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THE REACTION OF 0,0-DIALKYL DITHIOPHOSPHORIC ACID–VI[1]

REACTION OF CARBOSTYRIL WITH 0,0-DIALKYL OR 0,0-DIPHENYL DITHIOPHOSPHORIC ACID

A. NAKANISHI and S. OAE*
Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sumiyoshiku, Osaka, Japan

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Abstract – In the reaction between carbostyril (1 mol) and 0,0-diethyl dithiophosphoric acid (3 mol) in refluxing C_6H_6 for 130 hr 30% of thiocarbostyril and 60% of 2-ethylthioquinoline were isolated, but under the different reaction conditions the ratio of 2-ethylthioquinoline to thiocarbostyril changed. The reaction of carbostyril with 0,0-di-n-propyl or 0,0-di-i-propyl dithiophosphoric acid gave similar results with different product ratio. Meanwhile, in the reaction of carbostyril with 0,0-diphenyl dithiophosphoric acid or N-methylcarbostyril with 0,0-diethyl dithiophosphoric acid the corresponding thiocarbostyril or N-methylthiocarbostyril were obtained in good yields.

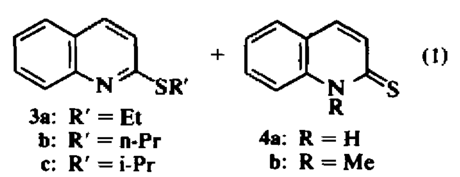
INTRODUCTION

Phosphorus pentasulfide has usually been used for the preparation of thiocarbostyril from carbostyril,[2] 2-pyridinethione from 2-pyridone,[3] 2-pyrrolidinethione from 2-pyrrolidinone,[4] and thioacetamide from acetamide.[5] There are other O–S interchange reactions, e.g., methylphenyl-n-propylphosphine sulfide converts stilbene oxide to the corresponding stilbene sulfide,[6] and the O–S interchange reaction of carbonyl compounds by 0,0-diethyl dithiophosphoric acid.[7] It has now been found that 0,0-dialkyl dithiophosphoric acid can act as an alkylating agent and that thiocarbostyril and 2-alkylthioquinoline can be obtained by this reaction. This paper will describe these reactions in detail.

RESULTS AND DISCUSSION

The overall reaction of carbostyril with 0,0-dialkyl or 0,0-diphenyl dithiophosphoric acid is illustrated by Eq. (1). Table 1 lists the results of the reaction of carbostyril with 0,0-diethyl dithiophosphoric acid under three different reaction conditions. These results show that thiocarbostyril, once formed, is further converted to 2-ethylthioquinoline.

Thiocarbostyril was, therefore, allowed to react with 0,0-diethyl dithiophosphoric acid under the same reaction condition and since 2-ethylthioquinoline was produced nearly quantitatively (Eq. 2), 0,0-diethyl dithiophosphoric acid acts as an alkylating agent. But it is possible that 0,0-diethyl thiophosphoric acid formed at the step of thiocarbostyril formation acts as the alkylating agent (Eq. 3) because 2-ethylthioquinoline was produced



1a: R = H
b: R = Me

2a: R' = Et
b: R' = n-Pr
c: R' = i-Pr
d: R' = Ph

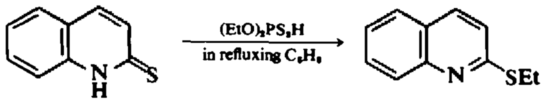
3a: R' = Et
b: R' = n-Pr
c: R' = i-Pr

4a: R = H
b: R = Me

Table 1. Reaction of carbostyril with $(EtO)_2PS_2H$ in refluxing C_6H_6

		Reaction time (hr)	Reaction product (% yield)		
1a (1 mol)	**2a** (1 mol)	50	**3a** (5%)	**4a** (65%)	**1a** (trace)
1a (1 mol)	**2a** (3 mol)	130	**3a** (60%)	**4a** (30%)	**1a** (trace)
1a (1 mol)	**2a** (1 mol)	130[a]	**3a** (78%)	**4a** (trace)	**1a** (15%)

[a] This reaction was carried out under the almost neat condition.



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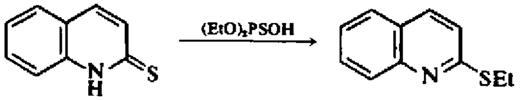


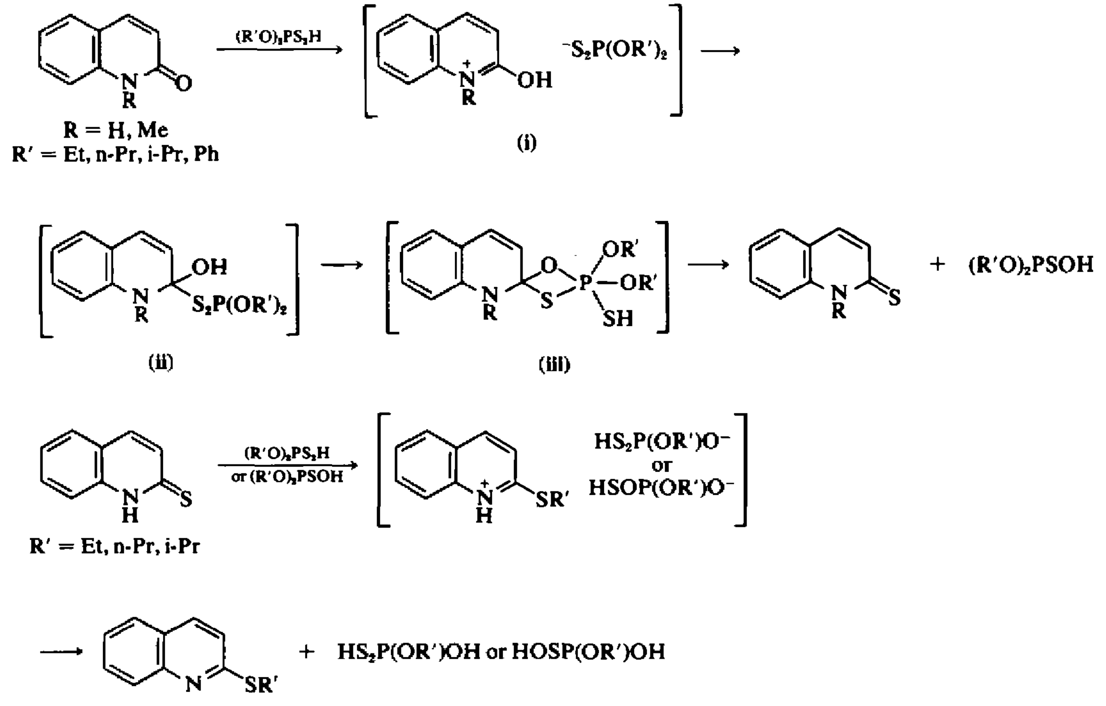
(3)

Table 2. Reaction of carbostyril with $(R'O)_2PS_2H$ in refluxing C_6H_6 for 130 hr

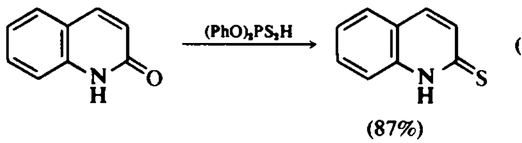
$(R'O)_2PS_2H$		Reaction product (% yield)		
1a (1 mol)	2a (3 mol)	3a (60%)	4a (30%)	1a (trace)
1a (1 mol)	2b (3 mol)	3b (54%)	4a (13%)	1a (15%)
1a (1 mol)	2c (3 mol)	3c (trace)	4a (69%)	1a (22%)

in an equimolar reaction of carbostyril with 0,0-diethyl dithiophosphoric acid in which 0,0-diethyl thiophosphoric acid exists only after the thiocarbostyril formation reaction was complete. It was anticipated that the product distribution would be very different in the reaction of carbostyril with 0,0-diethyl, 0,0-di-n-propyl or 0,0-di-i-propyl dithiophosphoric acid since the alkylthioquinoline formation proceeds via the nucleophilic substitution reaction on the C atom of the dithiophosphoric acid. In Table 2 the results of the reaction of carbostyril with three different 0,0-dialkyl dithiophosphoric acids under the same reaction condition are listed. In the reaction of carbostyril with 0,0-di-i-propyl dithiophosphoric acid only a small amount of 2-i-propylthioquinoline was obtained and thiocarbostyril was isolated in 69% yield. These results support clearly that the S atom of thiocarbostyril attacks the alkyl group of the dithiophosphoric acids as in the case of S_N2 reaction to give 2-alkylthioquinoline. Therefore, it is expected that in the reaction of carbostyril with 0,0-diphenyl dithiophosphoric acid or N-methylcarbostyril with 0,0-diethyl dithiophosphoric acid only the corresponding thiocarbostyril should be obtained in nearly quantitative yield if 2-alkylthioquinoline formation proceeds via an S_N2 attack of the S atom of thiocarbostyril on the C atom of the dithiophosphoric acid. In these reactions only thiocarbostyril or N-methylthiocarbostyril was isolated as expected (Eqs. 4 and 5). From these results it has become clear that thiocarbostyril once produced in good yield can be further converted into 2-alkylthioquinoline by the action of 0,0-dialkyl dithiophosphoric acid.

The first step of the thiocarbostyril formation would be the protonation on the O atom of carbostyril to give 2-hydroxyquinolinium 0,0-dialkyl or 0,0-diphenyl dithiophosphate (i) and then this intermediate (i) is converted into a 1,2-dihydroquinoline



SCHEME



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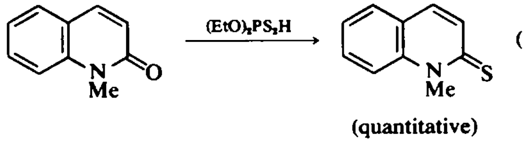
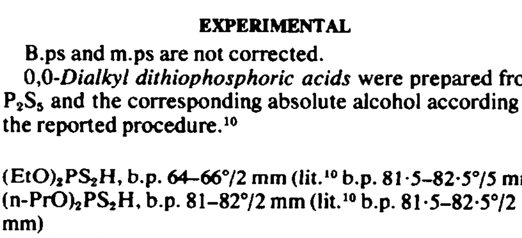


(5)

derivative (II) which would then be converted to the intermediate (III) formed from II as in the case of Wittig reaction. In the last step the intermediate (III) would decompose into thiocarbostyril and 0,0-dialkyl or 0,0-diphenyl thiophosphoric acid exclusively. After the thiocarbostyril formation 2-alkylthioquinoline would be formed if both proton transfer of thiocarbostyril and the attack of the S atom on the alkyl group of the dithiophosphoric acids are possible, as shown in the Scheme.

Trialkyl phosphates have been used as alkylating agents of amines, e.g. N,N-dialkylaniline from aniline by the action of trialkyl phosphates[8] (Eq. 6), and the reaction between β-naphthylamine and trimethyl phosphate to produce α-methyl-β-dimethylaminonaphthalene and β-dimethylaminonaphthalene[9] (Eq. 7).

$$3PhNH_2 + 2(RO)_3PO \xrightarrow{\Delta} 3PhNR_2 + 2H_3PO_4 \qquad (6)$$



(7)

EXPERIMENTAL

B.ps and m.ps are not corrected.

0,0-*Dialkyl dithiophosphoric acids* were prepared from P_2S_5 and the corresponding absolute alcohol according to the reported procedure.[10]

$(EtO)_2PS_2H$, b.p. 64–66°/2 mm (lit.[10] b.p. 81·5–82·5°/5 mm)
$(n\text{-}PrO)_2PS_2H$, b.p. 81–82°/2 mm (lit.[10] b.p. 81·5–82·5°/2 mm)
$(i\text{-}PrO)_2PS_2H$, b.p. 71–72°/2 mm (lit.[10] b.p. 71–72°/3 mm)

0,0-*Diphenyl dithiophosphoric acid* was prepared from P_2S_5 and phenol according to the reported procedure,[11] m.p. 59–60° (lit.[11] m.p. 61°).

Carbostyril was prepared from the alkaline decomposition of the product formed in the reaction between quinoline N-oxide and TsCl, m.p. 193–194° (lit.[12] m.p. 194°).

N-*Methylcarbostyril* was prepared from the methylation of carbostyril by MeI in aqueous alkaline solution, m.p. 73–74° (lit.[13] m.p. 74°).

General procedure for reaction between carbostyril and 0,0-*dialkyl dithiophosphoric acid.* The C_6H_6 soln of carbostyril (1 mol) and 0,0-dialkyl dithiophosphoric acid was heated under reflux, and then this C_6H_6 soln was chromatographed through an activated Al_2O_3 column using C_6H_6–$CHCl_3$ as an eluent. The first elution involved 2-alkylthioquinoline including a small amount of the decomposition product of 0,0-dialkyl dithiophosphoric acid, and the second thiocarbostyril, m.p. 171–173° (lit.[2] m.p. 174°). The last elution involved the recovered carbostyril. These reaction results are listed in Tables 1 and 2.

Reaction of N-*methylcarbostyril with* 0,0-*diethyl dithiophosphoric acid.* N-Methylcarbostyril (318 mg, 2×10^{-3} mole) and 800 mg (4×10^{-3} mole) of 0,0-diethyl dithiophosphoric acid were dissolved in C_6H_6, and this soln was heated under reflux. After 100 hr this mixture was chromatographed through an activated Al_2O_3 column using $CHCl_3$ as an eluent to afford 348 mg of N-methylthiocarbostyril, m.p. 117–118° (lit.[14] m.p. 118°).

Reaction of carbostyril with 0,0-*diphenyl dithiophosphoric acid.* Carbostyril (290 mg, 2×10^{-3} mole) and 1·692 g (6×10^{-3} mole) of 0,0-diphenyl dithiophosphoric acid were dissolved in C_6H_6, and this soln was heated under reflux for 130 hr. The activated Al_2O_3 column chromatography using C_6H_6–$CHCl_3$ as an eluent gave 280 mg of thiocarbostyril (87%) and a small amount of phenol, the decomposition product of 0,0-diphenyl dithiophosphoric acid.

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