,N-diethylpropylamine, not triethylamine, was formed during the reaction of II with Raney nickel in propanol. Therefore, the formation of triethylamine is probably due to the participation of ethanol during the reductive cleavage of II.

From these results, II was found to be cleaved by reduction with Raney nickel as follows:



Low recovery of N,N-diethylmethylamine and toluene from II is mainly due to their adsorption on Raney nickel as suggested by the result shown in Table II.

Although detailed experiment is not described, Raney nickel treatment of sodium N,N-diethyldithiocarbamate in ethanol afforded N,N-diethylmethylamine (59.4%) and a trace of triethylamine.

Characterization of the Reaction Products of Methyl N-Phenylthiocarbamate (III) with Raney Nickel

The test solution prepared from III did not show any UV absorption, and TLC on Avicel SF plate revealed three spots positive to both the Ninhydrin reagent and the Dragendorff reagent (Table III). The result of GC analysis is shown in Table III and Fig. 1. Peaks 1, 2, and 3 in Fig. 1 correspond to each product having *Rf* of 0.70, 0.74, and 0.81, respectively. One of the products, having *Rf* 0.74, assumed to be the main product of III as judged from Fig. 1, was isolated as a crystalline hydrochloride (mp 159.5°) by the reaction carried out on a preparative scale. The data of elemental analysis and mass spectrometry agreed with those of N-methyl-N-ethylcyclohexylamine.

Table III. Chromatographic Data of the Reaction Products of Methyl N-Phenylthiocarbamate with Raney Nickel

	Thin-layer chromatography *Rf* on Avicel SF layer	Gas chromatography[a] Retention time (min)
Reaction product 1[b]	0.70	10.0
Reaction product 2[b]	0.74	14.0
Reaction product 3[b]	0.81	18.5

a) column: Chromosorb 103; column temp.: 240°; carrier gas: N_2 2.0 kg/cm²
b) Reaction products 1, 2, and 3 correspond to peaks 1, 2, and 3 of the gas chromatogram in Fig. 1, respectively.

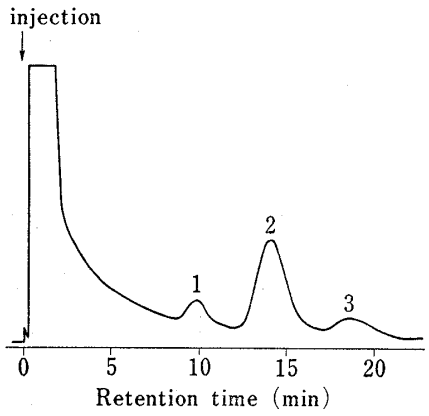
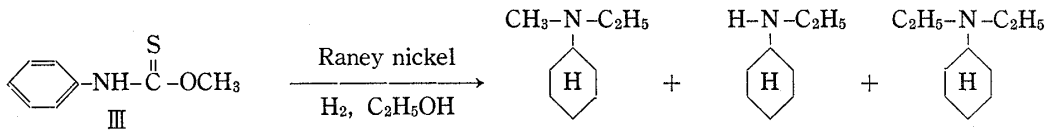


Fig. 1. Gas Chromatogram of the Reaction Products of Methyl N-Phenylthiocarbamate with Raney Nickel

column: Chromosorb 103; column temp.: 240°; carrier gas: N_2 2.0 kg/cm²

After separation of N-methyl-N-ethylcyclohexylammonium chloride, the mother liquor was submitted to GC–mass analysis. GC–mass spectrometry on each single peak (peaks 1 and 3) revealed the presence of molecular ion peaks (M^+) at *m/e* 127 and 155, which agree with the molecular weights of N-ethylcyclohexylamine and N,N-diethylcyclohexylamine, respectively. The presence of other peaks of *m/e* 56, 71, 84, 99, and 112 also suggested formation of these two amines.[10]

From these results, III was found to be cleaved by reduction with Raney nickel as follows:



Yields of N-ethylcyclohexylamine and its analogs from III could not be determined by lack of authentic samples.

In contrast with the results of I and II, N-phenyl group in III was completely hydrogenated. Formation of N-ethylcyclohexylamine and its analogs strongly suggest that ethanol participates in both solvolysis of N-C bond and N-alkylation during the reaction of III with Raney nickel.

10) J.H. Beynon, R.A. Saunders, and A.E. Williams, "The Mass Spectra of Organic Molecules," Elsevier Publ. Co., Amsterdam, London, New York, 1968, p. 266.

Conclusion

Reductive cleavage of three types of the carbamates (I, II, and III) with Raney nickel afforded the corresponding reduction products as follows: I→N,N-diethylformamide, toluene, and hydrogen chloride; II→N,N-diethylmethylamine and toluene; III→N-ethylcyclohexylamine, N-methyl-N-ethylcyclohexylamine, and N,N-diethylcyclohexylamine.

Formation of some of the reduction products indicated an effective participation of ethanol in the processs of reduction of the carbamates. Because most of the products were adsorbed more or less on Raney nickel, resulting in their unsatisfactory recovery, application of this reaction on their quantitative determinations seems to be difficult.

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Mechanism for Interference of Ethinamate in Zimmermann Test for Determination of Urinary 17-Ketosteroids[1]

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The mechanism by which dosage of ethinamate elevates falsely the values for the urinary 17-ketosteroids has been investigated. A specimen of urine collected following oral administration of ethinamate to man was hydrolyzed with sulfuric acid and then extracted with dichloromethane. From the urinary extract two non-steroidal chromogens responsible for the Zimmermann reaction were isolated. The spectral and chromatographic properties indicated that these chromogens would be 1-acetylcyclohex-1-en-4-ol and 1-acetylcyclohex-1-en-5-ol. Their structures were unequivocally characterized by comparison with the synthetic samples. It has been disclosed that during the acid-catalyzed hydrolysis of the conjugates in the process of 17-ketosteroids determination the 4- and 3-hydroxylated metabolites formed from ethinamate are converted artificially into the ketones which give a typical color for the 17-ketosteroids in the Zimmermann reaction.

In the course of running a routine diagnostic laboratory the interferences due to the commonly used medications in the assay procedure have recently become more of a problem. It has been previously shown that after ingestion of ethinamate (1-ethynylcyclohexyl carbamate) (**1**) the urinary 17-ketosteroids values by the Zimmermann reaction are greatly increased.[3] Although the metabolic fate of ethinamate has fully been investigated in man,[4] the metabolites so far identified fail to account for a marked enhancement in the Zimmermann coloration. The present paper describes the mechanism by which dosage of ethinamate elevates falsely the values for the urinary 17-ketosteroids.

A specimen of urine collected following oral administration of an officinal dose of ethinamate to man was hydrolyzed with mineral acid and then extracted with the organic solvent

1) Part CIV of "Studies on Steroids" by T. Nambara; Part CIII: T. Nambara, K. Kigasawa, T. Iwata, and M. Ibuki, *J. Chromatogr.*, **114**, 81 (1975).
2) Location: *Aobayama, Sendai.*
3) S. Borushek and J.J. Gold, *Clin. Chem.*, **10**, 41 (1964).
4) *a*) T. Murata, *Chem. Pharm. Bull.* (Tokyo), **8**, 629 (1960); *b*) *Idem, ibid.*, **9**, 146 (1961); *c*) *Idem, ibid.*, **9**, 335 (1961); *d*) R. Preuss and G. Willing, *Arzneimittel-Forsch.*, **13**, 155 (1963); *e*) *Idem, ibid.*, **13**, 234 (1963); *f*) R. Preuss and E. Mayer, *ibid.*, **15**, 747 (1965).