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Reaction of Biguanides and Related Compounds. X.[1] The Cyclization of Arylbiguanides with Acyl Isothiocyanates

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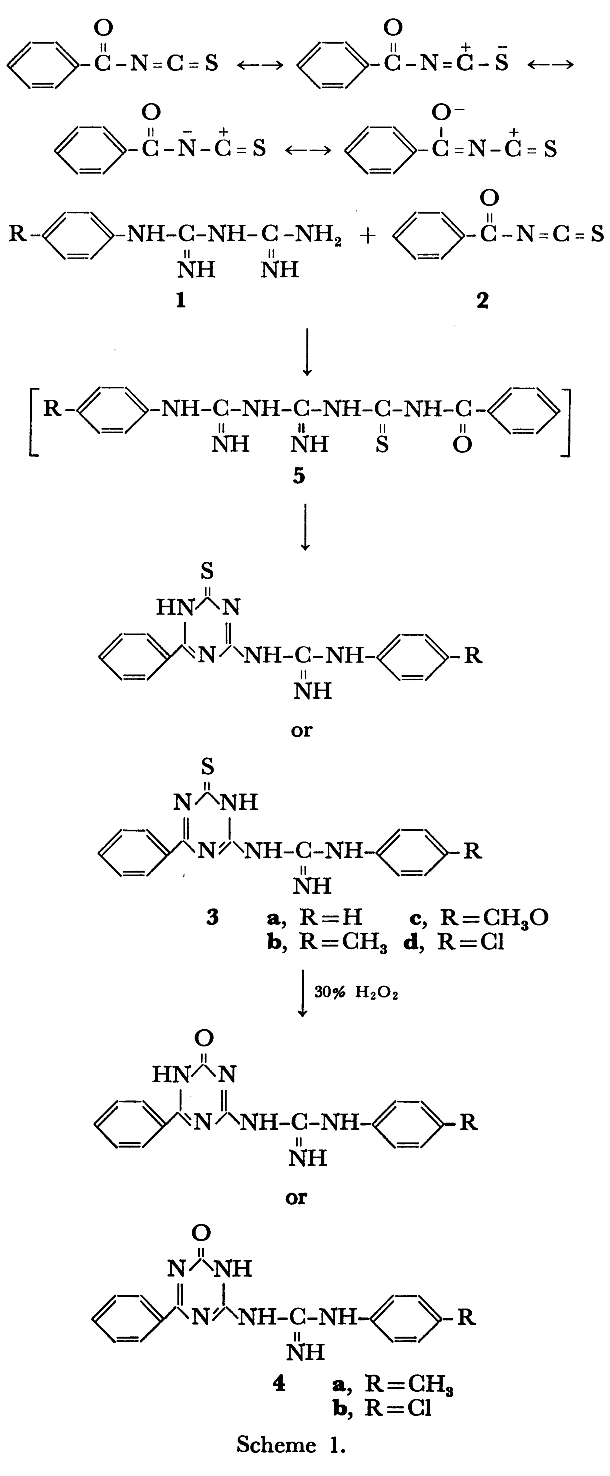
The reactions of arylbiguanides with benzoyl and ethoxycarbonyl isothiocyanates gave 4(or 2)-arylguanidino-2(or 4)-phenyl-6-thioxo-1,6-dihydro-*s*-triazines and 4-arylguanidino-2-oxo-6-thioxo-1,4,5,6(or 1,2,3,6)-tetrahydro-*s*-triazines respectively, both of which were then converted into the corresponding oxo compounds, in which the thioxo group was converted into the oxo group, by oxidation with hydrogen peroxide. The condensation of 3-amidino-1-aryl-2-thioureas with aryl isothiocyanates afforded 1-aryl-2-arylimino-4-imino-6-thioxo-1,4,5,6-tetrahydro-*s*-triazines, which were also formed by the pyrolysis of 3-amidino-1-aryl-2-thioureas.

It has been reported by Somogyi[2] that the reaction of phenylbiguanide with an equimolar quantity of phenyl isothiocyanate gave 4,6-diimino-1-phenyl-2-phenyliminohexahydro-*s*-triazine, 6-amino-2,4-dianilino-*s*-triazine, and 4-imino-1-phenyl-2-phenylimino-6-thioxohexahydro-*s*-triazine in 29, 14—16, and 19% yields respectively, all *via* the same intermediate addition product. The interaction of biguanide and phenyl isothiocyanate has also been reported by Kurzer[3] to afford an excellent yield of 4,6-diimino-1-phenyl-2-thioxohexahydro-*s*-triazine, though no unequivocal evidence for its structure was provided. As an extension of our work on the reaction of biguanides with carbonyl compounds, we investigated the reaction of arylbiguanides with benzoyl and ethoxycarbonyl isothiocyanates, in both of which a carbonyl group is involved in the position adjacent to the isothiocyanate group.

Reaction of Arylbiguanides with Benzoyl Isothiocyanate. By analogy with the reaction of phenylbiguanide with phenyl isothiocyanate, several cyclization products are possible in the reaction between arylbiguanides (**1**) and benzoyl isothiocyanate (**2**). In addition, the participation of the carbonyl group in the cyclization is also possible.

When equimolar quantities of **1** and **2** were heated in ethanol for 4 hr, one product was obtained in a low yield. The product was positive in a lead acetate test for the sulfur atom. The infrared (IR) absorption spectra of the product exhibited the characteristic absorptions assignable to amino and imino groups near 3340 and 3140 cm^{-1} and that due to the thiocarbonyl group near 1250 cm^{-1}, but no absorption assignable to the carbonyl group was observed. Although the absorption assigned to the thiocarbonyl group was at a higher frequency than the normal absorption band of a thiocarbonyl group, its identity was confirmed by the fact that the absorption disappeared upon conversion to the carbonyl group by oxidation. The ultraviolet (UV) absorption spectra showed the maximum absorption at 265 nm. On the basis of these results and the analytical data, the product is presumed to be 4(or 2)-arylguanidino-2(or 4)-phenyl-6-thioxo-1,6-dihydro-*s*-triazines (**3**). A similar cyclization reaction has been known in the condensations of *N*-unsubstituted amidino compounds with aroyl isothiocyanates[4] and with substituted imidoyl isothiocyanates.[5] Support for the assigned structure **3** was provided by the mass spectra, in which the molecular ion and the fragment ion peaks



Scheme 1.

TABLE 1. 4(OR 2)-ARYLGUANIDINO-2(OR 4)-PHENYL-6-THIOXO-1,6-DIHYDRO-*s*-TRIAZINE

Compd.	Mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis % Found (Calcd) C	H	N	IR cm^{-1} (KBr) $\nu_{C=S}$	UV λ_{max}^{EtOH} nm (log ε)
3a	269—270	20	EtOH	$C_{16}H_{14}N_6S$	59.65 (59.62)	4.37 (4.38)	26.22 (26.07)	1250	264 (4.56)
3b	251—252	10	EtOH+H_2O	$C_{17}H_{16}N_6S$	60.85 (60.70)	4.85 (4.80)	24.80 (24.99)	1260	265 (4.57)
3c	281—282	16	DMF+H_2O	$C_{17}H_{16}ON_6S$	58.05 (57.95)	4.54 (4.58)	23.64 (23.85)	1260	265 (4.51)
3d	271—272	19	DMF+H_2O	$C_{16}H_{13}N_6SCl$	53.67 (53.85)	3.73 (3.67)	23.20 (23.55)	1260	265 (4.51)

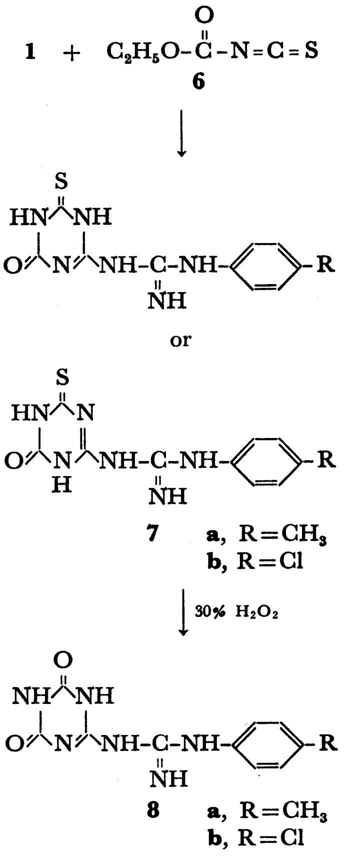
due to arylamidyl and arylamino ions were observed as an abundant peak.

In order to further elucidate the assigned structure, the product was converted into 4(or 2)-arylguanidino-2 (or 4)-phenyl-6-oxo-1,6-dihydro-*s*-triazines (**4**). The conversion was successfully carried out by heating with a 30% aqueous hydrogen peroxide solution in acetic acid at 80 °C for 30 min. The structure of **4** was established by the good agreement of the elemental analyses and by the IR spectra, in which the absorption of the thiocarbonyl group disappeared and the absorption assignable to the carbonyl group was observed near 1680 cm^{-1}. The absorption pattern was quite similar to that of **3**.

Somogyi[2)] has reported that the cyclization reaction of phenylbiguanide with phenyl isothiocyanate proceeds through the intermediate addition product which is formed by the addition of the terminal amino group of phenylbiguanide to the isothiocyanate group. In view of the resonance formula of **2**, it seems that the initial addition of **1** to **2** would analogously occur at the positive carbon atom of the isothiocyanate group, but not at the adjacent carbonyl carbon atom, to form a similar intermediate (**5**), followed by cyclization to **3** by dehydration, though all efforts to isolate the intermediate under milder reaction conditions failed. The results are summarized in Table 1.

Reaction of Arylbiguanides with Ethoxycarbonyl Isothiocyanate. Recently Goerdeler and Neuffer[6)] have reported that the amidino compounds, such as isoureas, isothioureas[7)] and guanidines, reacted with ethoxycarbonyl isothiocyanate, with the elimination of ethanol, to give oxothioxotetrahydro-*s*-triazines. Compound **1** is also presumed to behave similarly toward ethoxycarbonyl isothiocyanate, because an amidino moiety is involved in the molecule.

When equimolecular quantities of **1** and ethoxycarbonyl isothiocyanate (**6**) were treated in ethanol at room temperature, 4-arylguanidino-2-oxo-6-thioxo-1,4,5,6(or 1,2,3,6)-tetrahydro-*s*-triazines (**7**) were obtained in comparatively good yields, as had been expected.

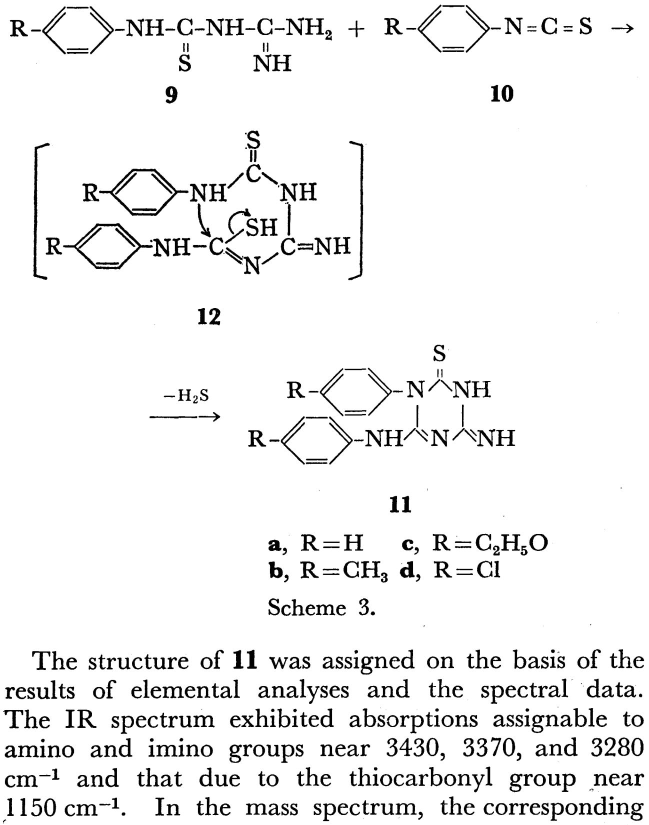


Scheme 2.

The structure of **7** was assigned on the basis of the results of elemental analyses and the spectral data. The IR spectra exhibited characteristic absorptions assignable to amino and imino groups near 3450 and 3300 cm^{-1} and that due to the thiocarbonyl group near 1235 cm^{-1}. The mass spectra showed the molecular ion peak as an abundant peak. Fragment ion peaks presumably corresponding to the arylamidyl ion, the arylamino ion, and arylcyanamide were also observed. The UV spectra indicated the maximum absorption bands at 270 nm in a 0.01 M hydrochloric acid solution and at 275 and 250 nm in a 0.01 M sodium hydroxide solution; they must be due to the keto and enol forms respectively. Evidence for the structure was achieved by conversion with hydrogen peroxide into 4-arylguanidino-2,6-dioxo-1,2,5,6-tetrahydro-*s*-triazines (**8**), whose structures were established on the basis of the results of elemental analyses and the spectral data.

Reaction of 3-Amidino-1-aryl-2-thioureas with Phenyl Isothiocyanate. Because of the structural similarity, 3-aminido-1-aryl-2-thioureas (**9**) may be expected to behave much like **1** toward isothiocyanates. Crowther *et al.*[8)] have reported that, in the preparation of 3-alkylamidino-1-*p*-chlorophenyl-2-thioureas from alkylguanidines and *p*-chlorophenyl isothiocyanate, 4-alkylamino-2-*p*-chloroanilino-1-*p*-chlorophenyl-6-thioxo-1,6-dihydro-*s*-triazines were formed as by-products. This cyclization is presumed to proceed through the intermediate addition product which is formed by addition of 3-alkylamidino-1-*p*-chlorophenyl-2-thiourea, alone with further *p*-chlorophenyl isothiocyanate. Thus the condensation of **9** with several aryl isothiocyanates (**10**) was examined.

When equimolecular quantities of **9** and **10** were heated in dimethylformamide (DMF) at 110 °C, 1-aryl-2-arylamino-4-imino-6-thioxo-1,4,5,6-tetrahydro-*s*-triazines (**11**) were obtained in moderate yields.



a, R=H **c**, R=C_2H_5O
b, R=CH_3 **d**, R=Cl

Scheme 3.

The structure of **11** was assigned on the basis of the results of elemental analyses and the spectral data. The IR spectrum exhibited absorptions assignable to amino and imino groups near 3430, 3370, and 3280 cm^{-1} and that due to the thiocarbonyl group near 1150 cm^{-1}. In the mass spectrum, the corresponding molecular ion was observed as the most abundant peak. Fragment ion peaks corresponding to the elimination of NCS group from the molecular ion and to arylamine were also observed. The reaction probably proceeds through the intermediate addition product (**12**), followed by the elimination of hydrogen sulfide, though attempts to isolate the intermediate were unsuccessful. The liberation of hydrogen sulfide was actually confirmed by the positive lead acetate test. Compound **11** was also obtained in a lower yield by the pyrolysis of **9** in DMF at 110 °C. It is probably formed by condensation of **9** with the **10** formed by the decomposition of **9**. The formation of **10** from **9** is detected in the mass spectrum of **9**.[9] The results are summarized in Table 2.

Contrary to expectations, however, the reactions of **9** with **2** and **6** resulted in failure, a small amount of the **9** being recovered unchanged and no anticipated product being isolated.

Experimental

*4(or 2)-Arylguanidino-2(or 4)-phenyl-6-thioxo-1,6-dihydro-*s*-triazine (**3**).* General Procedure: A solution of arylbiguanide (10 mmol) and benzoyl isothiocyanate (10 mmol) in ethanol (20 ml) was heated for 4 hr under reflux. The precipitates deposited during heating were collected by filtration. The filtrate was concentrated under reduced pressure, and the precipitates deposited on cooling were collected by filtration. The combined precipitates were recrystallized from a suitable solvent. The detailed data are summarized in Table 1. These compounds exhibited the corresponding molecular ion as an abundant peak in the mass spectra.

*2(or 4)-Phenyl-4(or 2)-*p*-tolylguanidino-6-oxo-1,6-dihydro-*s*-triazine (**4a**).* Into a suspension of 2(or 4)-phenyl-4 (or 2)-*p*-tolylguanidino-6-thioxo-1,6-dihydro-*s*-triazine (0.6 g, 1.8 mmol) in acetic acid (7 ml), we stirred, drop by drop, a 30% aqueous hydrogen peroxide solution (0.3 ml) at 80 °C over a 5-min period. Stirring was continued for an additional 30 min, keeping the temperature at 80 °C, and then the insoluble parts were filtered off. The filtrate was basified with concentrated aqueous ammonia. The precipitates deposited upon cooling were collected by filtration, washed with water, and recrystallized from DMF–water to give colorless prisms (0.15 g, 26.3%) melting at 304—305 °C. IR(KBr): 1680 cm^{-1} (C=O). MS: 320 (M^+). Found: C, 63.34; H, 5.24; H, 25.84%. Calcd for $C_{17}H_{16}ON_6$: C, 63.73; H, 5.04; N, 25.84%.

*4(or 2)-*p*-Chlorophenylguanidino-2(or 4)-phenyl-6-oxo-1,6-dihydro-*s*-triazine (**4b**).* Into a suspension of 4(or 2)-*p*-chlorophenylguanidino-2(or 4)-phenyl-6-thioxo-1,6-dihydro-*s*-triazine (0.8 g, 2.24 mmol) in acetic acid (8.2 ml), we stirred, drop by drop, a 30% aqueous hydrogen peroxide solution (0.7 ml) at 80 °C over a 5-min period. The reaction mixture was then treated by the same procedure as that described above. The resulting product was recrystallized from DMF

Table 2. 1-Aryl-2-arylamino-4-imino-6-thioxo-1,4,5,6-tetrahydro-*s*-triazine

Compd.	Mp (°C)	Yield (%) Method a	Yield (%) Method b	Appearance	Formula	Analysis % Found(Calcd) C	H	N	IR cm^{-1} (KBr) $\nu_{C=S}$
11a	252	68	3	prism	$C_{15}H_{13}N_5S$	61.01 (61.01)	4.50 (4.44)	23.42 (23.72)	1155
11b	244	80	17	needle	$C_{17}H_{17}N_5S$	62.77 (63.14)	5.29 (5.30)	21.37 (21.66)	1155
11c	268	52	18	plate	$C_{19}H_{21}O_2N_5S$	59.49 (59.52)	5.54 (5.52)	18.18 (18.27)	1158
11d	290	31	23	needle	$C_{15}H_{11}N_5SCl_2$	50.30 (50.85)	3.00 (3.13)	19.55 (19.77)	1148

to give colorless prisms (0.2 g, 26.3%) melting at 314—315 °C. IR(KBr): 1660 cm^{-1} (C=O). MS: 341 (M$^+$). Found: C, 56.13; H, 3.96; N, 24.81%. Calcd for $C_{16}H_{13}ON_6Cl$: C, 56.39; H, 3.85; N, 24.66%.

*4-p-Tolylguanidino-2-oxo-6-thioxo-1,4,5,6(or 1,2,3,6)-tetrahydro-s-triazine (**7a**).* Into a solution of *p*-tolylbiguanide (1.9 g, 10 mmol) in ethanol (20 ml), we stirred, drop by drop, ethoxycarbonyl isothiocyanate (1.3 g, 10 mmol) at 0 °C under a stream of nitrogen gas. Stirring was continued for an additional 24 hr at room temperature under a nitrogen stream. The precipitates which were gradually deposited in the course of the reaction were collected by filtration, washed with water, dried, and recrystallized from DMF to give colorless prisms (1.86 g, 67.5%); mp>360 °C. IR (KBr): 1680 (C=O) and 1235 (C=S) cm^{-1}. UV $\lambda_{\max}^{0.01\text{M HCl}}$ nm (log ε): 271 (4.42). UV $\lambda_{\max}^{0.01\text{M NaOH}}$ nm (log ε): 248 (4.44) and 275 (4.44). Found: C, 47.99; H, 4.23; N, 29.95 %. Calcd for $C_{11}H_{12}ON_6S$: C, 47.82; H, 4.38; N, 30.42%.

*4-p-Chlorophenylguanidino-2-oxo-6-thioxo-1,4,5,6(or 1,2,3,6)-tetrahydro-s-triazine (**7b**).* Into a solution of *p*-chlorophenylbiguanide (2.12 g, 10 mmol) in ethanol (20 ml), we stirred, drop by drop, ethoxycarbonyl isothiocyanate (1.31 g, 10 mmol) at 0 °C under a stream of nitrogen gas. The reaction mixture was then treated by the same procedure as that described above to give colorless prisms (1.84 g, 62.0%); mp>360 °C. IR (KBr): 1680 (C=O) and 1235 (C=S) cm^{-1}. UV $\lambda_{\max}^{0.01\text{M HCl}}$ nm (log ε): 270 (4.47). UV $\lambda_{\max}^{0.01\text{M NaOH}}$ nm (log ε): 250 (4.37) and 275 (4.41). Found: C, 40.94; H, 3.08; N, 28.01%. Calcd for $C_{10}H_9ON_6SCl$: C, 40.47; H, 3.06; N, 28.32%.

*4-p-Tolylguanidino-2,6-dioxo-1,2,5,6-tetrahydro-s-triazine (**8a**).* Into a solution of 4-*p*-tolylguanidino-2-oxo-6-thioxo-1,4,5,6(or 1,2,3,6)-tetrahydro-*s*-triazine (0.5 g, 1.8 mmol) in an aqueous 1 M sodium hydroxide solution (16 ml), we stirred, drop by drop, an aqueous 30% hydrogen peroxide solution (4 ml) at 0 °C over a 20-min period. Stirring was continued for an additional 2 hr at room temperature. The precipitates which had been deposited were then collected by filtration. The filtrate was acidified with a 2 M sulfuric acid solution, and the precipitates thus deposited were collected by filtration. The combined precipitates were then washed with water, dried, and recrystallized from DMF to give colorless prisms (0.30 g, 64.1%); mp>360 °C. IR(KBr): 1720 and 1660 cm^{-1} (C=O). Found: C, 50.74; H, 4.72; N, 32.01%. Calcd for $C_{11}H_{12}O_2N_6$: C, 50.76; H, 4.65; N, 32.30%.

*4-p-Chlorophenylguanidino-2,6-dioxo-1,2,5,6-tetrahydro-s-triazine (**8b**).* Into a suspension of 4-*p*-chlorophenylguanidino-2-oxo-6-thioxo-1,4,5,6(or 1,2,3,6)-tetrahydro-*s*-triazine (0.8 g, 2.7 mmol) in an aqueous 1 M sodium hydroxide solution (20 ml), we added, drop by drop, an aqueous 30% hydrogen proxide solution (5.4 ml) at 0 °C over a 10-min period. Stirring was continued for an additional 1 hr at room tempreature, and then the insoluble part was filtered off and the filtrate was acidified with an aqueous 2 M sulfuric acid solution. The resulting precipitates were collected by filtration, washed with water, dried, and recrystallized from DMF to give colorless prisms (0.50 g, 65.8%) melting at 358—360 °C. IR(KBr): 1720 and 1660 cm^{-1} (C=O). Found: C, 42.92; H, 3.34; N, 29.73%. Calcd for $C_{10}H_9O_2N_6Cl$: C, 42.79; H, 3.23; N, 29.94%.

*1-Aryl-2-arylamino-4-imino-6-thioxo-1,4,5,6-tetrahydro-s-triazine (**11**).* General Procedure: a) A mixture of 3-amidino-1-aryl-2-thiourea (10 mmol), aryl isothiocyanate (10 mmol), and DMF (5 ml) was heated at 110 °C for 5 hr. After cooling, the mixture was poured into cold water and the precipitates thus deposited were collected by filtration, washed with water, and recrystallized from ethanol. The detailed data are summarized in Table 2. These compounds exhibited the corresponding molecular ions as the most abundant peak in the mass spectra. b) A solution of 3-amidino-1-aryl-2-thiourea (10 mmol) in DMF (5 ml) was heated at 110 °C for 10 hr. After cooling, the solution was poured into cold water and the resulting precipitates were collected by filtration, washed with water, and recrystallized from ethanol. The yield of the product is illustrated in Table 2. These compounds were identified with authentic samples obtained by the method described above by a mixed-melting-point determination and by an IR comparison.

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