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Syntheses of Some Isothiourea Derivatives of 2-Butyne and 2-Butyne-1-ol. Antifungal Substances*

(Received August 8, 1959)

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Abstract

The condensations of thiourea, *N*-allylthiourea, *N,N'*-diallylthiourea and ethylenethiourea with 1,4-dichlorobutynes in absolute ethanol gave 2-butyne-1,4-bis(isothiuronium chloride), 2-butyne-1,4-bis(*N*-allylthiuronium chloride), 2-butyne-1,4-bis(*N,N'*-diallylthiuronium chloride), and 2-butyne-1,4-bis(ethylenethiuronium chloride), respectively. Similar condensations could be effected using 1-chloro-2-butyne-4-ol to give 1-hydroxy-2-butyne-4-(isothiuronium chloride) and 1-hydroxy-2-butyne-4-(ethylenethiuronium chloride). These stable, crystalline products have been found to exert some inhibitory action on fungi, yeasts and mycobacterium. It was noteworthy to find that, unlike the common *S*-alkylisothioureas, some of the free bases of this series mentioned above could be readily isolated from their hydrochlorides by treatment with aqueous sodium carbonate.

I. Introduction

Interest in the remarkable physiological activities of thiourea and its derivatives induced us to synthesize the acetylenic derivatives of isothiourea. Thiourea is used to protect clothing and furs from insects. α -Naphthylthiourea is well known as a rodenticide. Phenylthiourea provokes in about seventy per cent of people a disagreeably bitter taste; some find it tasteless. This peculiar property has made the compound valuable in tracing the heredity of the taste gene¹⁾. *S*-Alkyl-iso-thioureas potentiate the pressor action of epinephrine²⁾.

* Some of this work was presented before the Organic Chemistry Division of the Annual Meeting of the Chemical Society of Japan held in Tokyo, April 6, 1957.

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1) Beadle: Chem. Eng. News, 24, 1366 (1946).

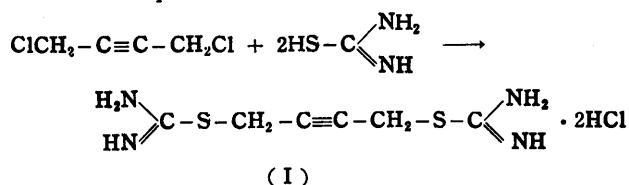
2) Fastier: Nature, 154, 429 (1944).

The present paper describes the condensation products of thioureas with 1,4-dichloro-2-butyne and 1-chloro-2-butyne-4-ol which have been found to be effective against fungi, yeast and mycobacterium.

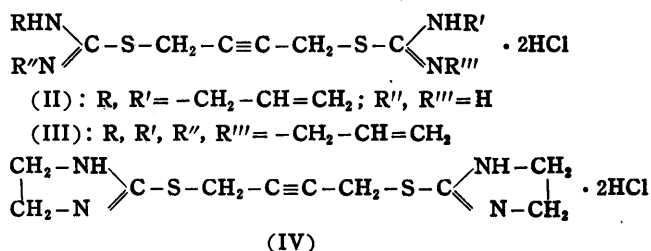
II. Methods and Results

1,4-Dichloro-2-butyne and 1-chloro-2-butyne-4-ol were prepared respectively from 2-butyne-1,4-diol and propargyl alcohol which were synthesized by the Reppe ethynylation³⁾.

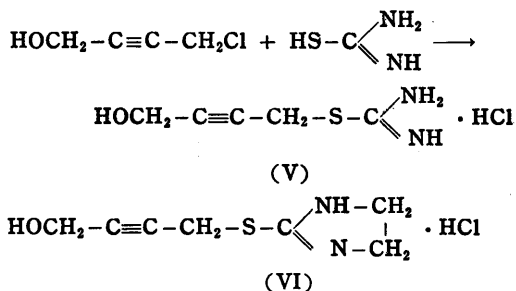
When the mixture of 1,4-dichloro-2-butyne and thiourea in absolute ethanol was refluxed, there was formed 2-butyne-1,4-bis(isothiuronium chloride) (I), a typical example of the condensation product.



By means of analogous procedures *N*-allylthiourea, *N,N'*-diallylthiourea and ethylenethiourea were condensed with 1,4-dichloro-2-butyne to afford 2-butyne-1,4-bis(*N*-allylthiuronium chloride) (II), 2-butyne-1,4-bis(*N,N'*-diallylthiuronium chloride) (III) and 2-butyne-1,4-bis(ethylenethiuronium chloride) (IV) respectively.



Condensation of 1-chloro-2-butyne-4-ol with thiourea and ethylenethiourea afforded 1-hydroxy-2-butyne-4-(isothiuronium chloride) (V) and 1-hydroxy-2-butyne-4-(ethylenethiuronium chloride) (VI) respectively.



3) Reppe: 'Chemie und Technik der Acetylene-Druck-Reaktionen', (1950).

These acetylenic derivatives were strong bases, forming well defined salts. It was noteworthy to find that, unlike the common *S*-alkylisothiouras, some of the free bases can be readily isolated from their hydrochlorides by treatment with aqueous sodium carbonate. The infrared spectra of all the free bases, namely 2-butyne-1,4-diisothiouraea (I'), 2-butyne-1,4-bis(ethyleneisothiouraea) (IV') and 1-hydroxy-2-butyne-4-(ethyleneisothiouraea) (VI') showed weak absorption at 4.35μ , indicating the presence of carbon triple bond in the centre of molecule.

The isothiouraea derivatives described above have been found to exert some inhibitory action on both fungi and yeasts. For instance, 1-hydroxy-2-butyne-4-(ethyleneisothiuronium chloride) (VI) inhibited the growth of *Penicillium chrysogenum* at a dilution of 1 in 16.000 in 48 hours. Generally speaking, these derivatives were remarkably active against *Penicillium chrysogenum* and *Trichophyton mentagrophytes*; higher concentrations were required for other fungi and yeasts that were tested. A summary of sensitivity tests determined by a 48 hours tube dilution test is presented in Table 1. It was noteworthy to find that certain derivatives described above exert some inhibitory action on mycobacterium, while *Staphylococcus aureus* was not affected at the dilutions tested.

Table 1. Antimicrobial Spectra of the Acetylenic Isothiouraea Derivatives *

Test Organisms	Dilution which completely inhibited growth; 1 part in thousand					
	Compounds					
	I	II	III	IV	V	VI
<i>Aspergillus oryzae</i>	1	1	1	1	1	1
<i>Candida albicans</i>	1	2	1	1	1	1
<i>Nocardia gardneri</i>	2	4	4	2	4	4
<i>Penicillium chrysogenum</i>	8	4	8	4	8	16
<i>Trichophyton mentagrophytes</i>	4	8	8	8	8	8
<i>Saccharomyces cerevisiae</i>	4	4	4	4	4	4
<i>Saccharomyces sake</i>	2	1	4	4	2	1
<i>Mycobacterium</i> 607	2	8	8	8	4	4

* Medium: beef extract 1.0, peptone 1.0, sodium chloride 0.3, glucose 1.0%

III Experimental

2-Butyne-1,4-diisothiouraea (I') and its Hydrochloride (I). — The preparation of 1,4-dichloro-2-butyne from 2-butyne-1,4-diol was carried out essentially as described by Johnson⁴. A mixture of 1,4-dichloro-2-butyne (3.0 g.) and thiourea (3.7 g.) in absolute ethanol (24 cc.) was refluxed for 1 hr. Towards the end of reaction the condensation product crystallized out of the solution. The resulting suspension was allowed to stand at room temperature, filtered and washed with

4) A. W. Johnson, J. Chem. Soc., 1946, 1009, 1014.

absolute ethanol. After drying in a desiccator, there were obtained 5.5 g. (82%) of material melting at 171–173°C (dec.). Two recrystallizations from absolute ethanol gave a pure sample of 2-butyne-1,4-bis(isothiuronium chloride) (I), crystallizing in colorless needles, m. p. 180–181°C (dec.).

Anal. Calcd. for $C_6H_{12}N_4S_2Cl_2$: C, 26.18; H, 4.36; N, 20.36.

Found: C, 26.68; H, 4.60; N, 19.98%.

Recrystallization from ethanol-water (6:1) gave a dihydrate, m. p. 176–178°C (dec., sinters at 97°C).

Anal. Calcd. for $C_6H_{12}N_4S_2Cl_2 \cdot 2H_2O$: N, 18.05; H_2O , 11.61.

Found: N, 17.91; H_2O , 11.02%.

To a saturated aqueous solution of I (2.23 g.) was added a saturated solution of sodium carbonate (0.76 g.) to precipitate colorless feathery crystals, which were collected after standing in a refrigerator; m. p. 102.5–103.5°C, yield 0.74 g. Since difficulty was encountered to find an adequate solvent to recrystallize this compound, it was suspended in hot 95% ethanol, filtered while hot, washed with the same solvent and dried. The analytically pure sample of 2-butyne-1,4-diisothiurea (I') melted at 110–111°C.

Anal. Calcd. for $C_6H_{10}N_4S_2$: C, 35.62; H, 4.98; N, 27.69.

Found: C, 35.77; H, 4.88; N, 27.37%.

The infrared spectrum of the material in Nujol showed absorptions at 3.08, 3.18, 3.25 and 6.10 (N–H); 4.35 ($C \equiv C$); 6.38 μ ($C=N$), as shown in Fig. 1.

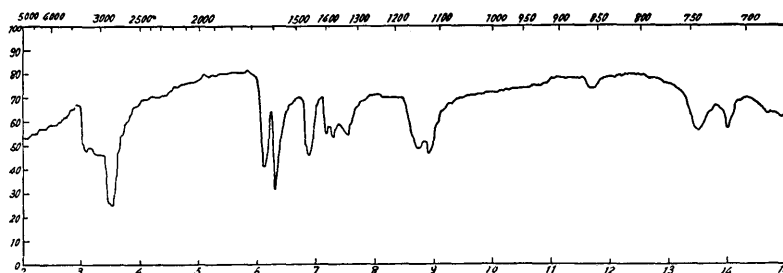


Fig. 1. Infrared absorption spectrum of 2-butyne-1,4-diisothiurea (I') in Nujol

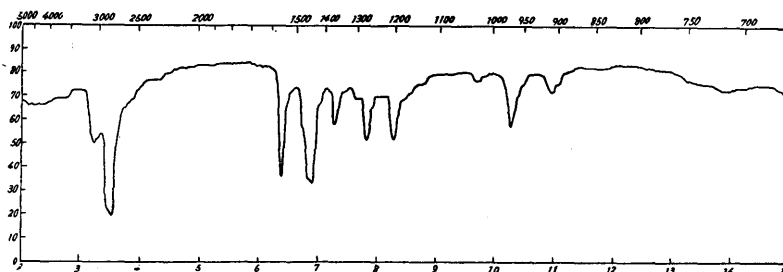


Fig. 2. Infrared absorption spectrum of 2-butyne-1,4-bis(ethyleneisothiurea) (IV') in Nujol

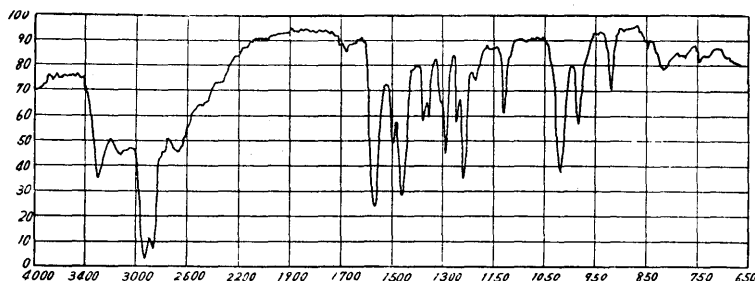


Fig. 3. Infrared absorption spectrum of 1-hydroxy-2-butyne-4-(ethyleneisothiourea) (VI') in Nujol

2-Butyne-1,4-bis(N-allylisothiourea) (II') and its *Hydrochloride (II)*.— Obtained from *N*-allylthiourea and 1,4-dichloro-2-butyne by the procedure similar to that described above in the preparation of I; yield of 2-butyne-1,4-bis(*N*-allylisothiuronium chloride) (II) 82.3%, m. p. 160–165°C (dec.). Two recrystallizations from absolute ethanol raised the m. p. to 165–166°C (dec.).

Anal. Calcd. for $C_{12}H_{20}N_4S_2Cl_2$: N, 15.77. Found: N, 15.80%.

Liberation of the free base (II') from its hydrochloride (II) was carried out by the procedure similar to that described in the preparation of I'. Since difficulty was encountered to recrystallize the free base, it was washed well with water and dried, m. p. 97–98°C; yield 46.2%.

Anal. Calcd. for $C_{12}H_{18}N_4S_2$: N, 19.85. Found: N, 19.83%.

2-Butyne-1,4-bis(N,N'-diallylisothiuronium chloride) (III).— Obtained from *N,N'*-diallylthiourea and 1,4-dichloro-2-butyne by the procedure similar to that described above in the preparation of I'. After removal of the solvent from the reaction mixture in vacuo, the residual syrup was allowed to stand in a refrigerator to afford colorless needles of III; m. p. 143–146°C, yield 77.2%. Recrystallization from isopropanol raised the m. p. to 150–151°C.

Anal. Calcd. for $C_{18}H_{28}N_4S_2Cl_2$: N, 12.88. Found: N, 12.75%.

Attempts to liberate the free base from III were unsuccessful.

2-Butyne-1,4-bis(ethyleneisothiourea) (IV') and its *Hydrochloride (IV)*.—

Obtained by the condensation of ethylenethiourea with 1,4-dichloro-2-butyne by the procedure similar to that described in the preparation of I'; yield 87.4%. Recrystallization from a large quantity of absolute ethanol gave a pure product of 2-butyne-1,4-bis(ethyleneisothiuronium chloride) (IV), melting at 202–203°C (dec.).

Anal. Calcd. for $C_{10}H_{16}N_4S_2Cl_2$: C, 36.69; H, 4.93; N, 17.12.

Found: C, 37.15; H, 4.63; N, 17.06%.

Liberation of the free base (IV') from the hydrochloride (IV) was carried out by the procedure similar to that described above in the preparation of I'; m. p. 126–127.5°C (dec.), yield 34%. The product was boiled with absolute ethanol, filtered while hot, washed with the same solvent and dried; m. p. 138.5–139°C

(dec.).

Anal. Calcd. for $C_{10}H_{14}N_4S_2$: H, 22.03. Found: N, 21.33%.

The infrared spectrum of IV' in Nujol showed absorptions at 3.23 (N-H), 6.38 (C=N) and 4.35 (C≡C), as shown in Fig. 2.

1-Hydroxy-2-butyne-4-(isothiuronium chloride) (V). — 1-Chloro-2-butyne-4-ol was prepared from 2-butyne-1,4-diol by the method of Fraser and Raphael⁵⁾. A mixture of 1-chloro-2-butyne-4-ol (3.0 g.) and thiourea (1.7 g.) in absolute ethanol (12 cc.) was refluxed for 1.5 hr. The resulting pale yellow solution was concentrated in vacuo and allowed to stand in a refrigerator to afford crude colorless crystals of m. p. 130–133°C; yield 3.72 g. (92.7%). Recrystallization from absolute ethanol gave an analytically pure sample of 1-hydroxy-2-butyne-4-(isothiuronium chloride), (V), m. p. 132–133°C.

Anal. Calcd. for $C_5H_9N_2OCl$: C, 33.24; H, 5.02; N, 15.51.

Found: C, 33.46; H, 4.37; N, 15.21%.

1-Hydroxy-2-butyne-4-(ethyleneisothiourea) (VI') and its Hydrochloride (VI). — Obtained from 1-chloro-2-butyne-4-ol and ethylenethiourea by refluxing in absolute ethanol for 2 hr; m. p. 132–134°C, yield 90%. Two recrystallizations from absolute ethanol gave an analytically pure sample of 1-hydroxy-2-butyne-4-(ethyleneisothiuronium chloride) (VI), m. p. 132–133°C.

Anal. Calcd. for $C_7H_{11}N_2OSCl$: C, 40.67; H, 5.36; N, 13.55.

Found: C, 40.20; H, 5.01; N, 13.28%.

The free base (VI') was liberated from the hydrochloride (VI) by the procedure similar to that described above in the preparation of I'; m. p. 106–108°C, yield 62%. Recrystallization from absolute ethanol followed by washing with hot ether gave a pure free base (VI') of m. p. 108–109°C,

Anal. Calcd. for $C_7H_{10}N_2OS$: C, 49.39; H, 5.92; N, 16.45.

Found: C, 49.49; H, 6.02; N, 16.13%.

The infrared spectrum of VI' in Nujol showed absorptions at 3.23 (N-H), 4.35 (C≡C) and 6.38 μ (C=N), as shown in Fig. 3.

Acknowledgment

The authors wish to thank the Nitto-Rikagaku Laboratories Inc. for the generous supply of 2-butyne-1,4-diol.

5) Fraser and Raphael, *ibid.*, 1952, 226.