Isothiocyanates. I.[1] Addition of Urea to Aroyl Isothiocyanates and Conversion of the Monoadducts into Monothiobiuret, 4-Thioxo-1,3,5-triazin-2-ones and 1,2,4-Thiadiazol-3-ones

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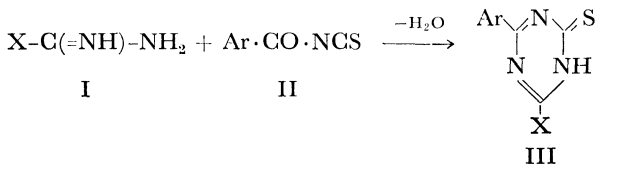
The hitherto unknown 1-aroyl-2-thiobiurets were synthesized by addition of urea to aroyl isothiocyanates. Treatment of 1-benzoyl-2-thiobiuret with concentrated hydrochloric acid effected hydrolysis to monothiobiuret. On the other hand, treatment of 1-aroyl-2-thiobiurets with alkali gave 6-aryl-4-thioxo-1,2,3,4(or 2,3,4,5)-tetrahydro-1,3,5-triazin-2-ones.† Oxidation of the 1-aroyl-2-thiobiurets with hydrogen peroxide in the presence of hydrochloric acid gave 5-aroylamino-2,3-dihydro-1,2,4-thiadiazol-3-ones.

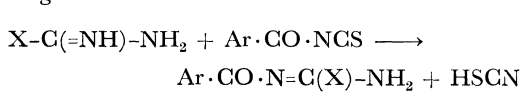
Amidines, isoureas, isothioureas and guanidines Ia—d have been added to aroyl isothiocyanates II to give 1,3,5-triazinethione derivatives IIIa—d.[2] Combination of weakly basic amidino compounds with weakly



I II III

a ; X=alkyl or aryl
b ; X=OR
c ; X=SR
d ; X=NR_2

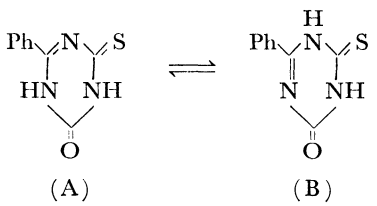
electrophilic isothiocyanates gave III in good yields. In other cases formation of aroylamidines predominated,[2] *e.g.*



Such an aroylation reaction during the course of addition of alkylamines[3] and hydrazines[4] to benzoyl isothiocyanate has been reported.

In the present investigation urea, a weaker nucleophile, was choosen for the study of its reaction with some aroyl isothiocyanates of varying electrophilicity, *i.e.* of different carbonyl activity, in order to obtain more precise information on the mode of addition of nucleophiles to the C=S and/or to C=O of the aroyl isothiocyanates. Reactions, *e.g.* actions of acids and alkalies and oxidation with hydrogen peroxide, on the monoadducts from the reaction under investigation were also carried out.

† Although the 2-phenyl derivative exists as tautomers (A) and (B),[2] it was erroneously named 6-oxo-2-phenyl-4-thioxo-1,4,5,6-tetrahydro-1,3,5-triazine. The present naming of this compound and its aryl analogs indicates that they can exist in two tautometric forms.



(A) (B)

Results and Discussion

Urea was added to the aroyl isothiocyanates IIa—f in dry acetone to give good yields (*cf.* Table 2) of the hitherto unknown 1-aroyl-2-thiobiurets IVa—f. Although equimolar amounts of the reactants were used, a small amount (see Experimental) of a diadduct V was obtained in the case of the addition of urea to benzoyl isothiocyanate IIa. However, when the addition was repeated using two moles of the benzoyl isothiocyanate the amount of the diadduct did not increase, the predominant product being the monoadduct IVa. The monoadducts IVa—f obtained from such a reaction could be obtained from urea by the reaction with the aroyl isothiocyanates prepared *in situ* from the corresponding aroyl chloride and ammonium thiocyanate in dry acetone (*cf.* Experimental).

II IV V

a ; Ar=phenyl
b ; Ar=*p*-tolyl
c ; Ar=*p*-methoxyphenyl
d ; Ar=*p*-bromophenyl
e ; Ar=*o*-chlorophenyl
f ; Ar=styryl

The structure of the monoadducts IVa—f was confirmed by their analytical data, infrared and electronic spectra. Thus, the strong absorption bands in the region 3360—3100 cm^{-1} can be correlated with ν_{NH} of primary and secondary amides (bonded NH);[5] those in the regions 1700—1680 cm^{-1} and 1740—1715 cm^{-1} can be attributed to the presence of acyclic thioimide groupings, namely ArCONHCS and CSNHCO.[5] The absence of a band at 2570 cm^{-1} suggests that the 1-aroyl-2-thiobiurets IVa—f exist in the thione form (thiolactam). The electronic spectra of IVa—c support their structural similarity. The infrared and electronic spectral data are given in Table 1. 1-Benzoyl-2-thiobiuret IVa was desulfurized[6] with aqueous chloroacetic acid to give benzoylbiuret[7] as an analytically pure sample.

Formation of the 1-aroyl-2-thiobiurets IVa—f in good yields by the addition of urea to the aroyl isothiocyanates IIa—f indicates that urea exclusively attacks the C=S function of the aroyl isothiocyanates. The

Table 1. Spectral data for compounds IV, VII, and X

Compound	Infrared spectra		Electronic spectra			
	$\nu_{C=O}$ / cm^{-1}	ν_{NH} / cm^{-1}	λ_{max} / nm	ε_{max}	λ_{mak} / nm	ε_{max}
IVa	1690, 1725	3200, 3290 3360	243.5	19695	285.5	15420
IVb	1680, 1720	3100, 3200 3350	253.5	22750	286	16350
IVc	1690, 1740	3100, 3300 3350	255	23500	287	16100
IVd	1680, 1720	3100, 3200 3330	256	24160	286.5	15400
IVe	1700, 1740	3140, 3200 3320	236	17510	285.5	14805
IVf	1650, 1700	3120, 3200 3220, 3400	232	27555	287.5	23130
VIIa	1675, 1735	3050—3200	260	23085	330	7890
VIIb	1690, 1740	2900—3200	260	14100	294	23250
VIIc	1700, 1740	3100—3200	260	15170	295	25580
VIId	1680, 1760	2900—3200	271.5	26410		
VIIe	1700, 1720	3100—3210	260	19400		
Xa	1660, 1720	3100—3200	244.5	19005	310.5	11050
Xb	1670, 1730	3120—3210	229 268.5	11480 7650	316.5	9180
Xc	1675, 1732	3110—3215	231	16810	309	5810

Table 2. 1-Aroyl-2-thiobiurets IV

Compound	Melting point	Yield/% Method A	Yield/% Method B	Formula	Found (%) C	Found (%) H	Found (%) N	Found (%) S	Calcd (%) C	Calcd (%) H	Calcd (%) N	Calcd (%) S
IVa	185—186[a] Yellow	92	85	$C_9H_9N_3O_2S$	48.5	4.2	19.2	14.6	48.4	4.1	18.8	14.3
IVb	178—179[a]	90	83	$C_{10}H_{11}N_3O_2S$	51.0	4.9	18.0	13.6	50.6	4.6	17.7	13.5
IVc	185—187[a]	85	80	$C_{10}H_{11}N_3O_3S$	47.6	4.6	16.2	12.8	47.4	4.35	16.6	12.6
IVd	192—195[b]	87	81	$C_9H_8BrN_3O_2S$	35.3	2.8	14.0	10.4	35.8	2.6	13.9	10.6
IVe	175—177[a]	94	88	$C_9H_8ClN_3O_2S$	42.3	3.5	16.3	12.6	41.9	3.1	16.3	12.4
IVf	213—215[a]	80	71	$C_{11}H_{11}N_3O_2S$	53.2	4.7	16.8	12.85	53.0	4.4	16.9	12.7

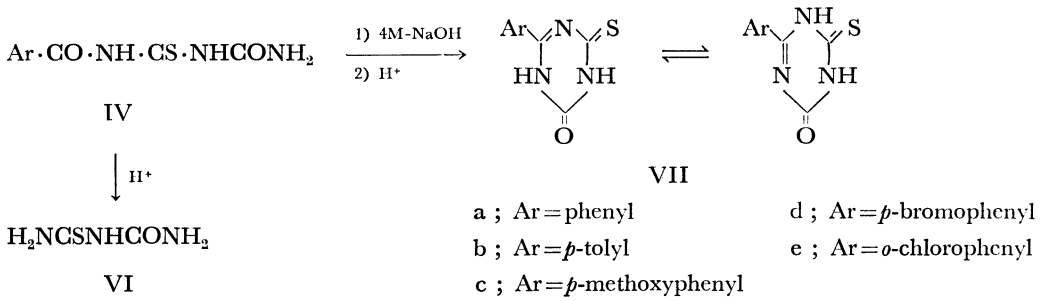
a) From ethanol. b) From acetic acid.

fact that no aroylureas were formed supports the view that no competing aroylation reaction, *i.e.* the direct nucleophilic substitution at the carbonyl function of the aroyl isothiocyanates IIa—f, of varying carbonyl activity, took place. This supports the previous conclusion[3,4] that only strong nucleophilic reagents such as alkylamines and hydrazines are capable of attacking the C=O function of the aroyl isothiocyanates to give the aroylated nucleophiles. The results show that the magnitude of the electrophilicity of the aroyl isothiocyanate makes a small contribution, if any, in determining the mode of addition of nucleophiles to the C=O and/or to the C=S of the dielectrophilic reagent, *i.e.* the aroyl isothiocyanate.

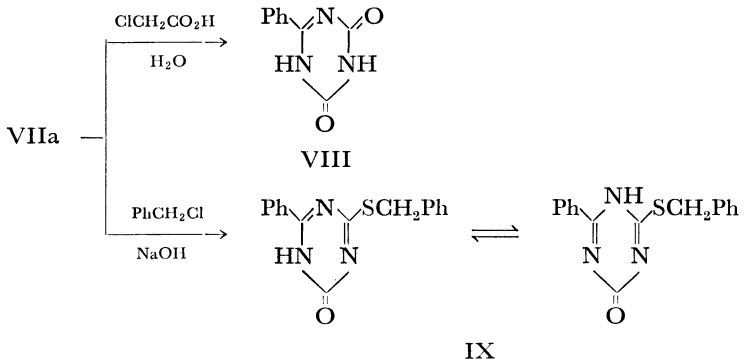
Treatment of an ethanolic solution of 1-benzoyl-2-thiobiuret IVa with concentrated hydrochloric acid (see Experimental) gave monothiobiuret VI, which is particularly useful as an intermediate in the production of thermoplastic and water-repellent resins and which may serve as a rubber accelerator, a plasticizer and an insecticide. The present route for the synthesis of VI from readily accessible starting materials is, therefore, superior to and more convenient than the reported procedures.[8-10]

On the other hand, treatment of an ethanolic solution of each of IVa—e with aqueous 4 M sodium hydroxide afforded, after acidification, 6-aryl-4-thioxo-1,2,3,4(or 2,3,4,5)-tetrahydro-1,3,5-triazin-2-ones VIIa—e in a good yield.

The structure of the 4-thioxo-1,3,5-triazin-2-one derivatives VIIa—e was confirmed by analytical data, infrared and electronic spectra. Their infrared spectra (*cf.* Table 1) exhibit bands in the regions 3210—3050 cm^{-1} (ν_{NH}) and 1740—1675 cm^{-1} ($\nu_{C=O}$) and their electronic spectra reflect their structural similarity (*cf.* Table 1).

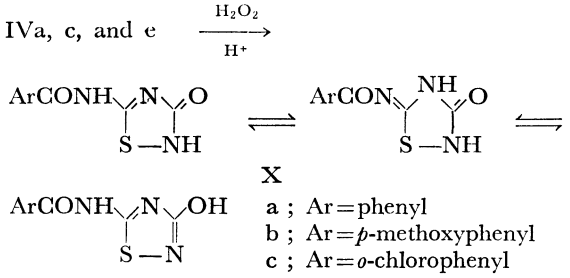


Although 6-phenyl-4-thioxo-1,2,3,4(or 2,3,4,5)-tetrahydro-1,3,5-triazin-2-one VIIa, mp 264—266 °C, has been prepared[2] by a different route which involves acidic hydrolysis of III (Ar=phenyl; X=OC_2H_5) and is reported to have mp 246—248 °C, the structure of the compound in our hands was established from the following chemical evidence: 1) it was desulfurized[6] with aqueous chloroacetic acid to give 6-phenyl-1,2,3,4-tetrahydro-1,3,5-triazin-2,4-dione VIII, which was analytically pure and its mp was in good agreement with that reported previously[7] for the same compound prepared by a different route, and 2) benzylation with benzyl chloride in the presence of sodium hydroxide gave 4-benzylthio-6-phenyl-1,2(or 1,4)-dihydro-1,3,5-triazin-2-one IX which was identical (mp, mixed mp and infrared spectroscopy) with an authentic specimen prepared by a different route.[2]



Oxidation of IVa, c, and e with hydrogen peroxide in the presence of hydrochloric acid gave 5-aroylamino-2,3-dihydro-1,2,4-thiadiazol-3-ones (or 5-aroylimino-tetrahydro-1,2,4-thiadiazol-3-ones) Xa—c whose structures were confirmed by analytical data, infrared and electronic spectroscopy. Thus, the infrared spectra of the products Xa—c show bands in the ranges 3215—3100 cm^{-1} (ν_{NH}) and 1732—1675 cm^{-1} ($\nu_{C=O}$) and their electronic spectra reflect their structural similarity. The presence of the thiadiazole ring was inferred from their behavior towards the action of sodium plumbite as compared with their precursors, namely 1-aroyl-2-thiobiurets IVa, c, and e. The latter open-chain adducts deposited black lead sulfide at room temperature, but the thiadiazole derivatives Xa—c deposited lead sulfide after being boiled for a few minutes.

5-Aroylamino-2,3-dihydro-1,2,4-thiadiazol-3-ones Xa—c can exist in the tautomeric forms indicated.



Experimental

All melting points are uncorrected. Infrared and electronic spectra were measured on a Unicam SP 1200 spectrophotometer (KBr discs) and Beckmann DK-2A Ratio Recording spectrophotometer (in dioxane), respectively.

Preparation of Aroyl Isothiocyanates IIa—f. These were prepared by known procedures.

a) *Benzoyl Isothiocyanate* IIa, bp 105—110 °C/5 mmHg. Bp 95—100 °C/2—3 mmHg by Kurzer and Hanks;[11] bp 143 °C/20 mmHg by Smith and Kan.[12]

b) p-*Toluoyl Isothiocyanate* IIb, bp 110—113 °C/1 mmHg; bp 92 °C/0.4 mmHg.[12]

c) p-*Anisoyl Isothiocyanate* IIc, bp 160—166 °C/4 mmHg; bp 148—152 °C/1 mmHg.[11]

d) p-*Bromobenzoyl Isothiocyanate* IId, mp 54—55 °C (from chloroform); mp 55 °C.[13]

e) o-*Chlorobenzoyl Isothiocyanate* IIe, bp 130—135 °C/5 mmHg; bp 119 °C/2 mmHg.[14]

f) *Cinnamoyl Isothiocyanate* IIf, bp 125—130 °C/4 mmHg; bp 119 °C/2 mmHg.[12]

Addition of Urea to Aroyl Isothiocyanates II. General Procedure Method A. To a solution of aroyl isothiocyanate (0.05 mol) in dry acetone (100 ml) was added urea (0.05 mol) portionwise with stirring. The reaction mixture was then refluxed for 2—3 h until all of the urea had dissolved. Evaporation of the acetone solution followed by trituration of the residue with hot water gave a crystalline solid. Recrystallization from an appropriate solvent gave 1-aroyl-2-thiobiurets IV. The results are given in Table 2.

Table 3. 6-Aryl-4-thioxo-1,2,3,4(or 2,3,4,5)-tetrahydro-1,3,5-triazin-2-ones VII

Compound	Melting point	Yield %	Formula	Found (%)				Calcd (%)			
				C	H	N	S	C	H	N	S
VIIa	264—266[a]	80	$C_9H_7N_3OS$	52.3	3.6	20.7	15.3	52.7	3.4	20.5	15.6
VIIb	250—253[b]	85	$C_{10}H_9N_3OS$	55.2	4.4	19.6	14.4	54.8	4.1	19.2	14.6
VIIc	258—260[c]	78	$C_{10}H_9N_3O_2S$	51.5	4.2	18.0	13.5	51.1	3.8	17.9	13.6
VIId	264—266[d]	82	$C_9H_6BrN_3OS$	38.4	2.5	15.1	11.5	38.0	2.1	14.8	11.3
VIIe	210—212[e]	75	$C_9H_6ClN_3OS$	44.7	2.8	17.3	13.2	45.1	2.5	17.5	13.3

a) From ethanol, Ref. 2, mp 246—248 °C. b) From ethanol, Ref. 16, mp 246—247 °C. c) From acetic acid, Ref. 16, mp 257—259 °C (from DMF/water). d) From acetic acid. e) From ethanol.

Table 4. 5-Aroylamino-2,3-dihydro-1,2,4-thiadiazol-3-ones X

Compound	Melting point	Yield %	Formula	Found (%)				Calcd (%)			
				C	H	N	S	C	H	N	S
Xa	225—228[a]	88	$C_9H_7N_3O_2S$	48.5	3.2	18.8	14.2	48.9	3.2	19.0	14.5
Xb	261—264[b]	83	$C_{10}H_9N_3O_3S$	47.5	4.0	16.3	12.6	47.8	3.6	16.7	12.75
Xc	251—253[b]	90	$C_9H_6ClN_3O_2S$	42.7	2.6	16.4	12.4	42.3	2.3	16.4	12.5

a) From 1-butanol. b) From acetic acid.

The mother liquor obtained after separation of IVa deposited colorless crystals of the diadduct V, mp 175—178 °C (from aqueous methanol), in 3% yield. Found: C, 52.8; H, 4.0; N, 14.6; S, 16.6%. Calcd for $C_{17}H_{14}N_4O_3S_2$: C, 52.8; H, 3.6; N, 14.5; S, 16.6%.

Method B. Urea (0.05 mol) was added to an acetone solution of the aroyl isothiocyanate II [prepared *in situ*[15] from the corresponding aroyl chloride (0.05 mol) and ammonium thiocyanate (0.08 mol) in acetone (100 ml) by refluxing for 15 min followed by filtration of inorganic solid] and the reaction mixture refluxed for 2—3 h. The reaction mixture was worked up as described in *Method A*. The yields of the monoadducts 1-aroyl-2-thiobiurets IV obtained by this method are included in Table 2.

Desulfurization of 1-Benzoyl-2-thiobiuret IVa with Aqueous Chloroacetic Acid. A solution of chloroacetic acid (4 g) in water (10 ml) was mixed with 1-benzoyl-2-thiobiuret IVa (2 g) and heated on an oil bath at 150—160 °C for 30 min. After being cooled to room temperature, the product was filtered off and recrystallized from methyl cellosolve to give benzoylbiuret almost quantitatively, mp 220—221 °C (lit,[7] mp 220 °C). Found: C, 52.4; H, 4.7; N, 20.1%. Calcd for $C_9H_9N_3O_3$: C, 52.1; H, 4.3; N, 20.3%.

Action of Concentrated Hydrochloric Acid on 1-Benzoyl-2-thiobiuret IVa. Isolation of Monothiobiuret VI. Ethanol (*ca.* 10 ml) was added to a suspension of 1-benzoyl-2-thiobiuret IVa (2 g) in concentrated hydrochloric acid. The reaction mixture was then refluxed until most of the benzoic acid (mp and mixed mp 121 °C) had sublimed into the condenser. The solution was evaporated *in vacuo* and the residue was neutralized with sodium hydrogencarbonate and then recrystallized from water to give monothiobiuret VI in 65% yield, mp 185—186 °C (lit,[10] mp 187—189 °C). It gave the biuret reaction and showed its infrared spectrum bands for ν_{NH} at 3540, 3440, 3380—3300, 3280—3140 cm^{-1} and for $\nu_{C=O}$ at 1730, 1700, 1660 and 1640 cm^{-1}. Its electronic spectrum showed λ_{max} 256 nm (ε 15490). Found: N, 30.25; S, 22.9%. Calcd for $C_2H_5N_3OS \cdot H_2O$: N, 30.65; S, 23.35%.

Action of Aqueous Sodium Hydroxide on 1-Aroyl-2-thiobiurets IVa—e. Synthesis of 6-Aryl-4-thioxo-1,2,3,4(or 2,3,4,5)-tetrahydro-1,3,5-triazin-2-ones VIIa—e. 1-Aroyl-2-thiobiuret (0.01 mol) was dissolved in aqueous 4 M sodium hydroxide (60 ml) and ethanol (30 ml) and the reaction mixture was left to stand at room temperature overnight. Acidification with 1M aqueous sulfuric acid (pH 6) gave a precipitate (quantitative yield) which was recrystallized from an appropriate solvent to give 6-aryl-4-thioxo-1,2,3,4(or 2,3,4,5)-tetrahydro-1,3,5-triazin-2-one VII as yellow to orange crystals. The results are given in Table 3.

Desulfurization of 6-Phenyl-4-thioxo-1,2,3,4(or 2,3,4,5)-tetrahydro-1,3,5-triazin-2-one VIIa to 6-Phenyl-1,2,3,4-tetrahydro-1,3,5-triazin-2,4-dione VIII. Compound VIIa (2 g) was desulfurized with a solution of chloroacetic acid (4 g) in water (10 ml) to give 6-phenyl-1,2,3,4-tetrahydro-1,3,5-triazin-2,4-dione (quantitative yield). It was recrystallized from water, mp 286—288 °C; mp 286—287 °C.[7] Goerdeler and Neuffer[16] reported mp 283—285 °C for the same compound recrystallized from ethanol. Found: C, 57.4; H, 4.1; N, 22.1%. Calcd for $C_9H_7N_3O_2$: C, 57.1; H, 3.7; N, 22.2%.

Preparation of 4-Benzylthio-6-phenyl-1,2(or 1,4)-dihydro-1,3,5-triazin-2-one IX. Benzyl chloride (0.011 mol) was added while being warmed to a stirred solution of 6-phenyl-4-thioxo-1,2,3,4(or 2,3,4,5)-tetrahydro-1,3,5-triazin-2-one VIIa (0.01 mol) in aqueous 0.5 M sodium hydroxide (30 ml) and ethanol (70 ml) over a period of 10 min. After the addition had been completed, stirring was continued for 1 h. The reaction mixture was then diluted with water and the precipitate was filtered off and recrystallized from ethyl acetate to give the *title compound* in 80% yield, mp 229 °C (lit,[2] mp 229 °C). Found: C, 65.0 H, 4.6; N, 14.0; S, 10.6%. Calcd for $C_{16}H_{13}N_3OS$: C, 65.1; H, 4.4; N, 14.2; S, 10.9%.

Oxidation of 1-Aroyl-2-thiobiuret IV to 5-Aroylamino-2,3-dihydro-1,2,4-thiadiazol-3-ones X with Hydrogen Peroxide. Hydrogen peroxide (10%, 15 ml) was added to a boiling solution of each of IVa, c, or e (0.01 mol) in ethanol (20 ml) containing concentrated hydrochloric acid (1 ml) over a period of 5 min. After being cooled to room temperature, the precipitated solid was filtered off and recrystallized from a suitable solvent to give the thiadiazoles Xa, b, or c. The results are given in Table 4.

Action of Sodium Plumbite on 1-Aroyl-2-thiobiurets IV and 5-Aroylamino-2,3-dihydro-1,2,4-thiadiazol-3-ones X. When

sodium plumbite was added to IV, a black precipitate (lead sulfide) was formed immediately. On the other hand, no precipitate was formed at room temperature on addition of sodium plumbite to X; the black lead sulfide separated after being warmed, its amount increasing by boiling for 3—5 min.

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