mide are highly branched, and isobutane has a marked lowering effect on the degree of polymerization. These effects have been attributed to tertiary hydrogen transfer from polymer chains or isobutane.[28] Branching in styrene polymerization could conceivably occur through hydride transfer (equation 3) followed by propagation from the resultant tertiary carbonium ion or alternatively through nuclear alkylation (equation 4).

(28) (a) C. M. Fontana, G. A. Kidder and R. J. Herold, *Ind. Eng. Chem.*, **44**, 1688 (1952); (b) C. M. Fontana, R. J. Herold, E. J. Kinney and R. C. Miller, *ibid.*, **44**, 2955 (1952).

The structural similarity of cumene and *p*-cymene to a segment of the polymer chain, and the expected steric hindrance toward attack on a hydrogen attached to the central carbon chain of polystyrene, make it highly probable that any branching in this system takes place through nuclear alkylation.

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BROOKLYN, N. Y.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# The Reaction of Thiosemicarbazide with Orthoesters

BY C. AINSWORTH

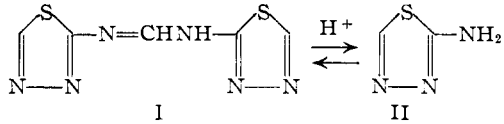
RECEIVED NOVEMBER 28, 1955

Thiosemicarbazide and excess ethyl orthoformate when heated together on the steam-bath formed N,N′-bis-(1,3,4-thiadiazole-2)-formamidine (I). The intermediates, ethyl formate thiosemicarbazone (III), 2-amino-1,3,4-thiadiazole (II) and ethyl N-(1,3,4-thiadiazole-2)-formimidate(IV), were isolated. A possible mechanism of these transformations is discussed.

Based on the report of Stolle and Bowles[1] that thiocarbohydrazide with ethyl orthoformate formed 4-amino-1,2,4-triazole-3-thiol, it was surmised that reaction of thiosemicarbazide and ethyl orthoformate might furnish a simple synthesis of 1,2,4-triazole-3(5)-thiol. The reaction, however, proved to be more complex.

When thiosemicarbazide was heated overnight on the steam-bath with excess ethyl orthoformate, a compound with the molecular formula $C_5H_4N_6S_2$ resulted. This compound was formulated as N,N′-bis-(1,3,4-thiadiazole-2)-formamidine (I). The evidence for this assignment was based on the

$$NH_2NHCSNH_2 + HC(OC_2H_5)_3 \longrightarrow$$



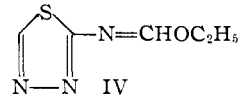
I II

fact that compound I on acid hydrolysis formed 2-amino-1,3,4-thiadiazole (II). The supposition that 2-amino-1,3,4-thiadiazole was an intermediate in the formation of compound I was substantiated by the fact that compound II with ethyl orthoformate yielded compound I. Further, thiosemicarbazide and only *one* mole of ethyl orthoformate when heated together on the steam-bath overnight formed 2-amino-1,3,4-thiadiazole. From the reaction of equimolar quantities of thiosemicarbazide and ethyl orthoformate, heated on the steam-bath for two hours, ethyl formate thiosemicarbazone (III) was isolated. A small yield of compound III

$$C_2H_5OCH{=}NNHCSNH_2 \quad III$$

was obtained from a mixture of thiosemicarbazide and excess ethyl orthoformate heated on the steam-bath for ten minutes.

When thiosemicarbazide and excess ethyl orthoformate were heated together at about 140° overnight, a liquid corresponding to ethyl N-(1,3,4-thiadiazole-2)-formimidate (IV) was obtained. Com-



IV

pound IV with a one molar ratio of 2-amino-1,3,4-thiadiazole formed compound I, indicating that IV might be an intermediate in the formation of I. After compound IV had stood for several months in a loosely stoppered bottle it appeared that a change had taken place. Upon analysis of the contents the following compounds were isolated: ethyl alcohol, ethyl formate, ethyl orthoformate and compounds I and IV. In addition, when a sample of compound IV was allowed to stand in an open container overnight, compound I was formed.

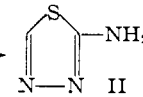
The reaction of aniline with ethyl orthoformate was reinvestigated recently by Roberts and DeWolfe.[2] From physical studies they arrived at the mechanism given below for this reaction, where R equals phenyl. We believe that these reversible

$$RNH_2 + HC(OC_2H_5)_3 \underset{r}{\overset{f}{\rightleftharpoons}} RN{=}CHOC_2H_5 + 2C_2H_5OH \quad (1)$$

$$RN{=}CHOC_2H_5 + RNH_2 \underset{r}{\overset{f}{\rightleftharpoons}} RN{=}CHNHR + C_2H_5OH \quad (2)$$

equations help explain our observations. The reaction of thiosemicarbazide and ethyl orthoformate likely passes through the intermediate III

$$NH_2NHCSNH_2 + HC(OC_2H_5)_3 \longrightarrow C_2H_5OCH{=}NNHCSNH_2 \longrightarrow$$



III II

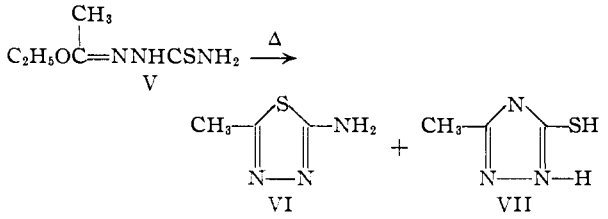
(1) R. Stolle and P. E. Bowles, *Ber.*, **41**, 1099 (1908).

(2) R. M. Roberts and R. H. DeWolfe, THIS JOURNAL, **76**, 2411 (1954).

which by loss of ethyl alcohol forms compound II. By placing compound II in the Roberts–DeWolfe equations, where R now equals 1,3,4-thiadiazolyl-2, the formation of compounds I and IV obtained under the different reaction conditions reported earlier is explained. Although compound I is the product isolated from the reaction of 2-amino-1,3,4-thiadiazole with ethyl orthoformate heated on the steam-bath, it is likely that compound IV is formed first (equation 1f) but by reaction with II (equation 2f) yields compound I which is relatively stable. On longer heating, however, with a small amount of ethyl alcohol present it appears that equations 2r and 1f are favored[3] with the result that compound IV is obtained.

The formation of compound I and other products from compound IV upon long standing can be explained by absorption of atmospheric moisture. By hydrolysis of compound IV the reversible equations 1 and 2 are set into operation. The isolation of ethyl alcohol and ethyl orthoformate from the stored mixture furnishes classical evidence in favor of the Roberts–DeWolfe equations.

Next, the reaction was extended to higher orthoesters. The product from a mixture of thiosemicarbazide and ethyl orthoacetate, heated on the steam-bath, was a compound with the molecular formula $C_5H_{11}N_3OS$, corresponding to ethyl acetate thiosemicarbazone (V). When compound V was heated at 180°, ethanol was evolved and 2-amino-



5-methyl-1,3,4-thiadiazole (VI) and 3-methyl-1,2,4-triazole-5-thiol (VII) were formed in about equal amounts. The formulation V was assigned on the basis that it is the only structure which without rearrangement can simultaneously cyclize by loss of ethanol to both compounds VI and VII. By analogy this leads to structure III for the similar compound obtained from the reaction of ethyl orthoformate and thiosemicarbazide. The main product from the reaction of thiosemicarbazide and ethyl orthopropionate was 2-amino-5-ethyl-1,3,4-thiadiazole.

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## Experimental[4]

**Thiosemicarbazide and Triethyl Orthoformate.**—(a) A mixture of 9.1 g. (0.1 mole) of thiosemicarbazide and 50 ml. of triethyl orthoformate was heated overnight on the steam-bath. The solid was collected by suction filtration and washed with ether. The yield of N,N'-bis-(1,3,4-thiadiazole-2)-formamidine (I), m.p. 240° dec., was 9.0 g. (85%). The material was recrystallized from dimethyl formamide–water and was obtained as a pale yellow solid, m.p. 245° dec.; $\lambda_{max}$ 238 mμ, log ε 3.60; $\lambda_{max}$ 304 mμ, log ε 4.15 (methanol).

*Anal.* Calcd. for $C_5H_4N_6S_2$: C, 28.29; H, 1.90; N, 39.60; S, 30.21. Found: C, 28.52; H, 2.10; N, 39.82; S, 30.40.

A sample of N,N'-bis-(1,3,4-thiadiazole-2)-formamidine and concentrated hydrochloric acid was heated on the steam-bath overnight. After removal of the acid by heating under reduced pressure, the residue was made basic and 2-amino-1,3,4-thiadiazole, identical with material prepared according to the procedure of Freund,[5] was obtained.

(b) A mixture of 9.1 g. (0.1 mole) of thiosemicarbazide and 14.8 g. (0.1 mole) of triethyl orthoformate was heated on the steam-bath overnight. About 500 ml. of boiling ethyl alcohol was added and the mixture, while still hot, was filtered to remove approximately 2 g. of N,N'-bis-(1,3,4-thiadiazole-2)-formamidine. The filtrate was concentrated to 100 ml. and then was cooled in an ice-bath. About 5.8 g. (57% yield) of 2-amino-1,3,4-thiadiazole, identical with authentic material,[5] was obtained.

(c) A mixture of 9.1 g. (0.1 mole) of thiosemicarbazide and 14.8 g. (0.1 mole) of triethyl orthoformate was heated on the steam-bath for 2 hours. About 250 ml. of acetonitrile was added and the mixture was heated to boiling. The mixture was filtered to remove a small amount of insoluble N,N'-bis-(1,3,4-thiadiazole-2)-formamidine. After cooling, the filtrate deposited 6 g. (41% yield) of ethyl formate thiosemicarbazone (III), m.p. 165° dec.; $\lambda_{max}$ 225 mμ, log ε 4.04; $\lambda_{max}$ 266 mμ, log ε 4.35 (methanol).

*Anal.* Calcd. for $C_4H_9N_3OS$: C, 32.64; H, 6.16; N, 28.55. Found: C, 32.69; H, 6.06; N, 28.39.

A mixture of 9.1 g. of thiosemicarbazide and 50 ml. of triethyl orthoformate was heated on the steam-bath for 10 minutes. The mixture was filtered while still hot. After the filtrate was cooled 0.5 g. of ethyl formate thiosemicarbazone was collected.

(d) A mixture of 9.1 g. (0.1 mole) of thiosemicarbazide and 200 ml. of triethyl orthoformate was placed in a 500-ml. flask and was heated overnight at 140°. The dark liquid product was distilled under reduced pressure and ethyl N-(1,3,4-thiadiazole-2)-formimidate (IV) was obtained as a pale yellow oil, b.p. 100° (0.3 mm.), $n^{25}D$ 1.5510. It solidified on standing, m.p. 42–44°; $\lambda_{max}$ 253 mμ, log ε 3.83 (methanol). The yield was 6.5 g. (41%).

*Anal.* Calcd. for $C_5H_7N_3OS$: C, 38.20; H, 4.49; N, 26.73. Found: C, 38.30; H, 4.62; N, 26.89.

After standing for several months in a loosely stoppered bottle, a solid began to separate from a liquid sample of ethyl N-(1,3,4-thiadiazole-2)-formimidate. The solid was collected on a fluted filter and was shown to be N,N'-bis-(1,3,4-thiadiazole-2)-formamidine. The filtrate was distilled and the various fractions were identified by infrared analysis as ethyl formate, ethyl alcohol, ethyl orthoformate and the starting material ethyl N-(1,3,4-thiadiazole-2)-formimidate.

To verify that atmospheric moisture was involved in the above change a sample of ethyl N-(1,3,4-thiadiazole-2)-formimidate was stored in a beaker overnight. The solid material that formed was identified as N,N'-bis-(1,3,4-thiadiazole-2)-formamidine.

**N,N'-Bis-(1,3,4-thiadiazole-2)-formamidine** (I).—(a) A mixture of 1.6 g. (0.01 mole) of ethyl N-(1,3,4-thiadiazole-2)-formimidate and 1.0 g. (0.01 mole) of 2-amino-1,3,4-thiadiazole was heated at 150° for 2 minutes. The product that was obtained was N,N'-bis-(1,3,4-thiadiazole-2)-formamidine.

(b) A mixture of 1 g. of 2-amino-1,3,4-thiadiazole[5] and 10 ml. of triethyl orthoformate was brought to boiling and then was heated on the steam-bath for 4 hours. After removal of the excess orthoester the resulting residue was recrystallized from water. The product was shown by infrared absorption analysis to be N,N'-bis-(1,3,4-thiadiazole-2)-formamidine.

**Ethyl Acetate Thiosemicarbazone** (V).—A mixture of 9.1 g. (0.1 mole) of thiosemicarbazide and 100 ml. of triethyl orthoacetate was heated overnight on the steam-bath. After cooling, the solid that separated was collected and air-dried. It was recrystallized from ethyl alcohol, and ethyl

(3) Pointed out by Roberts and DeWolfe[2] in the aniline–ethyl orthoformate study.

(4) The melting points were determined with a Fisher–Johns assembly and are uncorrected.

(5) M. Freund and C. Meinecke, *Ber.*, **29**, 2511 (1896).

acetate thiosemicarbazone was obtained as a white solid, m.p. 151–152°; $\lambda_{max}$ 221 mμ, log ε 4.09; $\lambda_{max}$ 264 mμ, log ε 4.44 (methanol). The yield was 9.0 g. (56%).

*Anal.* Calcd. for $C_5H_{11}N_3OS$: C, 37.25; H, 6.88; N, 26.06. Found: C, 37.24; H, 6.75; N, 25.93.

When 8 g. (0.05 mole) of ethyl acetate thiosemicarbazone was heated at 180° for one hour, ethyl alcohol was evolved. The residue was extracted with 50 ml. of 1 *N* sodium hydroxide solution, and the insoluble material was collected by suction filtration. The solid was recrystallized from water and about 3 g. of 2-amino-5-methyl-1,3,4-thiadiazole (VI) was obtained as prisms, m.p. 233° dec. (lit.[5] m.p. 235°).

*Anal.* Calcd. for $C_3H_5N_3S$: C, 31.29; H, 4.38; N, 36.49. Found: C, 31.37; H, 4.41; N, 36.39.

The basic solution was acidified, and the resulting solid was collected. It was recrystallized from water, and about 3 g. of 3-methyl-1,2,4-triazole-5-thiol (VII) was obtained as feathery needles, m.p. 263–264° (lit.[6] m.p. 260–261°)

*Anal.* Calcd. for $C_3H_5N_3S$: C, 31.29; H, 4.38; N, 36.49. Found: C, 31.52; H, 4.46; N, 36.34.

**2-Amino-5-ethyl-1,3,4-thiadiazole.**—A mixture of 9.1 g. (0.1 mole) of thiosemicarbazide and 20 ml. of triethyl orthopropionate was heated overnight on the steam-bath. After the mixture was cooled the solid was collected and air-dried. The product was recrystallized from acetonitrile, and 2-amino-5-ethyl-1,3,4-thiadiazole was obtained as prisms, m.p. 200° (lit.[7] m.p. 198°); yield 4 g. (31%).

*Anal.* Calcd. for $C_4H_7N_3S$: C, 37.19; H, 5.46. Found: C, 37.35; H, 5.50.

(6) M. Freund, *Ber.*, **29**, 2483 (1896).

(7) M. Ohta and T. Higashijima, *J. Pharm. Soc. Japan*, **72**, 376 (1952).

INDIANAPOLIS 6, INDIANA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN AUSTRALIA]

# The $S_N$ Mechanism in Aromatic Compounds. XVIII

BY ROBERT L. HEPPOLETTE, JOSEPH MILLER[1] AND VINCENT A. WILLIAMS

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The unusual order of *ortho* substituent effects in aromatic $S_N$ reactions previously obtained in a mononitro series,[2b] *viz.* activating power $CO_2^- < H < COPh < CO_2Me < COMe < CONH_2$, is confirmed in a similar dinitro series, except for the relative position of the parent H compound, which is associated with a constant steric hindrance due to an *ortho* $NO_2$ group. The activating power, both as a *para* and *ortho* substituent, of the $CONMe_2$ group has been investigated; it is normal in the former, and showing marked steric hindrance in the latter. A solvent comparison of methanol and 1/1 (v./v.) methanol–dioxane was made incidentally. The anomalous behavior of CHO and CN groups is further investigated.

Three previous papers of this series—parts VI,[2a] X[2b] and XII[3]—have dealt specifically with compounds containing CO·X (and CN) groups as *para* and *ortho* substituents in series containing also one nitro group,[2a,b] and as *para* substituents in a series containing also two nitro groups.[3]

The present paper, with reference also to a separate paper[4] dealing with some infrared investigations, is intended to complete a phase of work on such substituents by (i) confirming and amplifying the *ortho* effects shown in the mononitro series,[2a,b] (ii) confirming[2a] the source of the anomalous effects of the CN (and by analogy the CHO) group, and (iii) investigating the $CONMe_2$ group as *para* and *ortho* substituent. A comparison of the solvent effect of methanol and 1:1 (v./v.) methanol–dioxane also is made.

Data for 19 compounds are used in the Discussion, and Tables I and II list rate constants at 50°, and some derived quantities, for the replacement in these compounds of an activated Cl by $OMe^-$ in absolute MeOH (except where stated). Some of our earlier results[2a,b,3] are included in the tables, but only the newly determined rate constants are given in the Experimental section.

## Discussion

As *para* substituents in both mono- and dinitro series the activating power of CO·X groups is in the theoretical order[2,3] $H < CO_2^- < CONH_2$ (and $CONMe_2$) $< CO_2Me < COMe < COPh$. As *ortho* substituents in the mononitro series the interesting order $CO_2^- < H < COPh < CO_2Me < COMe < CONH_2$ was obtained[2b] and explanations offered. As *ortho* substituents in the dinitro series the same order is obtained, except for the over-all position relative to H, *viz.*, $CO_2^- < COPh < H < CO_2Me < CONH_2$. This corresponds to the operation of the same factors as before, plus a further steric (inhibition) effect due to the additional, though invariant, group ($NO_2$) in the *ortho* position. This shows up also in the S.I. values, which are some 11–15 times larger in the dinitro series, except for

TABLE I

6-SUBSTITUENT OF 1-CHLORO-2,4-DINITROBENZENE OR 4-SUBSTITUENT OF 1-CHLORO-2,6-DINITROBENZENE

| Substituent | Rate constant at 0°, $10^5k_2$, l. mole$^{-1}$ sec.$^{-1}$ | Substituent rate factor (S.R.F.)[5] | Steric index (S.I.)[6] | Activation ($E$), cal. | Frequency factor, $\log_{10} B$ |
|---|---|---|---|---|---|
| 6-H | 655[a] | ..... | ... | $170_{50}$ | 11.5 |
| 6-H | 200 | 1 | 1 | $174_{50}$ | $11.2_5$ |
| 4-H | 4.96 | 1 | | $175_{50}$ | $9.7_5$ |
| 6-$CO_2^-$ | 1.40 | 0.00702 | 1640 | 22000 | 12.9 |
| 4-$CO_2^-$ | 57.0 | 11.5 | | 15500 | 9.2 |
| 6-$CONH_2$ | 5580 | 27.9 | 8·60 | 17200 | 12.5 |
| 4-$CONH_2$ | 1190 | 240 | | 15300 | 10.3 |
| 6-$CONMe_2$ | 123[a] | | | 20500 | 13.5 |
| | [37.5][b] | [0.188] | 344 | [20900] | $[13.2_5]$ |
| 4-$CONMe_2$ | 322 | 64.7 | | $158_{50}$ | 10.2 |
| 6-$CO_2Me$ | 1110 | 5.57 | 131 | 17300 | 10.9 |
| 4-$CO_2Me$ | 3610 | 728 | | $165_{50}$ | 11.8 |
| 6-COPh | 123 | 0.613 | 1340 | 17300 | 10.9 |
| 4-COPh | 4070 | 821 | | 14000 | 9.7 |

[a] For reaction with $OMe^-$ in 1:1(v./v.) methanol–dioxane. [b] Values in brackets estimated for reaction with $OMe^-$ in MeOH using comparison made for 1-chloro 2,4-dinitrobenzene.

(1) To whom inquiries should be made.

(2) (a) J. Miller, THIS JOURNAL, **76**, 448 (1954); (b) J. Miller and V. A. Williams, *ibid.*, **76**, 5482 (1954).

(3) J. Miller, *ibid.*, **77**, 182 (1955).

(4) N. S. Bayliss, R. L. Heppolette, L. H. Little and J. Miller, *ibid.*, **78**, 1978 (1956).

(5) J. Miller, *J. Chem. Soc.*, 3550 (1952).

(6) J. Miller and V. A. Williams, *ibid.*, 1475 (1953).