AMINO NITRILES

III. REACTION OF AMINO NITRILES WITH ISOTHIURONIUM SALTS[1]

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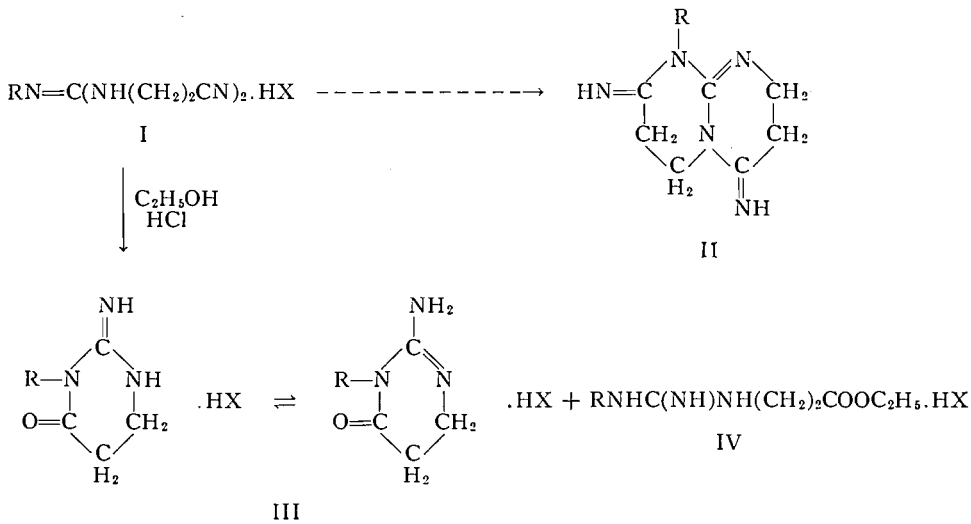
ABSTRACT

N-Substituted-N′,N″-di-(2-cyanoethyl)-guanidines have been cyclized with the elimination of acrylonitrile to 2-imino-3-substituted-4-keto-hexahydropyrimidines. These pyrimidine derivatives also were prepared by treating 1-substituted-3-(2-cyanoethyl)-S-methyl isothiuronium iodide salts with ammonia. 1-(3,4-Dichlorobenzyl)-3-(2-cyanoethyl)-urea was cyclized in the presence of absolute ethanolic hydrogen chloride to 2,4-diketo-3-(3,4-dichlorobenzyl)-hexahydropyrimidine.

A series of N-substituted-N′,N″-di-(2-cyanoethyl)-guanidines (I) (Table IA) was prepared from the corresponding thioureas (Table IB) in order to study their propensity for cyclization. The desired bicyclic derivatives (II) were not obtained. Under the reaction



conditions employed, the guanidine derivatives (I) lost 1 mole equivalent of acrylonitrile and the monocyclic 2-imino-3-substituted-4-keto-hexahydropyrimidines (III) were formed together with N-substituted-N′-(2-carbethoxyethyl)-guanidine (IV). When N-(3,4-dichlorobenzyl)-N′,N″-di-(2-cyanoethyl)-guanidine (I, R = 3,4-$Cl_2C_6H_3CH_2$) or its hydrochloride or hydroiodide salts were refluxed in absolute ethanol for 8 hours, the original compounds were recovered unchanged.

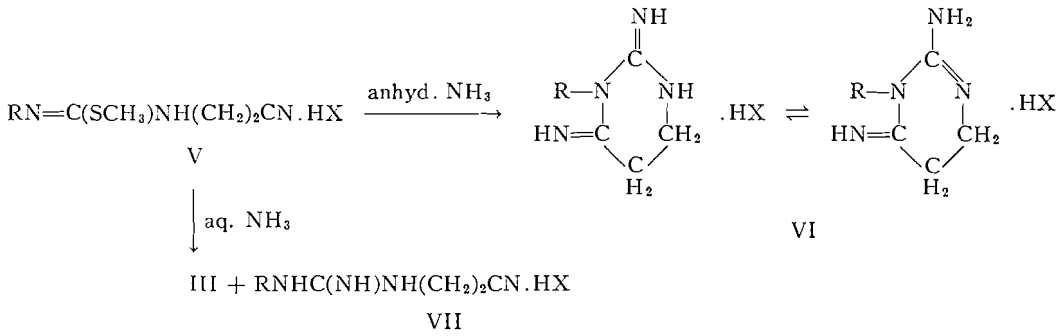
1-Phenyl-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide (V, R = C_6H_5) on treatment with anhydrous ammonia in ethanol or anhydrous α-aminoisobutyronitrile gave 2,4-diimino-3-phenyl-hexahydropyrimidinium iodide (VI, R = C_6H_5). When aqueous

[1]*Contribution No. 33.*

TABLE I

R	M.p. (°C)	Yield (%)	Formula	C		H		N		X or S	
				Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
A. Guanidine derivatives, $RN{=}C(NH(CH_2)_2CN)_2.HX$											
C_6H_5	208.5–209	59.6	$C_{13}H_{16}IN_5$*	42.30	42.38	4.37	4.38	18.97	18.72	34.38	34.50
	200.5–202	63.8	$C_{19}H_{18}N_8O_7$†	48.51	48.92	3.86	3.97	23.81	23.83		
3,4-$Cl_2C_6H_3$	187–188	90.2	$C_{13}H_{14}Cl_2IN_5$*	35.64	35.67	3.22	3.27	15.99	15.49	45.15	45.12
	218.5–219	79.8	$C_{19}H_{16}Cl_2N_8O_7$†	42.33	42.55	2.99	3.06	20.77	20.41	13.15	13.01
	228–229	80.0	$C_{13}H_{14}Cl_3N_5$‡	45.03	45.32	4.07	4.32	20.20	19.99	30.68	30.61
	180–181	79.3	$C_{13}H_{13}Cl_2N_5$§	50.34	50.35	4.22	4.37	22.58	22.36	22.86	22.68
3,4-$Cl_2C_6H_3CH_2$	156–157	67.1	$C_{20}H_{18}Cl_2N_8O_7$†	43.42	43.70	3.28	3.42	20.25	20.21	12.82	12.82
B. Thiourea derivatives, $RNHC(S)NH(CH_2)_2CN$											
CH_3	115.5–116	93‖	$C_5H_9N_3S$	41.94	41.98	6.33	6.36	29.35	29.60	22.39	22.22
C_6H_5	123.5–125	95¶									
3,4-$Cl_2C_6H_3$	174.5–175.5	91.2	$C_{10}H_9Cl_2N_3S$**	43.79	43.76	3.31	3.24	15.33	15.07	11.69	11.78
3,4-$Cl_2C_6H_3CH_2$	122–122.5	89.7	$C_{11}H_{11}Cl_2N_3S$††	45.83	45.95	3.85	3.91	14.58	14.36	11.13	10.87

*Hydroiodides.
†Picrates.
‡Hydrochloride.
§Free base.
‖Reported m.p. 112–113°, D. J. Brown, J. Appl. Chem. (London), **7**, 109 (1957).
¶Reported m.p. 123–124°, A. F. McKay *et al.*, J. Am. Chem. Soc. **81**, 4328 (1959).
**Cl: calc. 25.86, found 26.18.
††Cl: calc. 24.60, found 24.43.



ammonia was employed in the same reaction, then the corresponding 2-imino-3-substituted-4-keto-hexahydropyrimidinium salts (III) were isolated. Treatment of 1-(3,4-dichlorobenzyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide (V, R = 3,4-$Cl_2C_6H_3CH_2$) with aqueous ammonia gave a mixture of 2-imino-3-(3,4-dichlorobenzyl)-4-keto-hexahydropyrimidinium iodide (III, R = 3,4-$Cl_2C_6H_3CH_2$) and N-(3,4-dichlorobenzyl)-N′-(2-cyanoethyl)-guanidinium iodide (VII, R = 3,4-$Cl_2C_6H_3CH_2$). When 1-methyl-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide was heated under reflux in anhydrous ethanolic ammonia solution, it gave N-methyl-N′-(2-cyanoethyl)-guanidinium iodide instead of the expected 2,4-diimino-3-methyl-hexahydropyrimidinium iodide (VI, R = CH_3).

In order to obtain the 2,4-diimino-3-substituted hexahydropyrimidine salts (VI) strictly anhydrous conditions must be employed. The presence of moisture during reaction or during crystallization will convert these salts (VI) into the corresponding 2-imino-3-substituted-4-keto-hexahydropyrimidine salts (III). Also, crystallization of 1-(3,4-dichlorophenyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide (V, R = 3,4-$Cl_2C_6H_3$) from ethanol–ether solution gave some 2-keto-3-(3,4-dichlorophenyl)-4-imino-hexahydropyrimidinium iodide.

Attempts (1) to cyclize 1,3-di-(2-cyanoethyl)-urea and 1-(2-cyanoethyl)-3-(cyanomethyl)-urea by refluxing in ethanol solution were unsuccessful. Now 1-(2-cyanoethyl)-3-(3,4-dichlorobenzyl)-urea has been cyclized by heating with anhydrous ethanolic hydrogen chloride. In the presence of 9.5 mole equivalents of hydrogen chloride an 83% yield of 1-(3,4-dichlorobenzyl)-3-(2-carbethoxyethyl)-urea and an 11.9% yield of 2,4-diketo-3-(3,4-dichlorobenzyl)-hexahydropyrimidine were obtained. The latter compound was obtained in 65% yield when the hydrogen chloride was reduced to 1.2 mole equivalents.

Infrared Spectra

The pyrimidines which are reported here have been described as hexahydropyrimidine derivatives. Spectral evidence (2, 3) at present favors the ketonic structures for 2-hydroxy-, 4-hydroxy-, and 2,4-dihydroxy-pyrimidines. Moreover, the spectra given in Table II indicate that the 4-amino group in this series of 2,4-diamino- and 2-keto-4-amino-dihydropyrimidines exists in the imino form. The amino group in position 2 of the dihydropyrimidines probably exists in the amino form but no conclusion can be drawn from the present spectral data. In this investigation the infrared spectra were used mainly to confirm the formation of cyclic reaction products. A number of the band assignments in the 1500–1750 cm^{-1} region for pyrimidines are still regarded as tentative.

The C ≡ N stretching band between 2250 and 2265 cm^{-1} is a weak band and it disappears completely with some of the salts where the general absorption is high in this region.

TABLE II

Infrared absorption band (cm^{-1}) assignments*

Compounds	Stretching modes				Bending modes
	N—H	C≡N	C=O	C=N	N—H
2,4-Diimino-3-phenyl-hexahydropyrimidinium chloride	3100 (br)			1674, 1638	1615, 1555, 1540
2,4-Diimino-3-(3,4-dichlorobenzyl)-hexahydropyrimidinium chloride	3120			1672, 1627	1568, 1557
2-Keto-3-(3,4-dichlorophenyl)-4-imino-hexahydropyrimidinium iodide	3340, 3180		1683	1745	1608
2-Imino-3-phenyl-4-keto-hexahydropyrimidinium chloride	3180		1730	1680	1613
2-Imino-3-(3,4-dichlorobenzyl)-4-keto-hexahydropyrimidinium chloride	3290, 3180, 3080		1730	1677	1607
2,4-Diketo-3-(3,4-dichlorobenzyl)-hexahydropyrimidine	3245, 3100		1725	1690	1570
1-(3,4-Dichlorobenzyl)-3-(2-carbethoxyethyl)-urea	3350		1726, 1613		1583
1-Methyl-3-(2-cyanoethyl)-thiourea	3345, 3300	2260			1560, 1508
1-(3,4-Dichlorophenyl)-3-(2-cyanoethyl)-thiourea	3400, 3310	2260			1555, 1515
N-Phenyl-N′,N″-di-(2-cyanoethyl)-guanidinium chloride	3245			1642	1604, 1567
N-(3,4-Dichlorophenyl)-N′,N″-di-(2-cyanoethyl)-guanidinium chloride	3220, 3150, 3050	2255		1660	1578, 1553
N-Methyl-N′-(2-cyanoethyl)-guanidinium iodide	3380, 3240, 3175			1638	1620, 1567, 1545
N-(3,4-Dichlorobenzyl)-N′-(2-cyanoethyl)-guanidinium iodide	3320, 3240, 3170			1647	1615, 1542
1-Methyl-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide	3450, 3260, 3160	2265		1613	1560, 1528
1-Phenyl-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide	3170	2250		1608	1589, 1517

*Nujol mulls of the crystalline compounds were used for spectral analyses.

EXPERIMENTAL[2]

1-Substituted-3-(2-cyanoethyl)-thioureas

All of the 1-substituted-3-(2-cyanoethyl)-thioureas which are listed in Table 1B were prepared by the following procedure for the preparation of 1-methyl-3-(2-cyanoethyl)-thiourea.

A solution of methyl isothiocyanate (5.4 g, 0.075 mole) in benzene (20 ml) was added slowly to a stirred solution of 3-aminopropionitrile (5.2 g, 0.075 mole) in benzene (15 ml) while the temperature was maintained at 20–30°. After addition was complete, the stirring was continued at room temperature for 1 hour. The thiourea was recovered by filtration and the product was purified by crystallizing from ethanol.

1-Phenyl-3-(2-cyanoethyl)-S-methyl-isothiuronium Iodide

Methyl iodide (7.4 g, 0.052 mole) was added over a period of 5 minutes to a refluxing solution of 1-phenyl-3-(2-cyanoethyl)-thiourea (9.73 g, 0.047 mole) in absolute methanol (75 ml). After the heating under reflux had been continued for 3 hours, the solution was evaporated to dryness *in vacuo*. The oily product crystallized on trituration with acetone (50 ml), yield 15.1 g (92.6%). Three crystallizations from absolute ethanol – ether (3:1) solution raised the melting point from 152–159° to 165–167°. Anal. calc. for $C_{11}H_{14}IN_3S$: C 38.04, H 4.06, I 36.55, N 12.10, S 9.23%; found: C 38.07, H 4.12, I 36.40, N 12.07, S 9.05%.

A picrate (m.p. 139–141°) was formed in 72% yield in the usual manner in aqueous solution. Anal. calc. for $C_{17}H_{16}N_6O_7S$: C 45.53, H 3.60, N 18.74%; found: C 45.83, H 3.87, N 18.51%.

1-Methyl-3-(2-cyanoethyl)-S-methyl-isothiuronium Iodide

1-Methyl-3-(2-cyanoethyl)-thiourea (9.3 g, 0.065 mole) was methylated by the procedure described above for the methylation of 1-phenyl-3-(2-cyanoethyl)-thiourea with the exception that the reflux period was 1 hour. After evaporation of the solvent *in vacuo*, the residual colorless oil was triturated with absolute ethanol. The crystals (m.p. 109–113°) were recovered by filtration, yield 4.3 g (30.2%). Three crystallizations from absolute ethanol raised the melting point to 116–117°. Anal. calc. for $C_6H_{12}IN_3S$: C 25.27, H 4.24, I 44.50, N 14.73, S 11.25%; found: C 25.16, H 4.39, I 44.34, N 14.61, S 11.25%.

1-(3,4-Dichlorophenyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium Iodide

1-(3,4-Dichlorophenyl)-3-(2-cyanoethyl)-thiourea (10.95 g, 0.04 mole) and methyl iodide (6.25 g, 0.044 mole) in methanol (75 ml) were heated under reflux for 3 hours. Evaporation of the solvent *in vacuo* gave 16.5 g (99.5%) of a semicrystalline product. Since this product lost methyl mercaptan readily it was used without further purification for the next reaction.

An attempt to purify a sample (8.25 g) of the semicrystalline product by crystallizing from ethanol–ether (5:1) solution gave 2.1 g of a white crystalline product melting at 176–288°. This product did not contain sulphur and several crystallizations from ethanol raised the melting point to 301–301.5° decomp. (evac. cap.). Anal. calc. for $C_{10}H_{10}Cl_2IN_3O$: C 31.11, H 2.61, N 10.88, total halogen 51.25%; found: C 31.43, H 2.67, N 11.04, total halogen 50.74%. This product was identified by analyses and infrared spectrum as 2-keto-3-(3,4-dichlorophenyl)-4-imino-hexahydropyrimidine.

1-(3,4-Dichlorobenzyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium Iodide

1-(3,4-Dichlorobenzyl)-3-(2-cyanoethyl)-thiourea (7.35 g, 0.025 mole) and methyl iodide (3.62 g, 0.025 mole) in absolute methanol were stirred at room temperature for 1 hour. The temperature was increased to 45° and the stirring was continued for 15 minutes. On the addition of ether to the cooled solution, crystals (m.p. 127–128°) separated, yield 6.3 g (57.5%). The melting point was not changed by recrystallization. Anal. calc. for $C_{12}H_{14}Cl_2IN_3S$: C 33.51, H 3.28, total halogen 46.00, N 9.77, S 7.45%; found: C 33.50, H 3.40, total halogen 45.56, N 10.06, S 7.38%.

A sample of the hydroiodide salt in methanol solution was converted into its picrate (m.p. 122.5–123.5°) in the usual manner. Anal. calc. for $C_{18}H_{16}Cl_2N_6O_7S$: C 40.69, H 3.04, Cl 13.35, N 15.82, S 6.03%; found: C 40.74, H 3.25, Cl 13.38, N 15.58, S 6.14%.

N-Substituted-N′,N″-di-(2-cyanoethyl)-guanidines

The N-substituted-N′,N″-di-(2-cyanoethyl)-guanidines listed in Table IA were all prepared by the following general procedure.

1-(3,4-Dichlorophenyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide (8.32 g, 0.02 mole) and 3-aminopropionitrile (1.4 g, 0.02 mole) were heated under reflux in absolute ethanol (50 ml) for 3 hours after which the evolution of methyl mercaptan had ceased. Evaporation of the solvent gave a crystalline residue which was purified by crystallizing from absolute ethanol.

A picrate (m.p. 218.5–219°) was prepared in 79.8% yield from aqueous solution in the usual manner. It was purified by crystallization from water.

Conversion of the guanidinium iodides into their corresponding hydrochlorides or free bases was accomplished by one of the following methods.

[2]*All melting points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois.*

Method A. A solution of N-(3,4-dichlorophenyl)-N′,N″-di-(2-cyanoethyl)-guanidinium iodide (2 g, 0.0046 mole) in absolute ethanol (30 ml) was passed through a column of IRA 400 resin (25 ml in the chloride form). The resin was washed with methanol (50 ml) and the combined washings and eluate were taken to dryness *in vacuo*. The crystalline hydrochloride was obtained in 80% (1.26 g) yield. It was crystallized from ethanol–ether (3:2) solution.

Method B. A solution of N-(3,4-dichlorophenyl)-N′,N″-di-(2-cyanoethyl)-guanidinium iodide (0.32 g, 0.0007 mole) in absolute ethanol was treated with 1.5 mole equivalents of 4% aqueous sodium hydroxide solution at 0°. It was then held at room temperature for 15 minutes after which the solution was diluted with water. The aqueous solution was extracted with chloroform. After the combined chloroform extracts had been washed with water, the chloroform layer was treated with excess 1 *N* hydrochloric acid. An oil separated which crystallized immediately, yield 0.19 g (76.9%).

The free base was obtained by passage of a solution of the iodide salt (0.62 g) in absolute ethanol (45 ml) through a column of IRA 400 resin (in the hydroxyl form). The resin column was washed with ethanol (80 ml) and the washings and eluate were evaporated to dryness *in vacuo* under nitrogen. N-(3,4-Dichlorophenyl)-N′,N″-di-(2-cyanoethyl)-guanidine was obtained in 79.3% (0.44 g) yield. The free base was crystallized from absolute ethanol for analyses.

2,4-Diimino-3-phenyl-hexahydropyrimidinium Iodide

1-Phenyl-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide (3.47 g, 0.01 mole) in absolute ethanol (25 ml) which had been saturated with anhydrous ammonia was heated under reflux for 12.5 hours. After evaporation of the solvent *in vacuo*, the semicrystalline product was crystallized from ethanol–ether solution. The crystals possessed a double melting point of 162–163° and 192°, yield 2.33 g (73.8%).

A sample of the hydroiodide salt in ethanol was converted into its picrate (m.p. 229–231°) in the usual manner. Anal. calc. for $C_{16}H_{15}N_7O_7$: C 46.05, H 3.62, N 23.50%; found: C 46.12, H 3.64, N 23.15%.

Reaction of 1-Phenyl-3-(2-cyanoethyl)-S-methyl-isothiuronium Iodide with 2-Aminoisobutyronitrile

A solution of 1-phenyl-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide (1.87 g, 0.005 mole) and 2-aminoisobutyronitrile (0.45 g, 0.005 mole) in absolute ethanol (25 ml) was heated under reflux for 7 hours. Since a crystalline hydroiodide could not be isolated from the reaction, the crude hydroiodide in ethanol was passed through a column of IRA 400 resin (in the chloride form). The resin was washed with ethanol and the combined washings and eluate were taken to dryness *in vacuo*. The residual semicrystalline solid crystallized on trituration with absolute ethanol, yield 0.6 g (51.7%). Crystallization from ethanol–ether (1:2) solution raised the melting point from 85–216° to 217–218°. This compound gave the correct analyses for 2,4-diimino-3-phenyl-hexahydropyrimidinium chloride. Anal. calc. for $C_{10}H_{13}ClN_4$: C 53.45, H 5.83, Cl 15.78, N 24.93%; found: C 53.55, H 5.93, Cl 16.03, N 24.87%.

The picrate (m.p. 225–230°) was formed in the usual manner from the hydrochloride salt in aqueous medium. Two crystallizations from water raised the melting point to 229°. This picrate did not depress the melting point of 2,4-diimino-3-phenyl-hexahydropyrimidinium picrate (229–231°) formed from the reaction of anhydrous ammonia with 1-phenyl-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide.

Reaction of 1-(3,4-Dichlorobenzyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium Iodide with Ammonia

Concentrated aqueous ammonia solution (5 ml) was added to 1-(3,4-dichlorobenzyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide (1.83 g, 0.004 mole) in ethanol (4 ml). After the solution had been heated under reflux for 10 hours, the solvent was removed *in vacuo*. The residual oil partially crystallized on addition of a small amount of absolute ethanol. The crystals (m.p. 262–264°, decomp.) were removed by filtration, yield 0.12 g (8.6%). Two crystallizations from aqueous ethanol raised the melting point to 267.8–268.6°. The analytical results indicate that two molecules of 2-imino-3-(3,4-dichlorobenzyl)-4-keto-hexahydropyrimidine are associated with one molecule of hydrogen iodide. Anal. calc. for $C_{22}H_{23}Cl_4IN_6O_2$: C 39.31, H 3.45, total halogen 39.98, N 12.50%; found: C 39.40, H 3.84, total halogen 39.92, N 12.39%.

A sample of the crude product in aqueous solution gave a crystalline picrate (m.p. 205–207°) in 94.5% yield on treatment with aqueous picric acid. One crystallization from aqueous ethanol raised the melting point to 206–207°. Anal. calc. for $C_{17}H_{14}Cl_2N_6O_8$: C 40.74, H 2.82, Cl 14.15, N 16.77%; found: C 41.04, H 3.08, Cl 14.00, N 16.74%.

The mother liquor from the above crude hydroiodide gave a second crystalline iodide (m.p. 157–159°) on addition of ether, yield 0.18 g (10.6%). Crystallization from ethanol–ether raised the melting point to 163.2–163.8°. This product was identified as N-(3,4-dichlorobenzyl)-N′-(2-cyanoethyl)-guanidinium iodide by elemental and infrared analyses. Anal. calc. for $C_{11}H_{13}Cl_2IN_4$: C 33.10, H 3.28, total halogen 49.57, N 14.04%; found: C 32.90, H 3.32, total halogen 49.50, N 13.86%.

A picrate (m.p. 198–198.5°) was formed in 80% yield in the usual manner from aqueous solution. Anal. calc. for $C_{17}H_{15}Cl_2N_7O_7$: C 40.80, H 3.02, N 19.60%; found: C 40.95, H 2.97, N 19.74%.

Reaction of 1-(3,4-Dichlorobenzyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium Iodide with 3-Aminopropionitrile

1-(3,4-Dichlorobenzyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide (6.89 g, 0.016 mole) and 3-aminopropionitrile (1.12 g, 0.016 mole) in absolute ethanol (40 ml) were heated under reflux for 4.5 hours. Evaporation of the solvent *in vacuo* gave 7 g of semicrystalline residue.

A portion (0.5 g) of the crude product was converted into a picrate (m.p. 60–65°) in the usual manner in water, yield 0.41 g (67%). Crystallization from aqueous acetone raised the melting point to 156–157°. The analyses are in agreement with those calculated for N-(3,4-dichlorobenzyl)-N′,N″-di-(2-cyanoethyl)-guanidine picrate. Anal. calc. for $C_{20}H_{18}Cl_2N_8O_7$: C 43.42, H 3.28, Cl 12.82, N 20.25%; found: C 43.70, H 3.42, Cl 12.82, N 20.21%.

The remainder of the original semicrystalline residue was dissolved in ethanol and passed through a column of IRA 400 resin (in the OH form). After the column was washed with ethanol, the washings and eluate were evaporated to dryness *in vacuo*. The oily product on solution in ethanol and acidification with concentrated hydrochloric acid gave a crystalline precipitate (m.p. 280–285°), yield 0.6 g (12%). One crystallization from ethanol raised the melting point to 288–290°. The analytical values for this compound agree with those calculated for 2-imino-3-(3,4-dichlorobenzyl)-4-keto-hexahydropyrimidinium chloride. Anal. calc. for $C_{11}H_{12}Cl_3N_3O$: C 42.80, H 3.92, Cl 34.46, N 13.62%; found: C 43.06, H 4.16, Cl 34.62, N 13.70%.

The picrate (m.p. 206–207°) was obtained in the usual manner from aqueous solution in 98% yield. A sample of this picrate on admixture with 2-imino-3-(3,4-dichlorobenzyl)-4-keto-hexahydropyrimidine picrate (m.p. 206–207°) from the reaction of ammonia with 1-(3,4-dichlorobenzyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide did not depress its melting point.

2-Imino-3-(3,4-dichlorophenyl)-4-keto-hexahydropyrimidine

Crude 1-(3,4-dichlorophenyl)-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide (0.83 g, 0.002 mole) was dissolved in ethanol (4 ml) and treated with an excess of concentrated ammonia (5 ml). The solution was heated under reflux for 6.25 hours. Crystals (m.p. 247°) separated from the cooled solution in 60.6% yield. Crystallization from aqueous ethanol raised the melting point to 262–262.5°. Anal. calc. for $C_{10}H_9Cl_2N_3O$: C 46.52, H 3.52, Cl 27.47, N 16.28%; found: C 46.90, H 3.53, Cl 27.16, N 16.36%.

N-Methyl-N′-(2-cyanoethyl)-guanidinium Iodide

1-Methyl-3-(2-cyanoethyl)-S-methyl-isothiuronium iodide (2.3 g, 0.008 mole) in saturated absolute ethanolic ammonia solution (25 ml) was heated under reflux for 21 hours. Evaporation of the solution to dryness *in vacuo* gave 1.92 g (93.7%) of crystals (double melting point at 159–160° and 169–170°). Crystallization from ethanol–ether (2:1) solution gave a product with a double melting point. It melted at 160°, resolidified, and remelted at 173–173.8°. Anal. calc. for $C_5H_{11}IN_4$: C 23.63, H 4.36, I 49.95, N 22.05%; found: C 23.87, H 4.35, I 50.08, N 22.00%.

1-(3,4-Dichlorobenzyl)-3-(2-cyanoethyl)-urea

A solution of 3,4-dichlorobenzyl isocyanate (5.02 g, 0.025 mole) in ether (50 ml) was added to a cooled ethereal solution of 2-aminopropionitrile (1.75 g, 0.025 mole). The reaction mixture was held at room temperature for 2 hours after which the crystals (m.p. 125–127°) were recovered by filtration, yield 6.4 g (94.5%). The melting point was raised to 133.6–134.2° by crystallizing from aqueous ethanol. Anal. calc. for $C_{11}H_{11}Cl_2N_3O$: C 48.55, H 4.07, Cl 26.06, N 15.44%; found: C 48.58, H 4.21, Cl 26.06, N 15.47%.

1-(3,4-Dichlorobenzyl)-3-(2-carbethoxyethyl)-urea

A solution of 1-(3,4-dichlorobenzyl)-3-(2-cyanoethyl)-urea (2.16 g, 0.008 mole) in ethanolic hydrogen chloride (2.8 g, 0.077 mole of hydrogen chloride in absolute ethanol (20 ml)) was heated under reflux for 3.5 hours. When the solution was cooled, a small amount of ammonium chloride separated, yield 0.35 g. The filtrate was evaporated to dryness and the semicrystalline residue was triturated with ethanol (10 ml). The crystals (m.p. 183–185°) were removed by filtration, yield 0.26 g (11.9%). These crystals were identified as 2,4-diketo-3-(3,4-dichlorobenzyl)-hexahydropyrimidine by a mixed melting point determination.

The filtrate on evaporation yielded a solid which melted at 89–93°. Recrystallization from ethanol–ether solution raised the melting point to 110.5–111°. The yield of 1-(3,4-dichlorobenzyl)-3-(2-carbethoxyethyl)-urea was 2.1 g (83%). Anal. calc. for $C_{13}H_{16}Cl_2N_2O_3$: C 48.91, H 5.05, Cl 22.21, N 8.78%; found: C 48.96, H 5.17, Cl 22.20, N 8.90%.

2,4-Diketo-3-(3,4-dichlorobenzyl)-hexahydropyrimidine

1-(3,4-Dichlorobenzyl)-3-(2-cyanoethyl)-urea (0.68 g, 0.0025 mole) in ethanolic hydrogen chloride (0.1 g, 0.003 mole) in absolute ethanol (5 ml) was heated under reflux for 2.3 hours. The reaction mixture on cooling gave crystals (m.p. 180–183°) of 2,4-diketo-3-(3,4-dichlorobenzyl)-hexahydropyrimidine, yield 0.46 g (65%). One crystallization from absolute ethanol raised the melting point to 183.5–185°. Anal. calc. for $C_{11}H_{10}Cl_2N_2O_2$: C 48.37, H 3.69, Cl 25.96, N 10.26%; found: C 48.07, H 3.88, Cl 26.01, N 10.22%.

Attempted Cyclization of N-Substituted-N′,N″-di-(2-cyanoethyl)-guanidines

Method A. N-(3,4-Dichlorobenzyl)-N′,N″-di-(2-cyanoethyl)-guanidinium chloride (1 g) in absolute ethanol was refluxed for 8 hours. After concentration and cooling of the solution, the starting material was recovered unchanged in 81.5% yield. The recovered material was identified by a mixed melting point determination.

Under similar conditions both N-(3,4-dichlorobenzyl)-N′,N″-di-(2-cyanoethyl)-guanidine and its hydroiodide salt were recovered unchanged.

Method B. N-Phenyl-N′,N″-di-(2-cyanoethyl)-guanidinium chloride (0.97 g, 0.0035 mole) was heated under reflux for 2 hours in absolute ethanol (7.5 ml) containing hydrogen chloride (1 g, 0.028 mole). The reaction mixture was cooled and the crystals (m.p. 280–282°) were recovered by filtration, yield 0.43 g (54.8%). Two crystallizations from absolute ethanol raised the melting point to 292.4–292.8°. This product was identified as 2-imino-3-phenyl-4-keto-hexahydropyrimidinium chloride by elemental analyses and infrared spectrum. Anal. calc. for $C_{10}H_{12}ClN_3O$: C 53.21, H 5.36, Cl 15.71, N 18.62%; found: C 53.47, H 5.44, Cl 15.58, N 18.89%.

The picrate (m.p. 242–244°) was formed in 41% yield in the usual manner from aqueous ethanol. Anal. calc. for $C_{16}H_{14}N_6O_8$: C 45.94, H 3.37, N 20.09%; found: C 45.83, H 3.39, N 19.73%.

The mother liquor from the crystals was evaporated to dryness *in vacuo*. A mixture of oil and crystals was obtained, yield 1.14 g. A portion (0.23 g) of this mixture in absolute ethanol on treatment with aqueous picric acid gave a crystalline picrate (m.p. 133.2–133.8°), yield 0.15 g (38.7%). The melting point was raised to 134.4–134.8° by two crystallizations from aqueous ethanol. The analyses agree with those calculated for the picrate of 1-phenyl-3-(2-carbethoxyethyl)-guanidine. Anal. calc. for $C_{18}H_{20}N_6O_9$: C 46.54, H 4.34, N 18.10%; found: C 46.65, H 4.36, N 18.29%.

When N-phenyl-N′,N″-di-(2-cyanoethyl)-guanidinium chloride was treated under the same conditions as above using approximately 1 mole equivalent of hydrogen chloride instead of 8, the starting material was recovered in 44.3% yield and a 42% yield of 2-imino-3-phenyl-4-keto-hexahydropyrimidinium chloride was obtained.

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