THE PREPARATION OF SOME THIOSEMICARBAZONES CONTAINING THE *s*-TRIAZINE RING[1]

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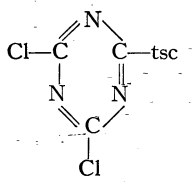
ABSTRACT

The reaction between cyanuric chloride and aliphatic thiosemicarbazones results in the formation of 1:1 adducts containing a dichloro-*s*-triazine ring. Chemical evidence, infrared spectroscopy, and microbiological studies indicate that the addition of the triazine ring takes place at the N^2 atom of thiosemicarbazones. Since cyanuric chloride failed to react similarly with aromatic thiosemicarbazones, a different type of condensation product was obtained by another method, in which cyanuric chloride was first condensed with *o*-, or *p*-hydroxybenzaldehyde to give 1:3 adducts containing free carbonyl groups. Reaction of these compounds with thiosemicarbazide gave the corresponding tri-thiosemicarbazones.

Continuing our work on thiosemicarbazones (tscs) as possible fungistatic agents (1), it became interesting to study the reaction of these compounds with cyanuric chloride for the following reasons: firstly, a number of cyanuric chloride derivatives have been described in which addition of the cyanuric chloride molecule enhances the antifungal activity of the original compounds (2–5); secondly, the *s*-triazines thus formed usually contain one or two chlorine atoms which can be used for further condensation reactions. Since it has been reported earlier (1) that aliphatic tscs with chain lengths ranging from C_7 to C_{12} were the most active fungistatic agents in this class, this particular series was used in the present study. Under the various experimental conditions used, it was found that only one chlorine atom was replaced so that the products, in all cases, were substituted 4,6-dichloro-1,3,5-triazines of the general formula (I).



(I)

The products are listed in Table I together with their melting points and analyses.

Thiosemicarbazones (II) are bifunctional compounds containing a thioamide and a thiocarbohydrazide residue, and it was of interest to find out the site of reaction with cyanuric chloride, hence which hydrogen atom was being replaced.

$$RR^1C{=}N^1{-}N^2H{-}C^3S{-}N^4H_2$$

(II)

Since the $-NH_2$ group is known to react easily with cyanuric chloride (6), the possibility of this group being the reactive site in tscs was the first one to be considered. It was found, however, that this was not the case and that tscs reacted with cyanuric chloride even when the terminal $-NH_2$ was replaced by $-NMe_2$; thus, *n*-undecanal-4,4-dimethyl tsc reacted normally with cyanuric chloride to give the 1:1 condensation product. The

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TABLE I

tscs	m.p., °C	Yield, %	Formula	Required, %	Found, %
n-Heptanal	179	75	$C_{11}H_{16}Cl_2N_6S$	C, 39.4 H, 4.77 Cl, 21.18 N, 25.05 S, 9.56	C, 40.32 H, 4.66 Cl, 20.60 N, 24.80 S, 9.48
n-Octanal	189	43	$C_{12}H_{18}Cl_2N_6S$	C, 41.25 H, 5.16 Cl, 20.33 N, 24.05 S, 9.16	C, 41.55 H, 5.32 Cl, 19.50 N, 24.60 S, 9.30
n-Nonanal	170	52	$C_{13}H_{20}Cl_2N_6S$	C, 43.00 H, 5.51 Cl, 19.55 N, 23.13 S, 8.82	C, 42.83 H, 5.03 Cl, 20.02 N, 23.20 S, 8.98
n-Decanal	167	50	$C_{14}H_{22}Cl_2N_6S$	C, 44.6 H, 5.85 Cl, 18.87 N, 22.32 S, 8.52	C, 44.59 H, 5.87 Cl, 19.06 N, 21.95 S, 8.65
n-Undecanal	156	65	$C_{15}H_{24}Cl_2N_6S$	C, 46.2 H, 6.16 Cl, 18.20 N, 21.52 S, 8.20	C, 46.43 H, 6.09 Cl, 18.24 N, 21.40 S, 8.48
9-Undecanal	160	38	$C_{15}H_{22}Cl_2N_6S$	C, 46.4 H, 5.68 Cl, 18.30 N, 21.62 S, 8.25	C, 46.39 H, 5.49 Cl, 18.24 N, 21.60 S, 8.59
n-Dodecanal	160	94	$C_{16}H_{26}Cl_2N_6S$	C, 47.45 H, 6.42 Cl, 17.51 N, 20.75 S, 7.90	C, 47.18 H, 6.57 Cl, 17.59 N, 20.39 S, 8.14

infrared spectrum of this product had no —N—H band indicating that the N^2 hydrogen atom had been substituted. It was also found that, with the terminal $—NH_2$ present but replacing the N^2 hydrogen atom by Me, the resulting 2-methyl tscs failed to react with cyanuric chloride. This shows the importance of the N^2 hydrogen atom and this is in complete agreement with earlier findings that 2-methyl tscs are quite stable, do not dissolve in alkali, and do not form complexes with copper (7, 8). There remains the possibility of reaction at the sulphur atom since tscs may undergo the following tautomeric change:

$$=N—NH—CS—NH_2 \rightleftharpoons =N—N=CSH—NH_2.$$

It is difficult to discriminate between addition of the triazine ring at the N^2 or at the sulphur atoms, since in both cases the hydrogen atom at the N^2 position would be involved. Of course, replacement of this hydrogen atom by a methyl group prevents the tautomerism and the possibility of reaction at either N^2 or S. Two reactions were carried out using the S-sodium salt of acetone tsc and the corresponding S-benzyl derivative with cyanuric chloride, but no condensation products were formed. It should be pointed out that the

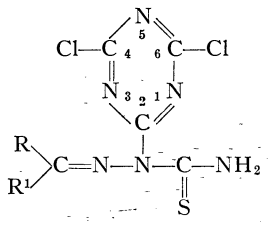
S-substituted derivatives also lacked the N^2 hydrogen atom. In spite of this difficulty, however, it is felt that the addition probably takes place at the N^2 atom, since the tautomerism discussed above is not likely to take place in acetone or dioxane solution in which these reactions were carried out. It was shown that the thione form was the only existing species in the solid state (9) and that the thiol form would be predominant in alkaline solution. Furthermore, infrared spectroscopy provides evidence in favor of the reaction at N^2. The C=S vibration in tscs has been shown to be in the 1080–1130 cm^{-1} region (7) and the spectra of tsc – cyanuric chloride adducts show this band, although it is shifted to higher frequencies by 4 to 20 cm^{-1}. Table II shows this particular region of the spectrum for some compounds.

TABLE II

C=S absorption bands (cm^{-1}) for tscs and their corresponding *s*-triazine derivatives

Carbonyl compounds	tscs (cm^{-1})	Triazines (cm^{-1})
n-Heptanal	1100	1120
n-Octanal	1103	1115
n-Nonanal	1106	1110
n-Decanal	1104	1120
n-Undecanal	1112	1118
9-Undecenal	1105	1120
n-Dodecanal	1110	1120

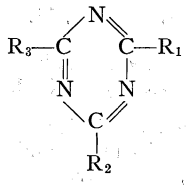
The probable structure for the condensation products is thus as follows:



(III)

A second chlorine atom can be substituted on heating (III) with methanol in the presence of sodium bicarbonate. Thus, 2-(*n*-decanal-tsc)-4,6-dichloro-1,3,5-triazine gave the corresponding monomethoxy derivative. The third chlorine atom was not replaced.

We failed to obtain 1:1 adducts between cyanuric chloride and benzaldehyde or the chlorobenzaldehyde tscs. However, aromatic tscs with a primary amino group on the ring gave compounds in which the triazine group is added onto the amino group. Thus, *m*-aminoacetophenone tsc afforded the corresponding substituted 2-amino-4,6-dichloro-1,3,5-triazine (IV). Similar reactions were carried out with the three isomeric hydroxybenzaldehyde tscs but without success. However, an indirect route led to triazine derivatives containing the hydroxybenzaldehydes which gave the corresponding tscs upon further reaction with thiosemicarbazide. The trisubstituted triazines (V*a*, V*b*, V*c*) were described by Allan (10) who obtained them from cyanuric chloride and *o*-, *m*-, and *p*-hydroxybenzaldehyde. The corresponding tri-tscs (V*f*, V*g*) were obtained by the usual method in fair yields (11). The reaction with the *m*-isomer (V*b*) gave a product which could not be purified satisfactorily.



(V)

(V*a*), $R_1 = R_2 = R_3 = o\text{-}OC_6H_4CHO$
(V*b*), $R_1 = R_2 = R_3 = m\text{-}OC_6H_4CHO$
(V*c*), $R_1 = R_2 = R_3 = p\text{-}OC_6H_4CHO$
(V*d*), $R_1 = Cl; R_2 = R_3 = o\text{-}OC_6H_3BrCHO$
(V*e*), $R_1 = Cl; R_2 = R_3 = o\text{-}OC_6H_3ClCHO$
(V*f*), $R_1 = R_2 = R_3 = o\text{-}OC_6H_4CH{=}NNHCSNH_2$
(V*g*), $R_1 = R_2 = R_3 = p\text{-}OC_6H_4CH{=}NNHCSNH_2$

5-Bromo- and 5-chlorosalicylaldehyde were found to be somewhat less reactive and 2:1 adducts containing one chlorine atom were obtained (V*d* and V*e*). Thiosemicarbazones have not as yet been obtained from these last two derivatives.

The fungistatic activities of all compounds described in this work were examined against two organisms and by two methods previously described (1). It was found that the triazines were generally less active than the original tscs so that addition of the cyanuric chloride ring did not enhance the fungistatic activities in this case. This is an interesting finding in itself since it supports the theory that the reaction between cyanuric chloride and tscs takes place at the N^2 atom of the latter. Indeed, it has been shown in this laboratory (12) that the N^2 hydrogen atom must be present for the tscs to have any fungistatic activity. This is related to the fact that N^2-substituted tscs do not form complexes with metals. This phase of the work is being examined further and will form the subject of a separate publication.

EXPERIMENTAL

Thiosemicarbazones and their derivatives not described in the following preparations were reported earlier (7, 11). Reactions between five 2-methyl tscs (from octanal to undecanal), and two *s*-substituted acetone tscs with cyanuric chloride were attempted but are not reported since no tractable products could be obtained. Cyanuric chloride was from commercial sources and was used without further purification. Melting points were taken on a Fisher-John apparatus and are corrected. Infrared spectra are from KBr pellets.

General Procedure for the Preparation of 2-(n-Alkyl tsc)-4,6-dichloro-1,3,5-triazines (III)

A solution of tsc (0.02 mole) in acetone (40 ml) was added slowly to a solution of cyanuric chloride (0.02 mole) in acetone (300 ml). After stirring for 15 minutes, a saturated aqueous solution of sodium bicarbonate was added to bring the pH to 7. The precipitated material was separated by filtration, freed from inorganic salts by washing with water, and after drying, was crystallized from benzene – *n*-hexane. The product was recrystallized from cyclohexane. The various compounds obtained are listed in Table I.

2-(n-Decanal tsc)-4-methoxy-6-chloro-1,3,5-triazine

A mixture of 2-*n*-decanal tsc-4,6-dichloro-1,3,5-triazine (3.56 g, 0.01 mole), methyl alcohol (35 ml), and sodium bicarbonate (1.68 g, 0.02 mole) was stirred for 15 minutes at room temperature, followed by heating under reflux for 30 minutes. After cooling, water was added until the mixture turned cloudy, and the methoxy derivative crystallized out overnight. It was collected and recrystallized twice from ethyl alcohol and finally from *n*-hexane. Yield, 3.2 g, 86.5%; m.p. 114° C. Required for $C_{15}H_{25}ClN_6OS$: C, 48.32; H, 6.71; Cl, 9.68; N, 22.55; S, 8.59%. Found: C, 48.21; H, 7.12; Cl, 9.53; N, 22.90; S, 8.46%.

n-Undecanal-4,4-dimethyl tsc

A solution of *n*-undecanal (6.12 g, 0.036 mole) in ethyl alcohol (150 ml) was added to a warm solution of 4,4-dimethyl thiosemicarbazide (13) (4.32 g, 0.036 mole) in water (100 ml). After addition of glacial acetic acid (5 ml) the resulting mixture was heated on a steam bath for 15 minutes. The mixture was then cooled in ice and enough sodium hydroxide solution to neutralize the acid was added. The 4,4-dimethyl tsc precipitated out, was collected, dried, and recrystallized twice from *n*-hexane. Yield, 8.75 g, 90%; m.p. 49° C

Required for $C_{14}H_{28}N_3S$: C, 62.8; H, 10.22; N, 15.33; S, 11.67%. Found: C, 61.50; H, 10.65; N, 15.75; S, 12.15%.

The infrared spectrum of this compound is of requisite character and shows only one —NH band at 3200 cm^{-1}. This band disappears in the 1:1 adduct with cyanuric chloride described below.

2-(n-Undecanal-4',4'-dimethyl tsc)-4,6-dichloro-1,3,5-triazine

To a solution of cyanuric chloride (3 g, 0.016 mole) and *n*-undecanal-4,4-dimethyl tsc (4.5 g, 0.016 mole) in acetone (150 ml) was added slowly, with stirring, a saturated aqueous solution of sodium bicarbonate in order to keep the pH of the mixture at 7. After 30 minutes, the acetone was distilled off and the product was extracted from the aqueous solution with chloroform. The chloroform extract was dried, the solvent evaporated, and the residue was dissolved in benzene and passed through a chromatographic column containing silica. A mixture of benzene–ether (4:1) eluted the required material which was further recrystallized from *n*-hexane. Yield, 3.2 g, 47%; m.p. 73° C. Required for $C_{17}H_{28}Cl_2N_6S$: C, 48.68; H, 6.68; Cl, 16.94; N, 20.05; S, 7.64%. Found: C, 48.23; H, 6.72; Cl, 17.45; N, 20.55; S, 7.65%.

2-(m-Aminoacetophenone tsc)-4,6-dichloro-1,3,5-triazine (IV)

A solution of cyanuric chloride (5.35 g, 0.03 mole) in acetone (150 ml) was poured onto crushed ice (ca. 600 ml). To this mixture were added slowly a solution of *m*-aminoacetophenone tsc in acetone (100 ml) and sufficient aqueous sodium hydroxide to keep the mixture neutral, the temperature being maintained between 0 and 5° C. A precipitate was formed and the mixture was stirred until the temperature reached 20° C. The precipitate was collected and recrystallized successively from acetone–water, dimethyl formamide – water, and finally twice from methyl alcohol. Yield, 97%; m.p. > 300° C. Required for $C_{12}H_{11}Cl_2N_7S$: C, 40.45; H, 3.09; Cl, 19.94; N, 27.53; S, 8.99%. Found: C, 39.43; H, 3.17; Cl, 20.20; N, 27.40; S, 9.29%.

Reactions between the three 2,4,6-Tri(formylphenoxy)-1,3,5-triazines (Va, Vb, Vc) and Thiosemicarbazide

Compounds (V*a*), (V*b*), and (V*c*) were prepared by the method of Allan and Allan (10). The reaction of (V*a*) and (V*c*) with thiosemicarbazide gave the corresponding tri-thiosemicarbazones (V*f*) and (V*g*). The procedure described below was used.

A solution of the triazine (8.8 g, 0.02 mole) in dioxane (180 ml) was added to thiosemicarbazide (5.82 g, 0.06 mole) dissolved in hot water (180 ml) containing acetic acid (12 ml). The resulting mixture was heated on the steam bath for 15 minutes and finally allowed to cool. The tri-tsc crystallized out and, after being collected, was recrystallized twice from dimethyl formamide – acetone. (V*f*): Yield, 8.5 g, 64%, m.p. 231° C. Required for $C_{27}H_{24}N_{12}O_3S_3$: C, 49.09; H, 3.64; N, 25.45; S, 14.55%. Found: C, 48.82: H, 3.84; N, 25.45; S, 14.20%. (V*g*): This was best recrystallized from dimethyl formamide – ethyl alcohol. Yield, 8.1 g, 60%; m.p. 243° C. Found: C, 48.20; H, 4.07; N, 25.35; S, 14.80%.

2,4-Di(2-formyl-5-bromophenoxy)-6-chloro-1,3,5-triazine (Vd)

A solution of cyanuric chloride (4.61 g, 0.025 mole) in dioxane (75 ml) was added dropwise to a mixture of 5-bromosalicylaldehyde (15.2 g, 0.075 mole) and sodium hydroxide (3 g, 0.075 mole) in dioxane (100 ml) and water (150 ml). After stirring the mixture for 1.5 hours, a precipitate formed. It was collected and treated with ethyl alcohol from which the unreacted 5-bromosalicylaldehyde (12.1 g) was recovered. The alcohol left a residue which, after recrystallization from dimethyl formamide – water, was shown to be the disubstituted triazine V*d*. Yield, 1 g, 7.8%; m.p. 225° C. Required for $C_{17}H_8Br_2Cl\,N_3O_4$: C, 39.73; H, 1.56; Br, 31.16; Cl, 6.91; N, 8.18%. Found: C, 39.66; H, 1.70; Br, 31.80; Cl, 7.33; N, 8.39%.

2,4-Di(2-formyl-5-chlorophenoxy)-6-chloro-1,3,5-triazine (Ve)

This was prepared as above and the disubstituted triazine V*e* was obtained in a 20% yield; m.p. 212° C. Required for $C_{17}H_8Cl_3N_3O_4$: C, 48.05; H, 1.88; Cl, 25.09; N, 9.89%. Found: C, 47.66; H, 1.82; Cl, 25.20; N, 10.50%.

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