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Reaction of Biguanides and Related Compounds. IX.[1] Condensation of N-Amidino-O-alkylisourea and 1-Substituted 3-Amidino-2-thiourea with Benzil

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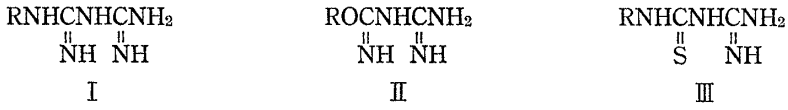
The reactions of N-amidino-O-alkylisourea and 1-substituted 3-amidino-2-thiourea with benzil were examined. The reaction of N-amidino-O-alkylisourea with an equivalent amount of benzil in ethanol gave 5,5-diphenylglycocyamidine by heating for 10 hr under reflux, 5,5-diphenylglycocyamidine and 2-alkoxyamidinylidene-5,5-diphenylhydantoin by heating for 2 hr under the similar conditions and 2-alkoxyamidinylidene-5,5-diphenylhydantoin and 3*a*,6*a*-diphenylglycoluril-2,5-dialkoximidoylimide by treatment for 1 hr at room temperature. Similarly, heating of 1-aryl-3-amidino-2-thiourea with benzil in ethanol for 10 hr under reflux gave 5,5-diphenylglycocyamidine. On the other hand, by heating in ethanol in the presence of potassium hydroxide for 2 hr under reflux, 2-arylthiocarbamoyl-5,5-diphenylglycocyamidine.

A number of base-catalyzed condensations of guanidines[3] and ureas[4] with benzil have been known to give 5,5-diphenylhydantoins and 3*a*,6*a*-diphenylglycolurils, the proportion of them depending upon the base concentration and the reaction temperature. Analogous condensations[5] of guanidine and urea with α,β-dicarbonyl compounds have been also reported. Recently, we found that 1-substituted biguanides (I) also reacted with benzil by heating in alcohol in the absence of any catalyst to give 2-substituted guanidylidene-5,5-diphenylhydantoins,[6] whose formation involved an anionotropic migration of a phenyl group. Owing

1) Part VIII: M. Furukawa, T. Yoshida, M. Goto and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 2594 (1973).
2) Location: *Oe-hon machi, Kumamoto.*
3) *a*) H.W. Carhart and P.C. Teague, *C.A.*, **47**, 1733 (1953); *b*) H. Adkins, J.E. Castle and E.E. Royals, *ibid.*, **48**, 2117 (1954); *c*) K. Lempert and M. Lempert-Sreter, *Chem. Ber.*, **94**, 796 (1961); *d*) M. Lempert-Sreter, V. Solt and K. Lempert, *C.A.*, **59**, 10022; *e*) M. Furukawa, Y. Kojima and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2102 (1972).
4) *a*) H. Biltz, *Chem. Ber.*, **40**, 4799, 4806 (1907); *idem, ibid.*, **41**, 167, 1379 (1908); *idem, Ann.*, **368**, **156**, 243 (1909); *b*) E. Ware, *Chem. Rev.*, **46**, 403 (1950); *c*) W.R. Dunnavant and F.L. James, *J. Am. Chem. Soc.*, **78**, 2740 (1956).
5) *a*) I.S. Bengelsdorf, *ibid.*, **75**, 3138 (1953); *b*) L. Siemonsen, *Ann.*, **333**, 101 (1904); *c*) H. Pauly and H. Sauter, *Chem. Ber.*, **63**, 2063 (1930); *d*) B.J. Sjollema and A.J.H. Kam, *Rec. Trav. Chim.*, **36**, 180 (1917); *e*) B.J. Sjollema and L. Seekles, *ibid.*, **44**, 827 (1925); *f*) H.J. Fisher, J.B. Ekeley and A.R. Ronzio, *J. Am. Chem. Soc.*, **64**, 1434 (1942); *g*) R.G. Neville, *J. Org. Chem.*, **23**, 1588 (1958).
6) M. Furukawa, Y. Fujino, Y. Kojima and S. Hayashi *Chem. Pharm. Bull.* (Tokyo), **20**, 521 (1972).

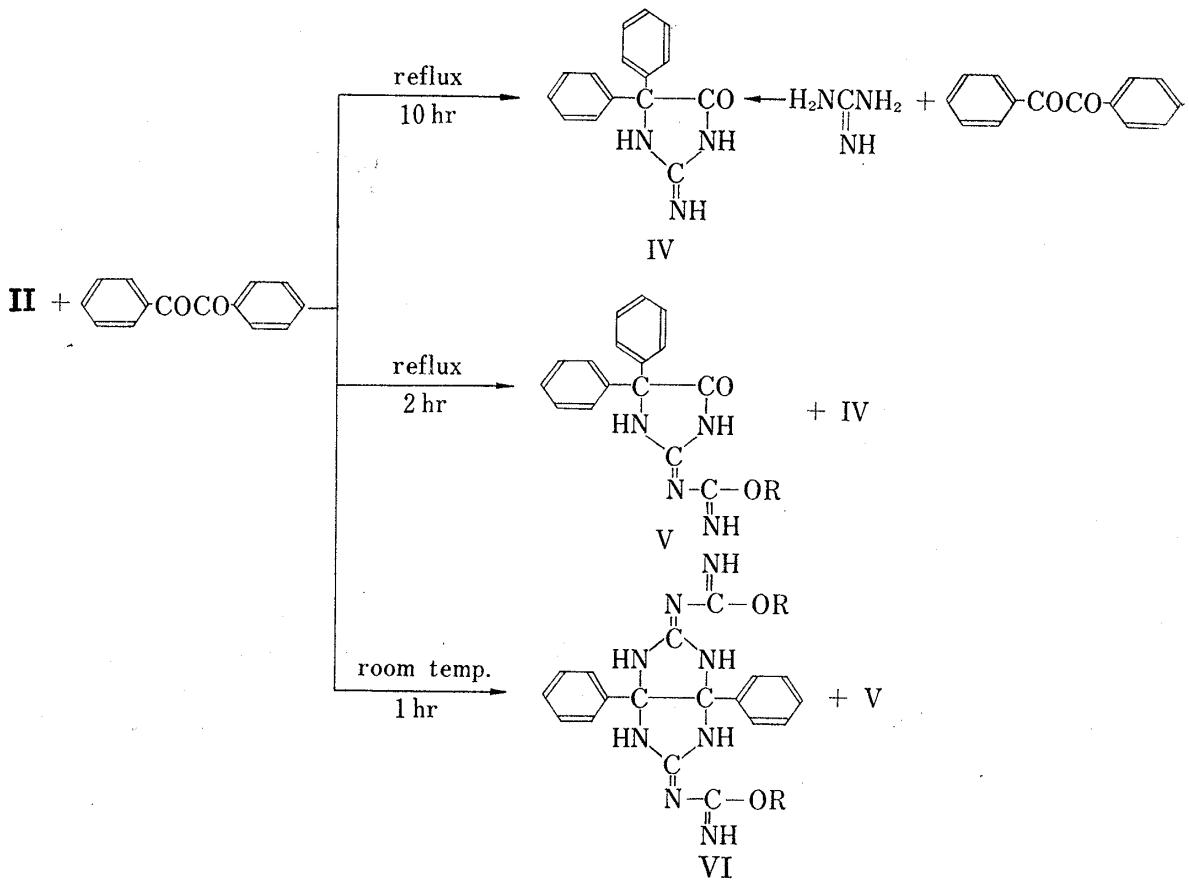
to the structural similarity, N-amidino-O-alkylisoureas (II)[7] and 1-aryl or alkyl-3-amidino-2-thiourea (III)[8] are expected to behave just like as I.



I II III

Chart 1

When N-amidino-O-ethylisourea (II, R=C_2H_5) was heated with an equivalent amount of benzil in ethanol in the absence of any catalyst for 10 hours under reflux, 5,5-diphenylglycocyamidine (IV) was obtained in 74% yield, no trace of any other product anticipated being isolated. IV was also obtained by the treatment of another N-amidino-O-alkylisourea (II) with benzil under the similar conditions. Evidence for the structure of IV was provided by identification with an authentic sample[3a,b] prepared by the reaction of guanidine with benzil. Probably the reaction between II and benzil would proceed through the formation of 2-ethoxyamidinylidene-5,5-diphenylhydantoin (V) anticipated followed by decomposition to give IV. When the same reaction was carried out for a shorter period of reaction time,



IV V VI

Chart 2

V was practically obtained in a moderate yield, accompanying a small amount of IV, whose proportion increased by the prolonged reaction time. The structure of V was confirmed by the elemental analysis and the spectral data which exhibited infrared (IR) absorptions assignable to the carbonyl group at near 1700 cm^{-1}, due to the amino and imino groups at

7) K. Kawano, *Kyushyu Kogyo Daigaku Kenkyu Hokoku* (*Japan*), **12**, 69 (1962).
8) *a*) F.H.S. Curd, J.A. Hendry, T.S. Kenny, A.G. Murray and F.L. Rose, *J. Chem. Soc.*, **1948**, 1630; *b*) T. Ueda, A. Takada, K. Takahashi and F. Ueda, *Chem. Pharm. Bull.* (Tokyo), **19**, 1990 (1971).

near 3400 cm^{-1}, 3250 cm^{-1} and 3120 cm^{-1} and attributed to the ether group at near 1090 cm^{-1} and the corresponding molecular ion as an abundant peak in the mass spectrum. On the other hand, when the equivalent amounts of II and benzil were treated with stirring in ethanol at room temperature, a different product in addition to V was obtained in a low yield. In this case no formation of IV was observed. The structure of this product was assigned to be 3*a*,6*a*-diphenylglycoluril-2,5-dialkoximidoylimide (VI) by the elemental analysis and the mass spectrum in which the molecular ion corresponding to VI was observed as an abundant peak. Support for the assigned structure of VI was also provided by the IR spectrum which exhibited absorptions assignable to the amino group at near 3420 cm^{-1}, due to the imino group at near 3260 cm^{-1} and attributed to the ether group at near 1100 cm^{-1}.

The mechanism of the formation of V is presumed to involve a molecular rearangement in which a phenyl substituent undergoes 1,2-shift just like as benzilic acid rearrangement.

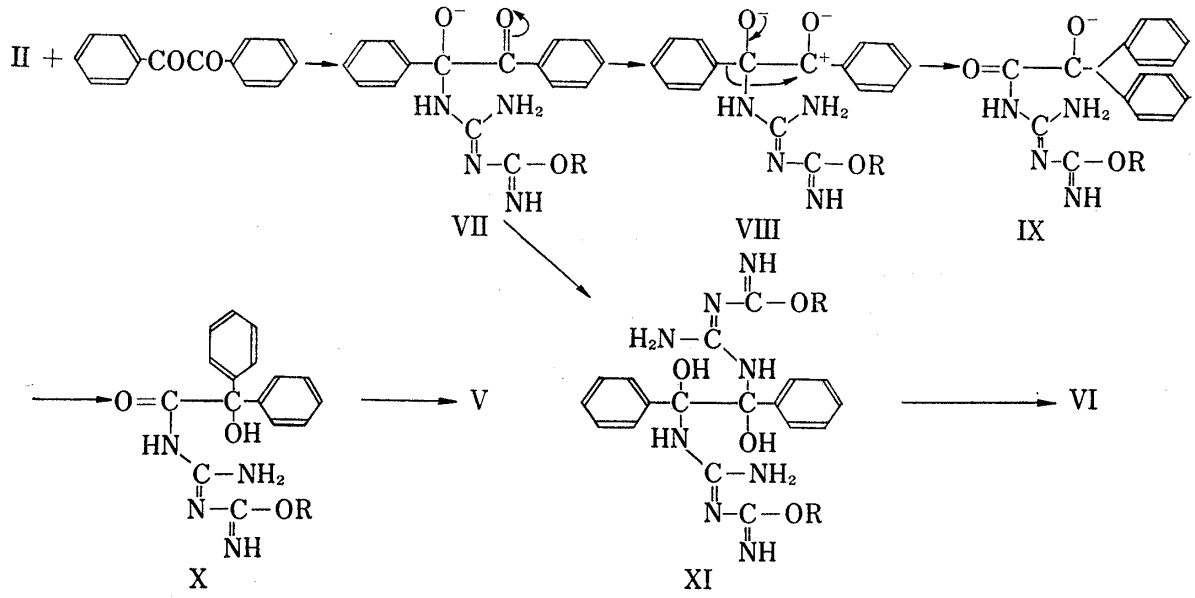
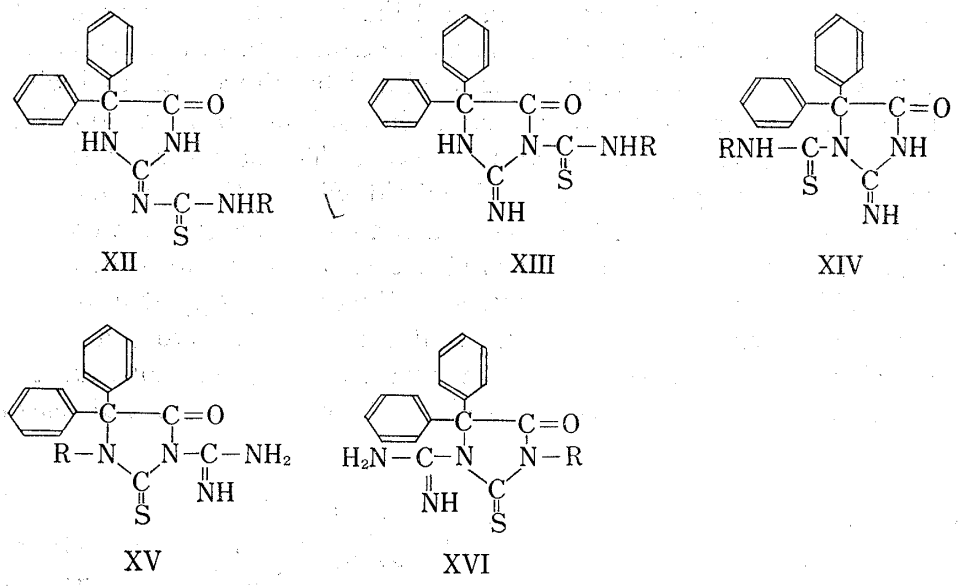


Chart 3

The rearrangement starts with addition of II onto the carbonyl carbon, resulting in the formation of VII. Because of the parallel inductive effects of the two negative oxygen function in VIII, anionotropic migration of a phenyl group results and forms the anion (IX) which is stabilized by formation of X followed by dehydration to give V. The formation of VI is explained by a mechanism through XI formed by condensation of VII with further II followed by dehydration.

Also in the reaction of III with benzil, the similar results are expected. When III was heated with an equivalent amount of benzil in ethanol in the absence of any catalyst for 10 hours under reflux, IV was obtained in a moderate yield. On heating for 2 hours under the similar conditions, only IV was obtained in a lower yield, no trace of another product anticipated being isolated. On the other hand, heating of 1-aryl-3-amidino-2-thiourea (III, R=aryl) with an equivalent amount of benzil in ethanol in the presence of potassium hydroxide for 2 hours under reflux, a different product was obtained in 25—60% yields. The IR spectrum of the product exhibited absorptions assignable to a carbonyl group at near 1740 cm^{-1}, due to an amino or imino group at near 3290 cm^{-1} and 3180 cm^{-1} and attributed to a thiocarbonyl group at near 1190 cm^{-1}. The absorption of the carbonyl group shifts from the region of 1700 cm^{-1} for V and 2-arylguanidylidene-5,5-diphenylhydantoin[6] to a higher frequency than that is expected. In the reaction of III with benzil, several isomeric compounds (XII—XVI) are possible to form.



XII XIII XIV

XV XVI

Chart 4

The elemental analysis of the product agreed with the calculated values of these possible compounds. When the product was heated at 200° for 1 minute under fusion, the product was readily converted into IV. This suggests that the product is not XV and XVI. The shift of the carbonyl absorption to the higher frequency is consistent with only XIII among the rest possible compounds. Therefore, it is reasonable to consider that XIII would be more likely for the product. The facile conversion of XIII into IV can be explained by the hydrogen shift through the formation of a six-membered ring (XVII) with elimination of isothiocyanate.

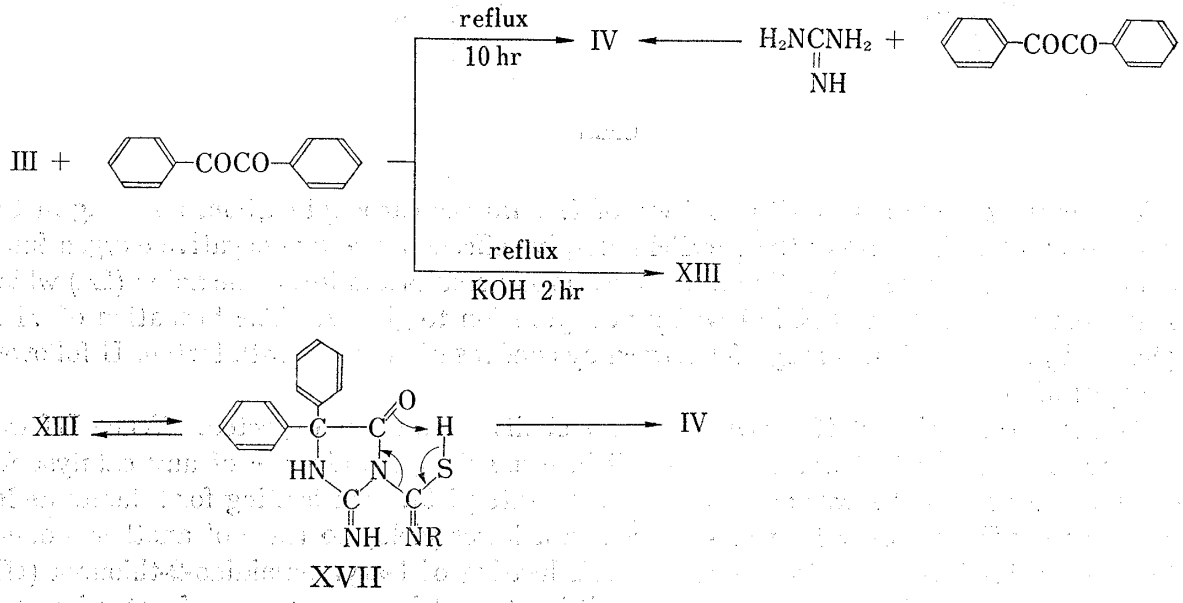


Chart 5

Different from 1-aryl-3-amidino-2-thiourea (III, R=aryl), 1-alkyl-3-amidino-2-thiourea (III, R=alkyl) gave a different result in the reaction with benzil. In the absence of any catalyst under the similar conditions, a product was obtained in a low yield. The IR spectrum of the product exhibited the carbonyl absorption at near 1690 cm^{-1} which was similar to those of IV and V. Therefore, it is likely to consider that the product is XII. Further extensions and developments of this work are in progress.

Experimental

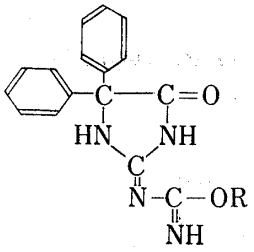
5,5-Diphenylglycocyamidine (IV)——a)[3] To an ethanolic solution of NaOEt prepared by dissolving 1.15 g (0.05 atom) of Na was added with stirring 4.8 g (0.05 mole) of powdered guanidine HCl and the mixture was stirred for additional 1 hr at room temperature. Deposited NaCl was filtered off and to the filtrate was added 10.5 g (0.05 mole) of benzil. After the solution was heated for 2 hr under reflux and then allowed to stand overnight, the solution was evaporated to dryness and the residue was recrystallized from EtOH.

b) To a solution of 1.67 g (0.01 mole) of N-amidino-O-ethylisourea HCl in 50 ml of dehyd. EtOH was added an ethanolic solution of NaOEt prepared by dissolving 0.23 g (0.01 atom) of Na. Deposited NaCl was filtered off and to the filtrate was added 2.1 g (0.01 mole) of benzil. The solution was heated for 10 hr under reflux and then concentrated. To the resulting oily product separated was added with stirring a large amount of benzene. The precipitates deposited were collected by filtration and recrystallized from EtOH to give 2.38 g (74%) of colorless needles melting at 362°, which was identified with an authentic sample[3] prepared by method a by mixed melting point determination and comparison of the infrared (IR) spectrum. The same compound was obtained by the reaction of another N-amidino-O-alkylisourea with benzil under the similar conditions.

c) A mixture of 0.01 mole of 1-aryl-3-amidino-2-thiourea and 0.01 mole of benzil in 50 ml of dehyd. EtOH was heated for 10 hr under reflux. The solution was evaporated to dryness and the residue was recrystallized from EtOH to give colorless needles melting at 362°, which was identified with an authentic sample prepared by method a.

2-Alkoxyamidinylidene-5,5-diphenylhydantoin (V)——To a solution of 0.01 mole of N-amidino-O-alkylisourea HCl in 50 ml of dehyd. EtOH was added an ethanolic solution of NaOEt prepared by dissolving 0.01 atom of Na in 10 ml of dehyd. EtOH. The precipitates deposited were filtered off and to the filtrate was added 0.01 mole of benzil. After the solution was heated for 2 hr under reflux, the solution was concentrated and allowed to stand in refrigerator overnight. Recrystallization of the resulting precipitates from EtOH gave a small amount of 5,5-diphenylglycocyamidine as first. Concentration of the filtrate and then recrystallization of the residue gave 2-alkoxyamidinylidene-5,5-diphenylhydantoin. Detailed data were summarized in Table I.

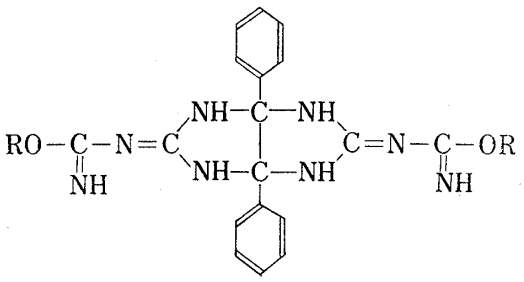
Table I. 2-Alkoxyamidinylidene-5,5-diphenylhydantoin



R	mp (°C)	Yield (%)	Formula	Analysis % Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} NH	=NH	CO	-O-
CH_3	216	21	$C_{17}H_{16}O_2N_4$	66.22	5.23	18.17	66.19	5.07	18.20	3375	3240	1705	1087
CH_3CH_2	214	16	$C_{18}H_{18}O_2N_4$	67.06	5.63	17.38	67.47	5.47	17.33	3380	3250	1704	1087
$CH_3CH_2CH_2$	202	39	$C_{19}H_{20}O_2N_4$	67.84	5.99	16.66	68.25	5.91	16.16	3400	3250	1704	1089
$(CH_3)_2CH$	204	2	$C_{19}H_{20}O_2N_4$	67.84	5.99	16.66	67.78	6.16	16.25	3380	3280	1700	1090
$CH_3CH_2CH_2CH_2$	198	11	$C_{20}H_{22}O_2N_4$	68.55	6.33	15.99	69.04	6.27	16.25	3410	3300	1694	1087

3a,6a-Diphenylglycoluril-2,5-dialkoxyimidoylimide (VI)——To a solution of 0.01 mole of N-amidino-O-alkylisourea HCl in 50 ml of dehyd. EtOH was added an ethanolic solution of NaOEt prepared by dissolving 0.01 atom of Na in 10 ml of dehyd. EtOH. Deposited NaCl was filtered off and to the filtrate was added with stirring 0.01 mole of benzil. The mixture was stirred for 1 hr and the precipitates deposited were collected by filtration and recrystallized from EtOH to give 3*a*,6*a*-diphenylglycoluril-2,5-dialkoxyimidoylimide. Detailed data were summarized in Table II. The concentration of the filtrate and the recrystallization of the residue from EtOH gave 2-alkoxyamidinylidene-5,5-diphenylhydantoin, which was identified with the product obtained by the procedure described above by mixed melting point determination and comparison of the IR spectrum.

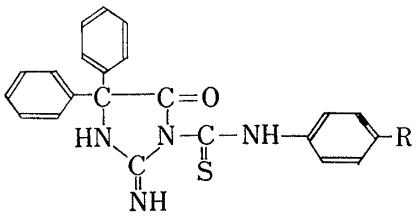
Table II. 3*a*,6*a*-Diphenylglycoluril-2,5-dialkoximidoylimide



R	mp (°C)	Yield (%)	Formula	Analysis % Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} NH	=NH	-O-
CH_3	219	18	$C_{20}H_{22}O_2N_8$	59.10	5.45	27.58	59.38	5.37	27.26	3425	3242	1095
CH_3CH_2	208	30	$C_{22}H_{26}O_2N_8$	60.79	6.03	25.78	61.19	5.88	25.65	3420	3290	1097
$CH_3CH_2CH_2$	233	23	$C_{24}H_{30}O_2N_8$	62.31	6.54	24.21	62.54	6.14	24.02	3422	3250	1093
$(CH_3)_2CH$	229	41	$C_{24}H_{30}O_2N_8$	62.31	6.54	24.21	62.30	6.56	23.81	3420	3160	1100
$CH_3CH_2CH_2CH_2$	228	50	$C_{26}H_{34}O_2N_8$	63.65	6.99	22.84	63.65	6.78	22.91	3425	3250	1097

2-Arylthiocarbamoyl-5,5-diphenylglycocyamidine (XIII)——A solution of 0.0166 mole of 1-aryl-3-amidino-2-thiourea, 0.0095 mole of benzil and 1 g of potassium hydroxide in 50 ml of MeOH was heated for 2 hr under reflux. The solution was poured into H_2O and the precipitates deposited were filtered off. The filtrate was neutralized with HCl and the precipitates deposited were collected by filtration and recrystallized from a suitable solvent. The compounds obtained did not show a regular melting point. Detailed data were summarized in Table III.

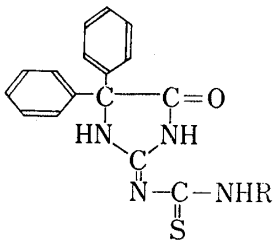
Table III. 2-Arylthiocarbamoyl-5,5-diphenylglycocyamidine



R	Yield (%)	Appearance	Recryst. solvent	Formula	Analysis % Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} (CO)	(CS)	(-O-)
H	37	prism	EtOH + DMF	$C_{22}H_{18}ON_4S$	68.38	4.70	14.50	67.87	4.70	14.93	1743	1185	
CH_3	42	prism	EtOH + DMF	$C_{23}H_{20}ON_4S$	68.99	5.03	13.99	68.78	5.00	14.22	1740	1187	
CH_3O	34	prism	EtOH	$C_{23}H_{20}O_2N_4S$	66.33	4.84	13.46	66.63	4.74	13.16	1741	1185	1251 1174
C_2H_5O	58	needle	DMF + H_2O	$C_{24}H_{22}O_2N_4S$	66.96	5.15	13.02	66.96	4.97	13.09	1742	1200	1245 1177
Cl	26	prism	DMF + H_2O	$C_{22}H_{17}ON_4SCl$	62.78	4.07	13.31	63.06	4.06	13.78	1742	1187	

N²-Alkylthiocarbamoyl-5,5-diphenylglycocyamidine (XII)——To a solution of 0.01 mole of 1-alkyl-3-amidino-2-thiourea maleate in 50—150 ml of dehyd. EtOH was added with stirring an ethanolic solution of NaOEt prepared by dissolving 0.01 atom of Na in a small amount of EtOH. The precipitates deposited

Table IV. N^2-Alkylthiocarbamoyl-5,5-diphenylglycocyamidine



R	Yield (%)	Appearance	Recryst. solvent	Formula	Analysis % Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} (CO)
CH_3	13	needle	EtOH	$C_{17}H_{16}ON_4S$	62.95	4.97	17.28	63.27	4.76	17.16	1688
C_2H_5	78	needle	EtOH	$C_{18}H_{18}ON_4S$	63.89	5.36	16.56	63.44	5.09	16.28	1688
n-C_3H_5	17	needle	EtOH	$C_{19}H_{20}ON_4S$	64.76	5.72	15.90	64.94	5.48	15.77	1695

were filtered off and to the filtrate was added 0.01 mole of benzil. After the solution was heated for 10 hr under reflux, the solution was evaporated to dryness and the residue was recrystallized from EtOH. The compounds obtained did not show a regular melting point. Detailed data were summarized in Table IV.

Pyrolysis of 2-Arylthiocarbamoyl-5,5-diphenylglycocyamidine——2-Arylthiocarbamoyl-5,5-diphenylglycocyamidine was heated for 1 min at 200—250° under fusion. Solidified mass on cooling was recrystallized from EtOH to give 5,5-diphenylglycocyamidine which was identified by mixed melting point determination and comparison of the IR spectrum with an authentic sample obtained by the procedure described above.

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