PYRIMIDINES AND CONDENSED DERIVATIVES, III* THE SYNTHESIS OF SOME ISOCYTOSINES AND RELATED IMIDAZO[1,2-a]- AND -[1,2-c]PYRIMIDINONES

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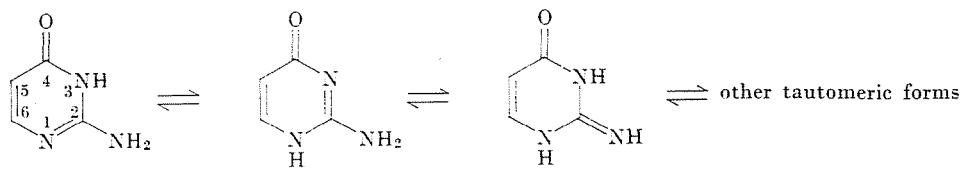
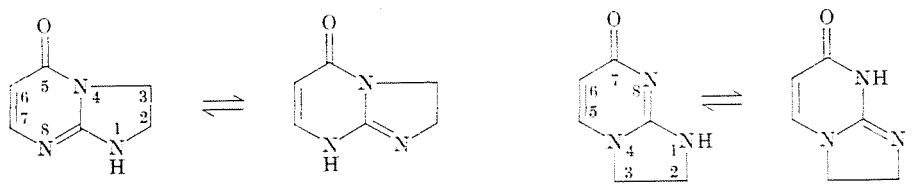
In Part I [2] of the present series the UV and IR spectra of isocytosine **(1)** and of a series of its derivatives (including such derivatives in which a six-membered carbocycle has been fused to side *e* of the isocytosine ring) as well as of related imidazo[1,2-*a*]pyrimidinones **(2, 3)** has been described.



1a **1b** **1c**



2a **2b** **3a** **3b**

All these compounds were either at least potentially tautomeric (similarly to the parent isocytosine) the three principal tautomeric forms being the conjugated **(1a, 2a)**, the cross-conjugated **(1b, 3a)** and the "exocyclic" **(2b, 3b)**, or had, as a result of the introduction of the maximum possible number of *N*-substituents, "fixed" structures. The actual structures of the potentially tautometric compounds have been derived by spectroscopic means.

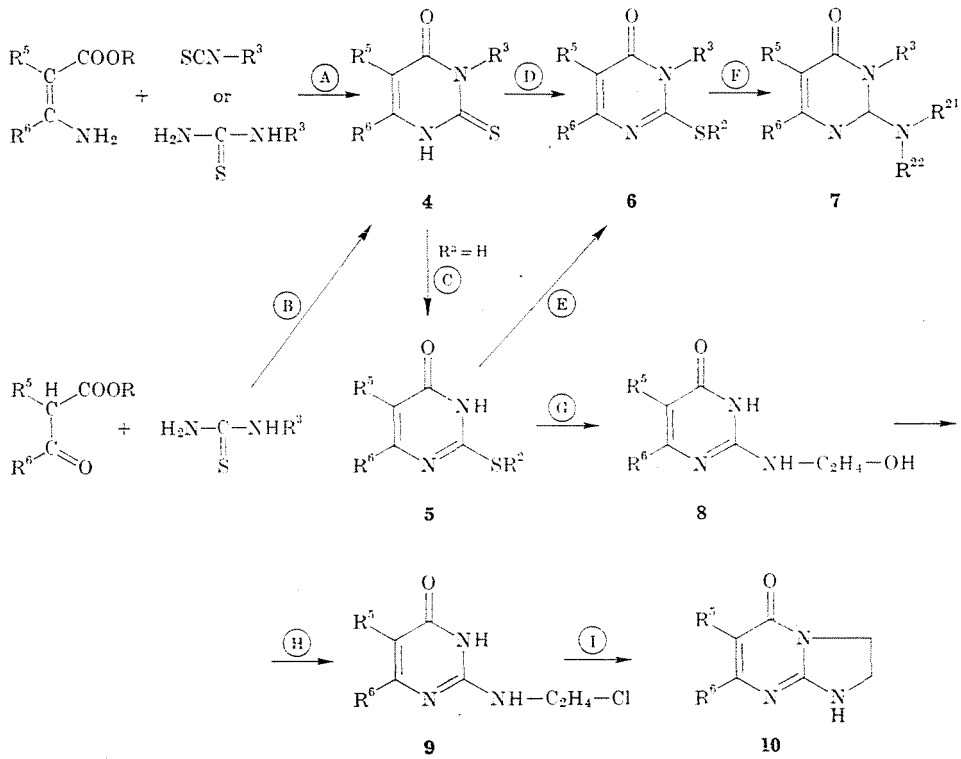
In the present paper we wish to describe the synthesis of those com-

* For Part II see Ref. [1].

pounds in Part I which were unknown. For the naming of the potentially tautometric compounds the names of their principal tautomeric modifications will be adopted and, in case the particular synthesis involves ring closures which might take place in more than one direction, emphasis will be laid on the proof of the actual orientation in these cyclizations. Similarly, detailed proofs will be given of the actual sites of alkylations performed in the course of the various syntheses in all cases where, theoretically, more than one alkylation product could be formed.

Our methods applied for the syntheses of the conjugated isocytosines **(7** and **8)** and imidazopyrimidinones **(10)** are shown in Chart 1.

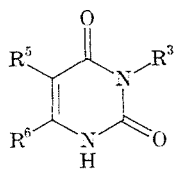
Chart 1



The starting 2-thiouracils **(4)** themselves were obtained by condensing the appropriate β-amino-α,β-unsaturated esters with isothiocyanates [3a, 4a] or thioureas [4b] (Method A) or by condensing β-oxoesters (or their equivalents) with thioureas [3b, 4c] (Method B). Only the first of these syntheses is always structure-proving, the latter two only if applied to *un*substituted thioureas ($R^3 = H$).

Methylation and benzylation of the thiouracils **(4)** in alkaline media furnished in most cases the corresponding *S*-substituted derivatives **5** and **6,**

respectively, both when $R^3 = H$ and $R^3 \neq H$ [4c, 5a]. Further alkylation of compounds **5** also resulted in smooth formation of the corresponding compounds **6.** The orientation in the latter reaction was proved either by establishing the presence of the conjugated chromophore system by UV and IR spectroscopy [2],* or by demonstrating the identity of the products obtained by the sequences *A* (or *B*, $R^3 \neq H$) → *D* and *B* ($R^3 = H$) → *C* → *E*, respectively. In a limited number of cases these structure assignments were corroborated by hydrolysis of compounds **6** to the corresponding uracils **11.**



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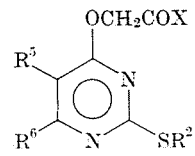

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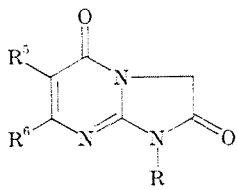

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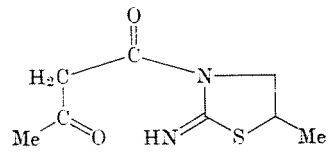

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When 2-methylthio-4(3*H*)-pyrimidinones **(5)** were reacted with bromo acetamide in the presence of base, isomeric *O*-substituted derivatives **12** ($X = NH_2$) were obtained in addition to the normal *N*(3)-substituted products **6** ($R^3 = —CH_2CONH_2$). The structures of the latter products were established by acid hydrolysis to the corresponding *N*-unsubstituted uracils (**11**, $R^3 = H$) and/or by UV and IR spectroscopy, whereby the presence of the aromatic pyrimidine chromophore (*cf.* Ref. [6]) and the absence of a lactam carbonyl group (as *e.g.* in compounds **6**) was readily demonstrated. When 6-methyl-2-methylthio-4(3*H*)-pyrimidinone (**5**, $R^2 = R^6 = Me$, $R^5 = H$) was reacted with methyl and ethyl bromoacetate, only the *O*-substituted products **12** ($R^2 = R^6 = Me$, $R^5 = H$, X = OMe and OEt, respectively) could be isolated whose structures were established by ammonolysis leading to **12** ($R^2 = R^6 = Me$, $R^5 = H$, $X = NH_2$).

Ammono- and aminolyses of compounds **5** and **6** to furnish compounds of type **7** and **8** took place smoothly (*cf.* Ref's [3b, 5b]). In the case of compounds **6** ($R^3 = —CH_2COOR$ and $—CH_2CONH_2$) ammono- and aminolyses in

* For the UV evidence *cf.* Ref. [6].

the substituent R^3, as well as, depending on the reaction conditions, ring closures to yield bi- or tricyclic compounds of type **13** were found to take place in addition to the desired aminolyses of the methylthio groups. Compounds of type **13** were earlier obtained by non-structure-proving syntheses [7]. In the course of the piperidinolysis of compound **5** (R^2 = Me, R^5 = H, R^6 = = —CH_2—CH_2—COOH) a different side reaction was observed: the side chain carboxyl group of part of the starting compound was converted into the —$CONC_5H_{10}$ group. In one case the starting compound **6** was successfully replaced by its 2-nitramino analogue, see Experimental.

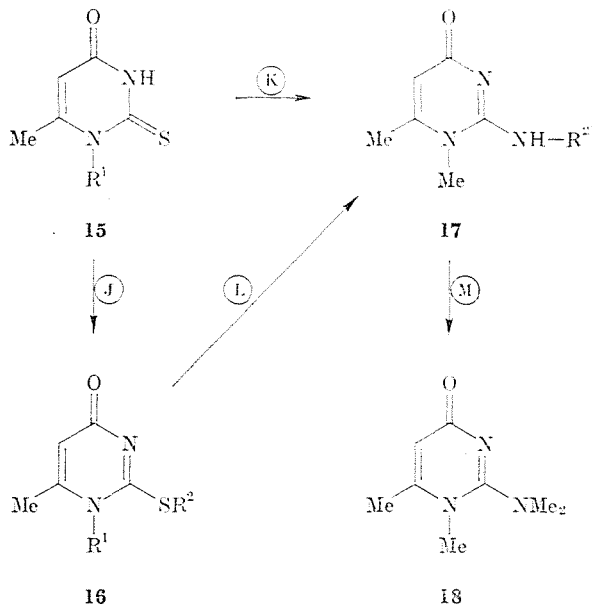
If, in the compounds **7** and **8**, respectively, R^5 was H, bromine could readily be introduced into this position (*cf.* Ref. [1]). In a limited number of cases the substituent R^6 in a compound of type **7** was subsequently modified.

The compounds **8** were transformed into the corresponding imidazopyrimidinones **10** in a two-step sequence (steps *H* and *I*). The site of ring closure of the intermediates **9**, as well as the tautomeric structures of the products **(10)** follow from the UV and IR spectra of the latter from which the presence of a conjugated chromophore system can unequivocally be deduced (*cf.* Ref. [2]).

A bicyclic analogue of the type **6** compounds, *viz.* 2,7-dimethyl-2,3-dihydrothiazolo[2,3-*b*]pyrimidin-5-one (**6**, $R^2 + R^3$ = —CHMe—CH_2 — , R^5= H, R^6 = Me) [8] has been prepared by a novel method through ring closure of the 3-acyl-2-iminothiazolidine **14**.

1,6-Dimethyl-2-thiouracil (**15**, R^1 = Me) was selected as the starting compound for the preparation of the cross-conjugated isocytosines **17** and **18**, see Chart 2.

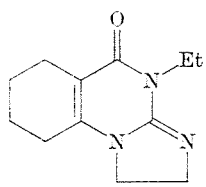
Chart 2



The starting compound was in most cases transformed into its *S*-methyl or *S*-benzyl derivative (Method *J*), and the latter were subsequently aminolysed (Method *L*), but **17** (R^{21} = —CH_2CH_2OH) could also directly be obtained by reacting **15** (R^{21} = Me) with 2-aminoethanol. The identity of the two products obtained by the sequence *J* and *L*, and directly by Method *K*, respectively, as well as the formation of thiols in the aminolysis step *L* clearly demonstrates the site of alkylation is step *J*. Methylation of **17** (R^{21} = Me) furnished the non-tautomeric compound **18**. The site of methylation was deduced from the IR and UV spectra, showing the presence of an amide group and, at the same time, the *absence* of the type **2** exocyclic chromophore system, respectively (*cf.* Ref. [2]).

1,6-Dimethyl-2-thiouracil (**15**, R^1 = Me) had been obtained by LACEY by condensing *N*-methylthiourea with diketene [9]. Surprisingly, when substituting *N*-phenyl- for *N*-methylurea, 6-methyl-3-phenyl-2-thiouracil (**4**, R^3 = Ph, R^5 = H, R^6 = Me) was obtained rather than the 1-phenyl isomer (**15**, R^1 = Ph) [9]. We reacted *N*-allylthiourea with diketene and obtained thereby 1-allyl-6-methyl-2-thiouracil (**15**, R^1 = C_3H_5), the proof of structure of the product coming from its non-identity with the known [8] 3-allyl isomer (**4**, R^3 = C_3H_5, R^5 = H, R^6 = Me), as well as from its transformation into 2,5-dimethyl- and 2-bromomethyl-5-methyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]-pyrimidin-7-one (**16**, $R^1 + R^2$ = —CH_2—CHMe— and $R^1 + R^2$ = = —CH_2—CH(CH_2Br)—, respectively) both possessing, according to their IR spectra, a cross-conjugated chromophore system. The orientation in the ring closure leading to the 2,5-dimethyl derivative, *viz.* that the sulfur containing ring of this product is five-membered, was established by the NMR spectrum which has two *C*-methyl signals.

Aminolysis of **16** ($R^1 + R^2$ = —CH_2—CHMe—) with 2-aminoethanol effected not only cleavage of the S—C(8a) bond but that of the N(4)—C(3) bond as well, and furnished, under elimination of the complete carbon-sulfur skeleton of the thiazole cycle, 2-(2-hydroxyethylamino)-6-methyl-4(3*H*)-pyrimidinone (**8**, R^5 = H, R^6 = Me).



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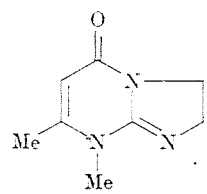

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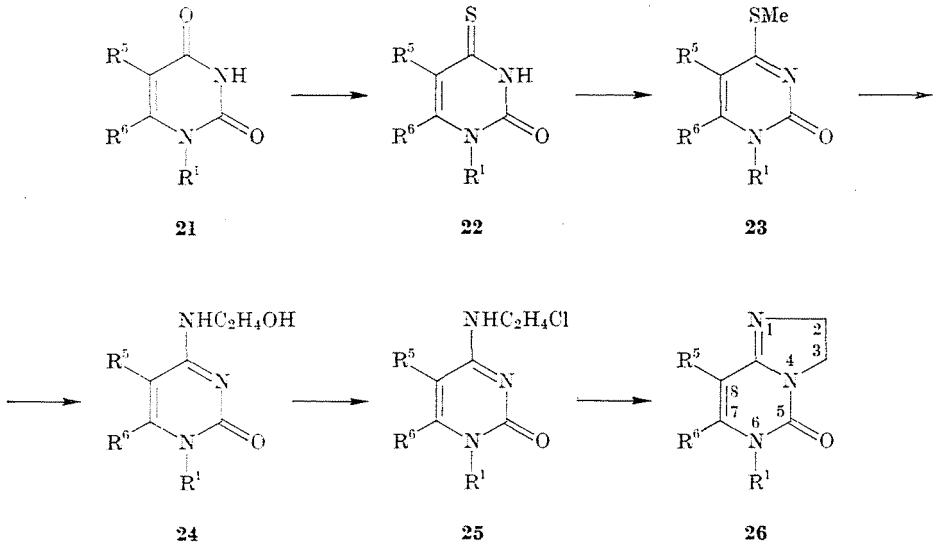
The two condensed isocytosines **19** and **20**, containing exocyclic C=N bonds (with respect two the pyrimidine ring) were obtained by thermal ring

closure of compounds **7** ($R^{21} = -CH_2CH_2Cl$, $R^{22} = H$, $R^3 = Et$, $R^5 + R^6 = -(CH_2)_4-$) and **17** ($R^{21} = -CH_2CH_2Cl$), respectively.

Chart 3



In addition to the monocyclic and condensed isocytosines thus far mentioned, a limited number of cytosines **(24)** and related imidazo[1,2-*c*]pyrimidinones **(26)** have been prepared. The starting 4-thiouracils **(22)** were obtained by selective thiation of the corresponding uracils **(21)** with phosphorus pentasulfide in pyridine, *cf.* Ref's [10a—c]. That it was indeed the 4-oxo oxygen which became replaced by sulfur, follows from the non-identity of the products with their known 2-thiouracil isomers of Type **4**. As shown by the considerable differences of their UV spectra from those of their *S*-methyl derivatives **(23)**, the 4-thiouracils exist, at least predominantly, in their oxo-thioxo forms as depicted in Chart 3. The site of methylation was established in the subsequent aminolysis step of the *S*-methyl derivatives **23**, in the course of which methanethiol was amply evolved. The presence of the conjugated chromophore system in the resulting cytosines **24** has been demonstrated by SZER and SHUGAR [11]. Ring closure of the cytosines **24** to the corresponding imidazo[1,2-*c*]pyrimidinones **26** has been effected by a two-step sequence similar to that used in the imidazo[1,2-*a*]pyrimidinone series.

Experimental

3-Ethyl-2-thioxo-1,2,5,6,7,8-hexahydroquinazolin-4(3H)-one (4, R^3 = Et, $R^5 + R^6 = -(CH_2)_4-$)

a) (Method A) A mixture of ethyl 3,4,5,6-tetrahydroanthranilate (7.2 g; 43 mmoles), ethyl isothiocyanate (6.0 g; 69 mmoles) and ethanol (30 ml) was refluxed for 30 min. Water (50 ml) was added. The product, 3.6 g (40%), colourless crystals, m.p. 253 °C (aqueous methanol) separated on cooling.

$C_{10}H_{14}N_2OS$ (210.3). Calc'd C 57.11, H 6.70, S 15.25. Found C 57.08, H 6.75, S 15.52%.

b) (Method A) A mixture of ethyl 3,4,5,6-tetrahydroanthranilate (1.0 g; 6 mmoles) and *N*-ethylthiourea (1.0 g; 10 mmoles) was heated for 25 min at 170—180 °C in vacuum. The residue was triturated with ethanol (5 ml) to yield 0.5 g (40%) of the desired product, m.p. and mixed m.p. with the product obtained according to (a): 253 °C.

c) (Method B) Metallic sodium (0.81 g; 35 mmoles) was dissolved in ethanol (25 ml), ethyl 2-oxocyclohexanecarboxylate (3.4 g; 20 mmoles) and *N*-ethylthiourea (3.1 g; 30 mmoles) were added, and the mixture was refluxed for 2.5 hrs and concentrated to about half its original volume. Water (50 ml) was added, the solution was treated with charcoal and the filtrate was neutralized with hydrochloric acid under cooling to yield 2.5 g (61%) of a product which was identical (m.p., mixed m.p.) with the product obtained according to (a).

Ethyl 4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydro-3-quinazolineacetate (4, R^3 = = CH_2COOEt, $R^5 + R^6 = -(CH_2)_4-$) (Method A)

A mixture of ethyl 3,4,5,6-tetrahydroanthranilate (1.5 g; 9 mmoles), ethyl isothiocyanatoacetate (1.4 g; 9 mmoles) and anhydrous ethanol (5 ml) was refluxed for 25 min to yield, after being allowed to cool, 2.5 g (86%) of the desired product, colourless crystals, m.p. 231 °C (EtOH).

$C_{12}H_{16}N_2O_3S$ (268.3). Calc'd C 53.71, H 6.01, S 11.95. Found C 54.23, H 6.19, S 11.60%.

6-(3-Butenyl)-2-thiouracil (4, $R^3 = R^5 = H$, $R^6 = -(CH_2)_2-CH=CH_2$) (Method B)

Metallic sodium (6.9 g; 0.3 moles) was dissolved in ethanol (350 ml), and ethyl 3-oxo-6-heptenoate [12] (30.1 g; 0.177 moles) and thiourea (19.0 g; 0.25 moles) were added. The resulting mixture was refluxed for 4 hrs and evaporated to dryness. The residue was dissolved in water (200 ml), the insoluble impurities were filtered off and the filtrate was acidified with conc'd hydrochloric acid (25 ml) to yield 28 g (87%) of the thiouracil, colourless crystals m.p. 202 °C (aqueous ethanol).

$C_8H_{10}N_2OS$ (182.3). Calc'd N 15.37, S 17.59 Found N 15.34, 15.29, S 17.38, 17.70%.

5-(2-Hydroxyethyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydro-6-pyrimidinepropionic acid (4, $R^3 = H$, $R^5 = HOCH_2—CH_2—$, $R^6 = —CH_2CH_2COOH$) (Method B)

a) Metallic sodium (4.6 g; 20 mmoles) was added to a mixture of γ-butyrolactone (15.2 ml; 20 mmoles) and diethyl succinate (35.2 ml; 21 mmoles) at 80—90 °C. The mixture was stirred for a further 3 hrs at this temperature, acidified with 50% aqueous acetic acid (about 30 ml) and poured into saturated aqueous NaCl solution (60 ml). The organic layer was separated and the aqueous layer was extracted with three portions of ether (30 ml, each). The combined organic solutions were washed with 10% aqueous $NaHCO_3$ solution and water, and dried over $MgSO_4$. The solvent was distilled off and the residue was distilled in vacuum to yield 20.5 g (48%) of ethyl 3-(2-oxo-1,2,3,4-tetrahydro-3-furoyl)propionate, b. p. 170—172 °C/1.5 Torr, which was used without further purification in the subsequent step.

b) Metallic sodium (0.50 g; 22 mmoles) was dissolved in ethanol (30 ml), and ethyl 3-(2-oxo-1,2,3,4-tetrahydro-3-furoyl)propionate (4.3 g; 20 mmoles) and thiourea (1.5 g; 20 mmoles) were added. The resulting mixture was refluxed for 3 hrs and evaporated to dryness. The residue was worked up as described in the previous preparation to yield 1.2 g (49%) of a faint yellow crystalline powder, m.p. 245 °C (dec.; water).

$C_9H_{12}N_2O_4S$ (244.3). Calc'd N 11.47, S 13.16 Found N 11.15, S 12.89%.

4-Oxo-2-thioxo-1,2,3,4-tetrahydro-6-pyrimidinepropionic acid (4, $R^3 = R^5 = H$, $R^6 = —CH_2CH_2COOH$) (Method B)

This compound was obtained in a similar way. (Starting oxoester: dimethyl 3-oxohexanedioate [20], reaction time: 6 hrs, 69% yield.) Faint yellow crystals, monohydrate, m.p. 272—274 °C (dec.; DMF-acetone).

$C_7H_8N_2O_3S + H_2O$ (218.2). Calc'd C 38.53, H 4.62, S 14.70. Found C 39.08, H 4.78, S 14.56%.

2-Benzylthio-5,6,7,8-tetrahydro-4(3H)-quinazolinone (**5**, $R^2 = PhCH_2$, $R^5 + R^6 = —(CH_2)_4—$) (Method C)

Metallic sodium (0.76 g; 33 mmoles) was dissolved in ethanol (100 ml), 2-thioxo-1,2,5,6,7,8-hexahydro-4(3*H*)-quinazolinone (4, $R^3 = H$, $R^5 + R^6 = —(CH_2)_4—$) [13] (6.0 g; 33 mmoles) and benzyl chloride (5 ml; 43 mmoles) were added, and the mixture was refluxed for 1 hr. The sodium chloride was filtered off and the filtrate was allowed to cool to yield 8.1 g (90%) of the *S*-benzyl derivative, m.p. 203 °C (EtOH).

$C_{15}H_{16}N_2OS$ (272.4). Calc'd N 10.29, S 11.77. Found N 9.81, S 11.74%.

6-(3-Butenyl)-2-methylthio-4(3H)-pyrimidinone (**5**, R^2 = Me, R^5 = H, R^6 = CH_2=CH—CH_2CH_2—) (Method C)

A solution of methyl iodide (20 ml) in methanol (30 ml) was added by drops in about 10 min to an aqueous (200 ml) solution of 4 (R^3 = R^5 = H, R^6= CH_2=CH—CH_2—CH_2—) (24 g; 0.13 mole) and NaOH (5.5 g; 0.14 mole). The mixture was stirred for 1 hr. at r.t., and the methanol and excess methyl iodide was distilled off. The resulting aqueous suspension was slightly acidified (pH = 6) with N/1 hydrochloric acid to yield 27 g (98%) of the methylthio derivative, colourless crystals, m.p. 144 °C (aqueous methanol).

$C_9H_{12}N_2OS$ (196.3). Calc'd N 14.28, S 16.34. Found N 14.03, S 16.23, 16.02%.

6-(3,4-Dibromobutyl)-2-methylthio-4(3H)-pyrimidinone (**5**, R^2 = Me, R^5 = = H, R^6 = CH_2Br—CHBr—CH_2—CH_2—)

A solution of bromine (3.2 g; 20 mmoles) in acetic acid (20 ml) was added by drops under continuous stirring and cooling to a solution of the above product (4.0 g; 20 mmoles) in acetic acid (50 ml) as such a rate that the temperature of the mixture was throughout kept below 25 °C. After disappearance of the colour of the bromine, the solvent was distilled off in vacuum at 60 °C. The residue was triturated with ether (50 ml) and subsequently with cold water (60 ml) to yield 6.5 g (90%) of a crystalline crude product. The latter was recrystallized first from aqueous methanol and subsequently from ethanol to yield 3.3 g (45%) of the pure product, m.p. 152 °C.

$C_9H_{12}Br_2N_2OS$ (356.1). Calc'd C 31.06, H 3.40, S 9.04. Found C 31.24, H 3.64, S 8.96%.

2-Methylthio-4-oxo-3,4-dihydro-6-pyrimidinepropionic acid (**5**, R^2 = Me, R^5 = H, R^6 = —CH_2CH_2COOH) (Method C)

A mixture of 4-oxo-2-thioxo-1,2,3,4-tetrahydro-6-pyrimidinepropionic acid (**4**, R^3 = R^5 = H, R^6 = —CH_2CH_2COOH) monohydrate (6.0 g; 27.5 mmoles), anhydrous methanol (40 ml), DMF (5 ml) and methyl iodide (10 ml) was refluxed for 3 hrs and evaporated to dryness in vacuum. The residue was treated with 10% aqueous $NaHCO_3$ solution until faintly alkaline (pH = 8), boiled up, filtered while still hot, and acidified with acetic acid to yield, after being allowed to cool, 3.6 g (57%) of the *S*-methyl derivative, in form of its colourless crystalline monohydrate, m.p. 174—175 °C (EtOH).

$C_8H_{10}N_2O_3S + H_2O$ (232.3). Calc'd S 13.80. Found S 13.89%.

5-(2-Hydroxyethyl)-2-methylthio-4-oxo-3,4-dihydro-6-pyrimidinepropionic acid (**5**, R^2 = Me, R^5 = $HOCH_2CH_2$—, R^6 = —CH_2CH_2COOH) (Method C)

A mixture of the corresponding thioxo compound (**4**, R^3 = H, R^5 = = $HOCH_2CH_2$—, R^6 = —CH_2CH_2COOH) (1.0 g; 4 mmoles), anhydrous

methanol (15 ml) and methyl iodide (2 ml) was refluxed for 10 hrs and subsequently worked up as above to yield 0.9 g (85%) of colourless crystalline plates, m.p. 174—175 °C (nitromethane).

$C_{10}H_{14}N_2O_4S$ (258.3). Calc'd N 10.85, S 12.42. Found N 10.60, S 12.57%.

Acetylation

The above product (1.0 g; 3.9 mmoles) was refluxed for 1/2 hr with acetic anhydride (4 ml). The mixture was allowed to cool and furnished 0.6 g (48%) of the colourless crystals of the 5-(2-acetoxyethyl) derivative which were washed with ether. M.p. 140 °C (benzene-petroleum ether).

$C_{12}H_{16}N_2O_5S$ (300.3). Calc'd N 9.33, S 10.68. Found N 9.06, S 10.72%.

2-Benzylthio-3,6-dimethyl-4(3H)-pyrimidinone (**6**, $R^2 = PhCH_2$, $R^3 = = R^6 = Me$, $R^5 = H$)

The preparation of this compound by method E has been described in Part II [1].

3-Ethyl-2-methylthio-5,6,7,8-tetrahydro-4(3H)-quinazolinone (**6**, $R^2 = Me$, $R^3 = Et$, $R^5 + R^6 = -(CH_2)_4-$)

a) (Method D). A mixture of **4** ($R^3 = Et$, $R^5 + R^6 = -(CH_2)_4-$) (178 mg; 0.85 mmoles), aqueous methanol (3 : 1, v/v, 4 ml), sodium hydroxide (34 mg; 0.85 mmoles) and methyl iodide (160 mg; 1.1 mmole) was shaken for 1/2 hr and allowed to stand overnight to yield 160 mg (84%) of the *S*-methyl derivative, colourless crystals, m.p. 116 °C (gasoline or from a small amount of methanol).

$C_{11}H_{16}N_2OS$ (224.3). Calc'd C 58.89, H 7.19, S 14.29. Found C 59.06, H 7.38, S 14.23%.

b) (Method E). Metallic sodium (0.46 g; 20 mmoles) was dissolved in ethanol (30 ml), 2-methylthio-5,6,7,8-tetrahydro-4(3*H*)-quinazolinone (**5**, $R^2 = = Me$, $R^5 + R^6 = -(CH_2)_4-$) [13] (3.9 g; 20 mmoles) and ethyl iodide (1.62 ml; 20 mmoles) were added, and the mixture was refluxed for 4 hrs. The residue, obtained on evaporation to dryness in vacuum, was washed with water until free from Na I. The product (3.8 g; 85%) was identical, according to m.p. mixed m.p. and IR spectra, with that obtained according to (a).

Ethyl 2-methylthio-4-oxo-1,2,3,4,5,6,7,8-octahydro-3-quinazolineacetate (**6**, $R^2 = Me$, $R^3 = CH_2COOEt$, $R^5 + R^6 = -(CH_2)_4-$)

a) (Method D). A mixture of the corresponding 2-thioxo derivative (**4**, R^3, R^5 and R^6 as for title compound) (1.0 g; 3.8 mmoles), ethanol (40 ml), in which metallic sodium (90 mg; 3.9 mmoles) had been dissolved, and methyl iodide (1.0 g) was stirred for 4 hrs at r.t. Water (100 ml) was added to precipitate 1.0 g (93%) of colourless crystals, m.p. 91 °C (aqueous ethanol).

$C_{13}H_{18}N_2O_3S$ (282.4). Calc'd C 55.30, H 6.42, N 9.92, S 11.36. Found C 55.21, H 6.63, N 10.01, S 11.41%.

b) (Method E). A mixture of **5** (R^2 = Me, $R^5 + R^6 = -(CH_2)_4-$) [13] (3.9 g; 20 mmoles), ethanol (20 ml), in which metallic sodium (0.46 g; 20 mmoles) had been dissolved, and ethyl chloroacetate (2.46 g; 20 mmoles) was refluxed for 3/4 hr. The solvent was distilled off and the residue was treated with water (15 ml) to yield 4.8 g (85%) of a crystalline product which proved in all respects identical with that obtained according to (a).

2-Benzylthio analogue (**6**, $R^2 = PhCH_2$, $R^3 = CH_2COOEt$, $R^5 + R^6 = -(CH_2)_4-$) (Method D)

A mixture of the thioxo derivative **4** (R^3, R^5, R^6 as for the title compound) (1.5 g; 5.6 mmoles), ethanol (30 ml), in which metallic sodium (0.13 g; 5.6 mmoles) had been dissolved, and benzyl chloride (1 ml; 8.7 mmoles) was shaken for 2 hrs and allowed to stand overnight. The resulting thick paste was mixed with water (50 ml) and filtered to yield 2.0 g (98%) of the benzylthio derivative, m.p. 98 °C (EtOH).

$C_{18}H_{22}N_2O_3S$ (358.5). Calc'd N 7.81, S 8.94. Found N 7.93, S 8.74%.

An attempt to prepare this compound by starting with 2-benzylthio-5,6,7,8-tetrahydro-4(3*H*)-quinazolinone [13] and ethyl chloroacetate according to Method E failed.

6-Methyl-2-methylthio-4-oxo-3,4-dihydro-3-pyrimidineacetamide (**6**, $R^2 = R^6 = Me$, $R^3 = -CH_2CONH_2$, $R^5 = H$) and *(6-methyl-2-methylthio-4-pyrimidyloxy)acetamide* (**12**, $R^2 = R^6 = Me$, $R^5 = H$, $X = NH_2$)

a) Metallic sodium (0.46 g; 20 mmoles), 6-methyl-2-methylthio-4(3*H*)-pyrimidinone (**5**, $R^2 = R^6 = Me$, $R^5 = H$) (3.1 g; 20 mmoles) and chloroacetamide (2.2 g; 24 mmoles) were dissolved in the above order in anhydrous ethanol (50 ml). The solution was refluxed for 6 hrs, the sodium chloride was filtered off while the mixture was still hot, and the filtrate was kept 1 hr at 0 °C to yield 2.8 g (65%) of the *N*(3)-substituted product, m.p. 241 °C (EtOH).

$C_8H_{11}N_3O_2S$ (213.3). Calc'd C 45.08, H 5.20, N 19.71, S 15.03. Found C 45.38, H 5.04, N 19.81, S 15.06%.

UV (EtOH), λ_{max} (log ε): 226 (3.78), 290 (3.94).

IR (KBr): Amide I 1690 and 1670 cm^{-1}.

b) The above procedure was repeated starting with 5.0 g (32 mmoles) of **5** ($R^2 = R^6 = Me$, $R^5 = H$) and using bromoacetamide (5.5 g; 40 mmoles) instead of the chloroamide. 3.2 g (47%) of the *N*(3)-substituted product, m.p. 241 °C (EtOH) were obtained as above.

The mother liquor of this product was evaporated to dryness, the residue was triturated with 0.5% aqueous NaOH (11 ml). 1.5 g (22%) of the *O*-sub-

stituted (type *12*) product were obtained as the insoluble residue. Colourless crystalline needles, m.p. 150—151 °C (ethanol).

$C_8H_{11}N_3O_2S$ (213.3). Calc'd C 45.08, H 5.20, N 19.71, S 15.03. Found C 45.36, H 5.07, N 19.38, S 14.77%.

UV (EtOH), λ_{max} (log ε): 251 (4.13).*

IR (KBr): Amide I 1695 cm^{-1}.

6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidineacetic acid (**11**, R^3 = = CH_2COOH, R^5 = H, R^6 = Me)

6 (R^2 = R^6 = Me, R^3 = CH_2CONH_2) (2.0 g; 9.4 mmoles) was refluxed for 12 hrs with 20% hydrochloric acid (20 ml). The solution was kept at 0 °C to yield 1.1 g (63%) of colourless crystalline prisms, m.p. 254—255 °C (water).

$C_7H_8N_2O_4$ (184.2). Calc'd C 45.65, H 4.38, N 15.22. Found C 45.63, H 4.82, N 14.97%.

UV (EtOH), λ_{max} (log ε): 206 (3.94), 260 (3.96).

6-Methyluracil (**11**, R^3 = R^5 = H, R^6 = Me)

12 (R^2 = R^6 = Me, R^5 = H, X = NH_2) (1.5 g; 7 mmoles) was refluxed with 20% hydrochloric acid (15 ml) for 8 hrs. The mixture was evaporated to dryness in vacuum, and the residue was triturated with acetone (10 ml) to yield 0.8 g (90%) of a colourless crystalline powder, m.p. 320—325 °C (dec.; EtOH), lit. m.p. 320 °C (dec.) [14].

Methyl and ethyl (6-methyl-2-methylthio-4-pyrimidyloxy)acetate (**12**, R^2 = = R^6 = Me, R^5 = H, X = OMe and OEt, respectively)

a) Metallic sodium (0.8 g; 35 mmoles), **5** (R^2 = R^6 = Me, R^5 = H) (5.0 g; 32 mmoles) and methyl bromoacetate (6.2 g; 40 mmoles) were dissolved in this order in anhydrous methanol (100 ml) and the mixture was refluxed for 3 hrs and cooled to 0 °C. The sodium bromide was filtered off, the solvent was distilled off and the residue was triturated with cold acetone (30 ml) to leave another portion of sodium bromide as the insoluble residue. The dry residue of the acetonic solution, a colourless oil, was crystallized from aqueous methanol to yield 6.4 g (87%) of the methyl ester in the form of colourless crystalline needles, m.p. 77—78 °C.

$C_9H_{12}N_2O_3S$ (228.3). Calc'd C 47.35, H 5.30, N 12.27, S 14.05. Found C 47.51, H 5.41, N 12.08, S 13.87%.

UV (EtOH), λ_{max} (log ε): 252 (4.12).

IR (KBr): νC=O 1750 cm^{-1}.

b) For the analogous synthesis of the corresponding ethyl ester (86% yield) the solvent methanol and the reagent methyl bromoacetate were replaced

* Reference compound (kindly furnished by Professor J. J. Fox): 4-ethoxy-2-ethylthio--6-methylpyrimidine, λ_{max} (log ε): 206 (4.00) and 251 (4.10).

by ethanol and ethyl bromoacetate, respectively. M.p. 48—49 °C (aqueous ethanol).

$C_{10}H_{14}N_2O_3S$ (242.3). Calc'd C 49.57, H 5.82, N 11.56, S 13.23. Found C 49.92, H 5.76, N 11.36, S 13.23%.

IR (KBr): νC=O 1745 cm^{-1}.

Aminolysis

The above ethyl ester (0.7 g; 3 mmoles) was dissolved in saturated ethanolic (10 ml) ammonia solution and kept for 5 days in a refrigerator. 0.35 g (55%) of the crystalline amide **12** ($R^2 = R^6 = Me$, $R^5 = H$, $X = NH_2$) were deposited, m.p. and mixed m.p. with a sample prepared as described above: 151 °C.

2-Methylthio-4-oxo-3,4,5,6,7,8-hexahydro-3-quinazolineacetamide (**6**, $R^2 = Me$, $R^3 = CH_2CONH_2$, $R^5 + R^6 = -(CH_2)_4-$) and *2-methylthio-5,6,7,8-tetrahydro-4-quinazolinyloxy)acetamide* (**12**, $R^2 = Me$, $R^5 + R^6 = -(CH_2)_4-$, $X = NH_2$) (Method D)

a) A mixture of **5** (R^2, R^5, R^6 as for the first title compound) [13] (19.6 g; 0.1 mole), anhydrous ethanol (250 ml), in which metallic sodium (2.3 g; 0.1 mole) had been dissolved, chloroacetamide (9.2 g; 0.1 mole) and potassium iodide (0.25 g) was refluxed for 8 hrs. The mixture was allowed to cool, and the crystalline product was filtered and washed with water to yield 10.3 g (41%) of the *N*(3)-substituted product, colourless crystals, m.p. 225 °C (EtOH).

$C_{11}H_{15}N_3OS$ (252.2). Calc'd C 52.25, H 5.95, S 12.64. Found C 52.50, H 5.66, S 12.30%.

b) The above reaction was repeated at the 73 mmole scale in the absence of potassium iodide, with bromoacetamide as the reagent. 8.0 g (43%) of the *N*(3)-substituted product were obtained.

The mother liquor of the crude product was evaporated to dryness and the residue was crystallized from water (400 ml) to yield 2.6 g of a mixture. The components of an aliquot part (120 mg) of this mixture were separated by preparative TLC (adsorben Kieselgel PF; development: $CHCl_3$—MeOH 4 : 1 v/v, eluting solvent: MeOH). The slower migrating component (53 mg) proved identical with the above *N*(3)-substituted product, while the faster migrating one (38 mg) turned out to be the isomeric *O*-substituted derivative **12** ($R^2 = Me$, $R^5 + R^6 = -(CH_2)_4-$, $X = NH_2$), m.p. 172.5 °C (benzene-petroleum ether).

$C_{11}H_{15}N_3OS$ (252.2). Calc'd C 52.25, H 5.95, S 12.64. Found C 52.31, H 5.87, S 12.65, 12.74%.

UV (EtOH), λ_{max} (log ε): ~200 (~4.0), 252 (4.20).

Total yields: *N*(3)-substituted product: 50%, *O*-substituted product: 4.5%.

Table 1

Aminolyses of the *S*-substituted 2-thiouracils **6**

Starting compound **6**				Amine $\frac{R^{21}}{R^{22}}>NH$		Reaction time, hrs
R^2	R^3	R^5	R^6	R^{21}	R^{22}	
Me	H	H	Me	$-(CH_2)_3OH$	H	3
Me	H	H	$CH_2=CH-CH_2-CH_2-$	$-(CH_2)_3-$		8
Me	H	H	$CH_2=CH-CH_2-CH_2-$	$-(CH_2)_4-$		6
Me	H	H	$-CH_2-CH_2-COOH$[b]	n-Bu	H	10
Me	H	$CH_2=CH-CH_2$	Me	$-(CH_2)_4-$		6
Me	H	$-(CH_2)_3-$[c]		$-(CH_2)_2OH$	H	2
Me	H	$-(CH_2)_4-$		$PhCH_2-$	H	1
Me	H	$-(CH_2)_4-$		$-(CH_2)_2OH$	H	1
Me	H	$-(CH_2)_4-$		$-(CH_2)_2OH$	Me	8
Me	H	$-(CH_2)_4-$		$-CH_2COOH$	H	20[d]
Me	Et	$-(CH_2)_4-$		$-(CH_2)_2OH$	H	3

a) R^{21}, R^{22}, R^3, R^5 and R^6 as in the starting *S*-substituted 2-thiouracil **(6)** and the reagent amine, respectively.
b) For the piperidinolysis of this *S*-methyl-2-thiouracil, see text.
c) For the starting compound see Ref. [15].
d) The reaction was performed in refluxing aqueous DMF (5 : 2, v/v) with a 30% excess of glycine.

Preparation of isocytosines **7** *and* **8** *by aminolyses of S-substituted 2-thiouracils* **5** *and* **6** (Methods *F* and *G*)

General procedure: The compounds **5** and **6** were refluxed for 1—13 hrs with a 8—10 fold excess of the appropriate amine. The excess reagent was distilled off in vacuum and the residue was recrystallized from the appropriate

to the isocytosines **7** and **8**

Product a)						
yield, %	m.p., °C	Recryst. from	Formula (Mol.wt.)	Calc'd/found		
				C%	H%	N%
74	168—169	DMF	$C_8H_{13}N_3O_2$ (183.2)	52.44 52.12	7.15 6.85	22.94 22.85
41	168	gasoline	$C_{12}H_{17}N_3O$ (219.3)	65.72 65.71	7.82 7.88	19.16 19.33
60	107—108	aqueous MeOH	$C_{13}H_{19}N_3O$ (233.3)	66.92 66.90	8.21 8.22	18.01 18.22
17	244—246	EtOH	$C_{11}H_{17}N_3O_3$ (239.3)	55.22 55.23	7.16 7.11	17.56 17.23
73	128—129	aqueous acetone	$C_{13}H_{19}N_3O$ (233.3)	66.92 66.82	8.21 8.23	18.01 17.93
60	214	water	$C_9H_{13}N_3O_2$ (195.2)	55.38 55.26	6.71 6.83	21.53 21.36
67	165	gasoline	$C_{15}H_{17}N_3O$ (255.3)	70.56 70.60	6.71 6.64	16.46 16.48
84	180	water	$C_{10}H_{15}N_3O_2$ (209.2)	57.40 57.36	7.23 7.19	20.08 20.15
78	175	water	$C_{11}H_{17}N_3O_2$ (223.3)	59.17 59.15	7.68 7.63	18.87 19.07
61	320—324	water	$C_{10}H_{13}N_3O_3$ (223.2)	53.80 54.19	5.87 5.86	18.83 18.67
75	175	dioxane	$C_{19}H_{19}N_3O_2$ (237.3)	60.73 60.71	8.07 8.06	17.71 17.65

solvent, see Table 1. For the preparation of compounds **7** (R^{21} = —CH_2CH_2OH, R^{22} = H, R^3 = R^6 = Me, R^5 = H) and **8** (R^6 = Me, R^5 = H and Br, respectively) see Ref. [1].

Ammono- and aminolyses of compounds **6** (R^3 = CH_2COOR and CH_2CONH_2)

a) A mixture of **6** (R^2 = R^6 = Me, R^3 = —CH_2CONH_2, R^5 = H) (1.1 g; 5 mmoles), ethanolic ammonia solution, saturated at 0 °C (10 ml) and NH_4Cl (0.1 g) was kept for 5 hrs at 135—140 °C in a sealed tube. The colourless crystal-

line product (**13**, R = R^5 = H, R^6 = Me), 0.6 g (68%), m.p. 310—312 °C (dec.; water) separated on cooling.

The same product has been earlier obtained by non-structure-proving synthesis, m.p. 310 °C [7a].

$C_7H_7N_3O_2$ (165.2). Calc'd 50.90, H 4.18, N 25.46. Found C 51.06, H 4.24, N 25.53%.

b) A mixture of **6** (R^2 = R^6 = Me, R^3 = —CH_2CONH_2, R^5 = H) (3.0 g; 14 mmoles), butylamine (1.4 ml; 14 mmoles), ethanol (30 ml) and butylammonium chloride (0.1 g) was kept in a sealed tube for 8 hrs at 155—160 °C. The solvent was distilled off and the residue recrystallized from water to yield 1.1 g (35%) of **13** (R = n-Bu, R^5 = H, R^6 = Me), colourless crystalline needles, m.p. 94—95 °C.

$C_{11}H_{15}N_3O_2$ (221.3). Calc'd C 59.58, H 6.38, N 18.99. Found C 59.71, H 6.26, N 19.33%.

c) A mixture of **6** (R^2 = Me, R^3 = —CH_2COOEt, R^5 + R^6 = —$(CH_2)_4$—) (2.0 g; 7.1 mmoles), ethanolic ammonia solution (50 ml) and ammonium chloride (0.1 g) was kept in a sealed tube for 10 hrs at 190 °C. 0.5 g (31%) of **7** (R^{21} = R^{22} = H, R^3 = CH_2CONH_2, R^5 + R^6 = —$(CH_2)_4$—), colourless crystals, m.p. 308 °C (MeOH), separated on cooling.

$C_{10}H_{14}N_4O_2$ (222.2). Calc'd C 54.04, H 6.35, N 25.21. Found C 54.04, H 6.31, N 25.40%.

The mother liquor of the crude product was evaporated to dryness and the residue was crystallized from nitromethane to yield 1.0 g (68%) of **13** (R = H, R^5 + R^6 = —$(CH_2)_4$—), m.p. 315 °C.

$C_{10}H_{11}N_3O_2$ (205.2). Calc'd C 58.53, H 5.42, N 20.48. Found C 58.67, H 5.53, N 20.61%.

d) A mixture of **6** (R^2 = Me, R^3 = CH_2CONH_2, R^5 + R^6 = —$(CH_2)_4$—) (1.5 g; 6 mmoles), ethanolic ammonia solution (20 ml), saturated at 0 °C, and ammonium chloride (0.1 g) was kept in a sealed tube for 20 hrs at 150—160 °C. The solvent was distilled off and the residue was recrystallized from nitromethane to yield 0.5 g (40%) of **13** (R = H, R^5 + R^6 = —$(CH_2)_4$—), m.p. 315 °C, identical with the second product obtained according to (c).

e) A mixture of **6** (R^2 = Me, R^3 = —CH_2COOEt, R^5 + R^6 = = —$(CH_2)_4$—) and an 8—10 fold excess of 2-aminoethanol was refluxed for 1 hr. The excess reagent was distilled off and the residue was crystallized from propanol-ether to yield 73% of **7** (R^{21} = —CH_2CH_2OH, R^{22} = H, R^3 = = —$CH_2CONHCH_2CH_2OH$, R^5 + R^6 = —$(CH_2)_4$—), m.p. 146 °C.

$C_{14}H_{22}N_4O_4$ (310.7). Calc'd C 54.18, H 7.15, N 18.05. Found C 54.64, H 7.16, N 18.00%.

f) The above reaction was repeated with benzylamine (reaction time 13 hrs), and a 77% yield of **7** (R^{21} = $PhCH_2$, R^{22} = H, R^3 = —$CH_2CONHCH_2Ph$, R^5 + R^6 = —$(CH_2)_4$—), m.p. 213 °C (nitromethane) was achieved.

$C_{24}H_{26}N_4O_2$ (402.5). Calc'd C 71.62, H 6.51, N 13.92. Found C 71.81, H 6.54, N 14.15%.

Piperidinolysis of 2-methylthio-4-oxo-3,4-dihydro-6-pyrimidinepropionic acid (**6**, $R^2 = Me$, $R^3 = R^5 = H$, $R^6 = —CH_2CH_2COOH$)

A mixture of the title compound (4.6 g; 20 mmoles) and piperidine (25 ml) was refluxed for 15 hrs. The excess amine was distilled off in vacuum and the residue was triturated with acetone (20 ml) to yield 1.8 g (36%) of **7** ($R^{21} + R^{22} = —(CH_2)_5—$, $R^3 = R^5 = H$, $R^6 = —CH_2CH_2COOH$), colourless crystals, m.p. 275 °C (dec.; nitromethane).

$C_{12}H_{17}N_3O_3$ (251.3). Calc'd C 57.35, H 6.82, N 16.71. Found C 57.12, H 6.76, N 16.76%.

The acetonic mother liquor was evaporated to dryness, and the colourless oily residue was crystallized from water to yield 1.7 g (27%) of **7** ($R^{21} + R^{22} = —(CH_2)_5—$, $R^3 = R^5 = H$, $R^6 = —CH_2CH_2CONC_5H_{10}$), colourless crystals, m.p. 135—136 °C.

$C_{17}H_{26}N_4O_2$ (318.4). Calc'd C 64.12, H 8.23, N 17.60. Found C 64.08, H 8.16, N 18.00%.

2-[N'-(2-Hydroxyethyl)hydrazino]-5,6,7,8-tetrahydro-4(3H)-quinazolinone (**7**, $R^{21} = —NHC_2H_4OH$, $R^{22} = R^3 = H$, $R^5 + R^6 = —(CH_2)_4—$)

2-Nitramino-5,6,7,8-tetrahydro-4(3*H*)-quinazolinone (**7**, $R^{21} = NHNO_2$, $R^{22} = R^3 = H$, $R^5 + R^6 = —(CH_2)_4—$) [16] was refluxed with an equivalent amount of 2-hydrazinoethanol for 1.5 hrs in ethanolic solution. The solvent was distilled off, and the residue was crystallized from ethanol to yield 82% of the desired product, m.p. 223 °C.

$C_{10}H_{16}N_4O_2$ (224.9). Calc'd C 53.54, H 7.17, N 24.98. Found C 53.56, H 7.39, N 25.04%.

2-Amino-5-bromo-3,6-dimethyl-4(3H)-pyrimidinone (**7**, $R^{21} = R^{22} = H$, $R^3 = R^6 = Me$, $R^5 = Br$)

Bromine (1.1 ml; 21 mmole) was added by drops to a slurry of 2-amino-3,6-dimethyl-4(3*H*)-pyrimidinone (**7**, $R^{21} = R^{22} = R^5 = H$, $R^3 = R^6 = Me$) [7c] (2.8 g; 20 mmoles) in acetic acid (40 ml) under continuous stirring at r.t. The mixture was allowed to stand for 1 hr, the crystalline product was filtered, washed with ether, dried and dissolved in water (50 ml). The solution was neutralized with aqueous $NaHCO_3$ solution to yield 3.1 g (71%) of colourless needles, m.p. 262 °C (dec., water).

$C_6H_8BrN_3O$ (219.0). Calc'd C 33.04, H 3.69, Br 36.65, N 19.27. Found C 33.43, H 3.86, Br 36.77, N 19.00%.

5-Bromo-6-(3-butenil)-2-piperidino-4(3H)-pyrimidinone (**7**, $R^{21} + R^{22} = -(CH_2)_5-$, $R^3 = H$, $R^5 = Br$, $R^6 = CH_2=CH-CH_2-CH_2-$)

NBS (1.8 g; 10 mmoles) was added to a mixture of 6-(3-butenyl)-2-piperidino-4(3*H*)-pyrimidinone (**7**, $R^{21} + R^{22} = (CH_2)_5$, $R^3 = R^5 = H$, $R^6 = CH_2=CH-CH_2-CH_2-$) (2.3 g; 10 mmoles), dioxane (30 ml) and water (10 ml). The mixture was refluxed for 5 min, warm water (40 ml) was added, and the mixture was allowed to cool to yield 2.2 g (70%) of colourless needles m.p. 150—151 °C (aqueous acetone).

$C_{13}H_{18}BrN_3O$ (312.3). Calc'd Br 25.60, N 13.46. Found Br 26.32, N 13.12%.

6-(3-Bromobutyl)-2-piperidino-4(3H)-pyrimidinone (**7**, $R^{21} + R^{22} = -(CH_2)_5-$, $R^3 = R^5 = H$, $R^6 = CH_3CHBrCH_2CH_2-$)

A solution of **7** ($R^{21} + R^{22} = -(CH_2)_5-$, $R^3 = R^5 = H$, $R^6 = CH_2=CHCH_2CH_2-$) (7.0 g; 30 mmoles) in 48% hydrobromic acid (40 ml) was refluxed for 10 min. The solvent was distilled off in vacuum. A small portion of the resulting highly viscous liquid was triturated with acetone to yield the hydrobromide of the title compound, m.p. 180—181 °C (EtOH-ether).

$C_{13}H_{21}Br_2N_3O$ (395.2). Calc'd C 39.51, H 5.36, N 10.63. Found C 39.52, H 5.00, N 10.83%.

The main portion of the crude non-crystalline hydrobromide was dissolved in water (70 ml), and the solution was made slightly alkaline (pH = 8) by the addition of 10% aqueous Na_2CO_3 solution. The precipitated product slowly solidified on standing to yield 6.4 g (68%) of the free base, m.p. 145 °C (from a small amount of methanol).

$C_{13}H_{20}BrN_3O$ (314.2). Calc'd C 49.69, H 6.42, N 13.37. Found C 49.73, H 6.94, N 13.61%.

2-(2-Chloroethylamino)-5,6,7,8-tetrahydro-4(3H)-quinazolinone (**9**, $R^5 + R^6 = -(CH_2)_4-$) (Method H)

The 2-(2-hydroxyethylamino) analogue **8** ($R^5 + R^6 = -(CH_2)_4-$) of the title compound (1.0 g; 4.8 mmoles) was refluxed for 10 min with thionyl chloride (10 ml). The excess of the reagent was distilled off in vacuum and the residue was triturated with ether to yield 1.0 g (80%) of the hydrochloride of the title compound, crystalline powder, m.p. 350 °C* (methanolic hydrogen chloride-ether).

$C_{10}H_{15}Cl_2N_3O$ (263.2). Calc'd C 45.23, H 5.95, N 16.25. Found C 45.46, H 5.75, N 15.91%.

* When the m.p. capillary was introduced into sulfuric acid preheated to 220 °C, rapid melting and resolidifying took place, and the resolidified product melted again at 350 °C. When the product was slowly heated, only the second m.p. was observed.

2,3,6,7,8,9-Hexahydroimidazo[2,1-b]quinazolin-5(1H)-one (**10**, $R^5 + R^6 = -(CH_2)_4-$) (Method I)

The above product (1.0 g; 3.8 mmoles) was kept for 20 min at 175—180 °C to yield 0.85 g (98%) of the hydrochloride of the title compound, m.p. 350 °C (MeOH-ether).

$C_{10}H_{14}ClN_3O$ (227.7). Calc'd C 52.75, H 6.19. Found C 52.68, H 5.98%.

The salt (1.0 g; 4.4 mmoles) was stirred for 30 min with ethereal diazomethane solution. The solvent was distilled off (caution!) and the residue was crystallized from acetone to yield 0.3 g (36%) of the free base, m.p. 240 °C (acetone or nitromethane).

$C_{10}H_{13}N_3O$ (191.2). Calc'd C 62.81, H 6.85. Found C 62.77, H 6.86%.

3-Acetoacetyl-2-imino-5-methylthiazolidine (**14**)

An aqueous solution (120 ml) of 2-imino-3-methylthiazolidine hydrochloride [17] (20 g; 0.132 moles) was treated at r.t. with sodium hydrogen carbonate (11.2 g; 0.132 moles). Freshly distilled diketene (10 ml; 0.132 moles) was added within a period of about 5 min, and the temperature of the mixture was thereby allowed to rise to 45 °C. The mixture was kept for another 5 min at this temperature and subsequently cooled to 10 °C to yield 11.7 g of a crystalline product as the first crop. The filtrate of this product was extracted with two portions of chloroform (40 ml, each), the combined chloroform solutions were dried over $MgSO_4$ and the solvent was distilled off to yield another 4.5 g of the product, m.p. 140 °C (CCl_4, gasoline or benzene). The total yield (16.2 g) amounted to 68%.

$C_8H_{12}N_2O_2S$ (200.3). Calc'd C 47.98, H 6.04, S 16.01. Found C 47.74, H 5.84, S 15.93, 15.62%.

2,7-Dimethyl-2,3-dihydrothiazolo[2,3-b]pyrimidin-5-one (**6**, $R^2 + R^3 = -CHMeCH_2-$, $R^5 = H$, $R^6 = Me$)

An anhydrous ethanolic (20 ml) solution of **14** (2.0 g; 10 mmoles) was saturated under cooling with dry hydrogen chloride to yield 1.9 g (87%) of the crystalline hydrochloride of the title compound, m.p. 275°, which, according to its IR spectrum proved identical with the product obtained, as described in the literature [8], starting with 3-allyl-6-methyl-2-thiouracil.

$C_8H_{11}ClN_2OS$ (218.7). Calc'd S 14.66. Found S 14.58%.

The free base was liberated as described in the literature [8]. M.p. 56 °C (gasoline).

1,6-Dimethyl-2-thiouracil (**15**, $R^1 = Me$)

This compound was prepared as described in Part II [1].

1-Allyl-6-methyl-2-thiouracil (**15**, $R^1 = C_3H_5$)

A mixture of freshly distilled diketene (40 ml; 0.51 mole) and acetic acid (35 ml) was added by drops to a hot solution of *N*-allylthiourea (58 g; 0.5 moles) in acetic acid (125 ml) at such a rate that the reaction mixture was kept boiling throughout. The mixture was refluxed for another 10 min and poured into warm (40 °C) water (1000 ml) to yield 39 g (44%) of crystalline plates, m.p. 167 °C (EtOH),* which were collected after the mixture had been allowed to cool.

$C_8H_{10}N_2OS$ (182.3). Calc'd C 52.71, H 5.53, S 17.59. Found C 52.70, H 6.04, S 17.59%.

1,6-Dimethyl-2-methylthio-4(1H)-pyrimidinone (**16**, $R^1 = R^2 = Me$) (Method J)

A mixture of 1,6-dimethyl-2-thiouracil (3.1 g; 20 mmoles), anhydrous methanol (50 ml) and methyl iodide (5 ml) was refluxed for 6 hrs. The solvent was distilled off in vacuum to yield 5.7 g (96%) of faint yellow crystals, m.p. 210—212 °C (EtOH-ether), of the hydriodide of the title compound.

$C_7H_{11}IN_2OS$ (298.2). Calc'd C 28.19, H 3.72, S 10.75. Found C 27.79, H 3.99, S 10.97%.

The free base was liberated from the salt in essentially quantitative yield by treating it with ethereal diazomethane solution. M.p. 224—225 °C (water).

$C_7H_{10}N_2OS$ (170.2). Calc'd C 49.38, H 5.92, N 16.46, S 18.94. Found C 49.80, H 5.90, N 16.73, S 18.66%.

2-Benzylthio-1,6-dimethyl-4(1H)-pyrimidinone (**16**, $R^1 = Me$, $R^2 = PhCH_2$) (Method J)

The preparation of this compound has been described in Part II [1]

1,6-Dimethyl-2-methylamino-4(1H)-pyrimidinone (**17**, $R^{21} = Me$) *and 2-dimethylamino-1,6-dimethyl-4(1H)-pyrimidinone* (**18**, $R^{21} = R^{22} = Me$) (Method L and M, respectively)

a) 2-Benzylthio-1,6-dimethyl-4(1*H*)-pyrimidinone (**16**, $R^1 = Me$, $R^2 = PhCH_2$) (1.0 g; 4 mmoles) was kept with an ethanolic methylamine solution (15 ml), saturated at 0 °C, in a sealed tube for 12 hrs at 150—160 °C. The solvent was distilled off in vacuum and the residue was triturated with ether to yield 0.6 g (98%) of the highly hygroscopic needles of **17** ($R^{21} = Me$), m.p. 241—242 °C (nitromethane).

b) A mixture of **17** ($R^{21} = Me$) (3.1 g; 20 mmoles), anhydrous methanol (20 ml) and methyl iodide (5 ml) was refluxed for 12 hrs and evaporated to dryness in vacuum. The crystalline residue was triturated with 10% aqueous

* The 3-allyl isomer melts at 189 °C [8].

NaOH solution to yield 1.5 g (44%) of **18** ($R^{21} = R^{22} = Me$), colourless needles, m.p. 77—78 °C (gasoline).

$C_8H_{13}N_3O + 1/4\ H_2O$ (171.7). Calc'd C 55.95, H 7.92, N 24.47. Found C 55.89, H 7.88, N 24.44%.

2-(2-Hydroxyethylamino)-1,6-dimethyl-4(1H)-pyrimidinone (**17**, $R^{21} = —CH_2CH_2OH$).

a) The preparation of this compound by Method L, starting with 2-benzylthio-1,6-dimethyl-4(1*H*)-pyrimidinone (**16**, $R^1 = Me$, $R^2 = PhCH_2$) has been described in Part II [1].

b) (Method K). A mixture of 1,6-dimethyl-2-thiouracil (**15**, $R^1 = Me$) was refluxed with an about 8 fold excess of 2-aminoethanol until the evolution of hydrogen sulfide ceased (1 hr). The excess amine was distilled off in vacuum and the residue was crystallized as described under (a) to yield 60% of a product, m.p. 255 °C, identical, according to their IR spectra, with the sample obtained according to (a).

$C_8H_{13}N_3O_2$ (183.2). Calc'd C 52.45, H 7.15, N 22.94. Found C 52.21, H 7.27, N 22.70%.

N-(1,6-Dimethyl-4-oxo-1,4-dihydro-2-pyrimidyl)-glycine (**17**, $R^{21} = —CH_2COOH$)

A thoroughly mixed mixture of 2-benzylthio-1,6-dimethyl-4(1*H*)-pyrimidinone (**16**, $R^1 = Me$, $R^2 = PhCH_2$) (2.5 g; 10 mmoles) and glycine (1.0 g; 13 mmoles) was kept for 2 hrs at 160 °C and, after being allowed to cool, extracted by refluxing it with methanol (50 ml). The methanolic solution was kept overnight in a refrigerator to yield 0.8 g (40%) of a colourless crystalline powder, m.p. 240—241 °C (dec.; MeOH).

$C_8H_{11}N_3O_3$ (197.2). Calc'd C 48.72, H 5.62, N 21.31. Found C 48.93, H 5.76, N 21.23%.

2,5-Dimethyl-2,3-dihydro-7H-thiazolo[3,2-a]pyrimidin-7-one (**16**, $R^1 + R^2 = —CH_2CHMe—$)

An ethanolic (50 ml) solution of 1-allyl-6-methyl-2-thiouracil (**15**, $R^1 = C_3H_5$) (5.0 g; 28 mmoles) was refluxed for 1.5 hrs under continuous introduction of a stream of dry hydrogen chloride to yield, after being allowed to cool, 4.9 g (81.5%) of the hydrochloride of the title compound, m.p. 289—290 °C (EtOH).

The salt was dissolved in methanol (70 ml) and refluxed in the presence of $NaHCO_3$ (5.0 g; 60 mmoles) until the evolution of carbon dioxide ceased. The inorganic salts were filtered off, and the filtrate was evaporated to dryness in vacuum. The residue was crystallized from $CHCl_3$-petroleum ether to yield 3.85 g (73%) of the free base, m.p. 187 °C.

$C_8H_{10}N_2OS$ (185.3). Calc'd C 52.72, H 5.53, S 17.59. Found C 52.68, H 5.65, S 17.30%.

NMR ($CDCl_3$): δ5.73, s, 6-**H**; 278—225 Hz, m, 2-**H** + 3-$\mathbf{H}_2$; δ2.23, s, 5-**Me**; δ1.56, d, J = 7 Hz, 2-**Me**.

IR (KBr): Amide I 1645 cm^{-1} (free base); 1725 + 1700 cm^{-1}, d (hydrochloride).

Aminolysis

The above product (2.0 g; 11 mmoles) was kept with 2-aminoethanol (8 ml) and catalytic amount of NH_4Cl for 1 1/2 hrs at 190 °C. (At about 165 °C slow evolution of H_2S started.) The excess reagent was distilled off, and the resulting gummy product was triturated with acetone to yield 1.6 g (87%) of 2-(2-hydroxyethylamino)-6-methyl-4(3*H*)-pyrimidinone, identical by m.p. (206 °C), mixed m.p. and IR spectra with an authentic sample prepared according to Method G [1].

2-Bromomethyl-5-methyl-2,3-dihydro-7H-thiazolo[3,2-a]pyrimidin-7-one (**16**, $R^1 + R^2 = -CH_2CH(CH_2Br)-$)

A solution of bromine (3.2 g; 20 mmoles) in acetic acid (10 ml) was added to a solution of 1-allyl-6-methyl-2-thiouracil (**15**, $R^1 = C_3H_5$, R^6 = Me) (3.65 g; 20 mmoles) in acetic acid (40 ml) under continuous stirring by drops to yield the hydrobromide of the title compound in form of a colourless crystalline powder.

$C_8H_{10}Br_2N_2OS$ (342.1). Calc'd Br, ionic 23.36, Br, total 46.72, N 8.19, S 9.37. Found Br, ionic 23.02, Br, total 46.06, N 8.23, S 9.36, 9.25%.

The methanolic (100 ml) solution of the salt was shaken with $NaHCO_3$ (3.2 g; 23 mmoles) until the evolution of carbon dioxide ceased, the inorganic salts were filtered off, and the filtrate was evaporated to dryness in vacuum. The filtered chloroformic solution of the residue was treated with petroleum ether to yield 4.1 g (89%) of the free base, m.p. 147 °C ($CHCl_3$-petroleum ether).

$C_8H_9BrN_2OS$ (261.2). Calc'd Br 30.60, N 10.73, S 12.27. Found Br 30.04, N 10.81, S 12.10%.

IR (KBr): Amide I 1640 cm^{-1} (free base); 1720—1700 cm^{-1}, br (hydrobromide).

2-(2-Chloroethylamino)-3-ethyl-5,6,7,8-tetrahydro-4(3H)-quinazolinone (**7**, $R^{21} = -CH_2CH_2Cl$, R^{22} = H, R^3 = Et, $R^5 + R^6 = -(CH_2)_4-$)

The 2-(2-hydroxyethylamino) analogue of the title compound (see Table 1, last compound) (1.1 g; 4.7 mmoles) was refluxed for 15 min with $SOCl_2$ (5 ml). The excess reagent was distilled off in vacuum, and the residue was triturated with cold 10% aqueous Na_2CO_3 solution (20 ml) to yield 0.7 g (59%) of a

crystalline product which melted unsharply between 80—90 °C and, after resolidification, at 210—213 °C.

$C_{12}H_{18}ClN_3O$ (255.7). Calc'd Cl 13.87. Found Cl (non-ionic!) 13.35%.

10-Ethyl-2,3,5,6,7,8-hexahydroimidazo[1,2-a]quinazolin-9(10H)-one **(19)**

The above product was kept for 1/2 hr at 150—160 °C and, after being allowed to cool, stirred for 3 hrs with an etheral diazomethane solution. The small amount of insoluble oily material was removed, the clear solution was evaporated to dryness (caution!) and the residue was recrystallized from gasoline to yield 0.8 g (38%) of **19**, m.p. 118 °C.

$C_{12}H_{17}N_3O$ (219.3). Calc'd C 65.71, H 7.82, N 19.16. Found C 65.82, H 7.87, N 19.05%.

7,8-Dimethyl-2,3-dihydro-5(8H)-imidazo[2,1-b]pyrimidinone **(20)**

2-(2-Hydroxyethylamino)-1,6-dimethyl-4(1*H*)-pyrimidinone (**17**, R^{21} = = $-CH_2CH_2OH$) (7.0 g; 38 mmoles) was refluxed with thionyl chloride (30 ml) for 15 min and the excess reagent was distilled off in vacuum. The residue was boiled up with methanol (20 ml) and the hydrochloride (7.4 g; m.p. 265 °C) of the title compound was precipitated by the addition of ether (45 ml). The salt was refluxed with methanol (100 ml) in the presence of $NaHCO_3$ (6.0 g), and the inorganic salts were filtered off. The dry residue of the filtrate was recrystallized from dioxane to yield 3.0 g (48%) of **20**, m.p. 183 °C (dioxane).

$C_8H_{11}N_3O$ (165.2). Calc'd C 58.16, H 6.71, N 25.44. Found C 58.25, H 6.67, N 25.02%.

1,6-Dimethyl-4-thiouracil (**22**, $R^1 = R^6 = Me$, $R^5 = H$)

A mixture of 1,6-dimethyluracil (**21**, $R^1 = R^6 = Me$, $R^5 = H$) [18] (4.0 g; 29 mmoles), anhydrous pyridine (50 ml) and P_2S_5 (6.0 g; 21 mmoles) was refluxed for 2 hrs, and the solvent was distilled off in vacuum. The residue was triturated with water (60 ml) to yield 3.0 g (67%) of a yellow crystalline product, m.p. 241 °C (DMF or n-BuOH).

$C_6H_8N_2OS$ (156.2). Calc'd C 46.13, H 5.16, S 20.53. Found C 45.92, H 4.89, S 20.68%.

UV (EtOH), λ_{max} (log ε): 202 (4.19), 252 (3.63), 336 (4.21).

4-Thioxo-3,4,5,6,7,8-hexahydro-2(1H)-quinazolinone (**22**, $R^1 = H$, $R^5 + R^6 = -(CH_2)_4-$)

This product was prepared in a similar way, starting with 5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione (**21**, $R^1 = H$, $R^5 + R^6 = -(CH_2)_4-$) [19] (5.0 g; 30 mmoles) and an equimolecular amount of P_2S_5. In order to purify the crude product, it was dissolved in 1N NaOH (150 ml) at 50 °C, and the

solution was filtered and the filtrate acidified with conc'd HCl (15 ml) to yield 4.5 (82%) of a yellow crystalline powder, m.p. 261 °C (dec.; DMF or n-BuOH).

$C_8H_{10}N_2OS$ (182.3). Calc'd C 52.72, H 5.61, S 17.59. Found C 53.08, H 5.86, S 18.01%.

UV (EtOH), λ_{max} (log ε): 202 (4.24), 243 (3.56), 334 (4.28).

1,6-Dimethyl-4-methylthio-2(1H)-pyrimidinone (**23**, $R^1 = R^6 = Me$, $R^5 = H$)

A mixture of the corresponding 4-thiouracil **(22)** (1.9 g; 12 mmoles), aqueous (25 ml) NaOH (0.5 g; 12.5 mmoles) solution and methyl iodide (2 ml; 32 mmoles) was shaken for 3 hrs, and the resulting yellow solution was extracted with three portions of chloroform (10 ml, each). The combined chloroformic solutions were dried, and petroleum ether (100 ml) was added to yield 1.3 g (63%) of yellow crystals, m.p. 173 °C ($CHCl_3$-petroleum ether).

$C_7H_{10}N_2OS$ (170.2). Calc'd C 49.40, H 5.92, S 18.84. Found C 49.23, H 5.82, S 18.84, 19.00%.

UV (EtOH), λ_{max} (log ε): 210 (4.08), 221 (3.82) sh, 268 (3.92), 303 (4.04).

4-Methylthio-5,6,7,8-tetrahydro-2(1H)-quinazolinone (**23**, $R^1 = H$, $R^5 + R^6 = -(CH_2)_4-$)

The corresponding thioxo compound **(22)** (5.5 g; 30 mmoles) was allowed to stand overnight with methyl iodide (5.0 g; 36 mmoles) in methanol (100 ml) in which metallic sodium (0.7 g; 30 mmoles) had been dissolved. The solvent was distilled off in vacuum and the residue was triturated with water (30 ml) to yield 5.3 g (90%) of a crystalline product, m.p. 263 °C (EtOH).

$C_9H_{12}N_2OS$ (196.3). Calc'd C 55.07, H 6.17, S 16.34. Found C 55.06, H 6.32, S 16.44%.

UV (EtOH), λ_{max} (log ε): 213 (4.13), 220 (4.05) sh, 266 (3.98), 308 (4.09).

4-(2-Hydroxyethylamino)-1,6-dimethyl-2(1H)-pyrimidinone (**24**, $R^1 = R^6 = Me$, $R^5 = H$)

The 4-methylthio analogue **(23)** (1.0 g; 5.9 mmoles) of the desired product was refluxed for 3/4 hrs with 2-aminoethanol (10 ml). The excess reagent was distilled off in vacuum and the residue was triturated with cold acetone (20 ml) to yield 0.8 g (74%) of a crystalline product, m.p. 167 °C (dioxane).

$C_8H_{13}N_3O_2$ (183.2). Calc'd C 52.45, H 7.15, N 22.94. Found C 52.40, H 7.15, N 22.83%.

UV (EtOH), λ_{max} (log ε): 205 (4.25), 276 (3.98).

4-(2-Hydroxyethylamino)-5,6,7,8-tetrahydro-2(1H)-quinazolinone (**24**, $R^1 = H$, $R^5 + R^6 = -(CH_2)_4-$)

A mixture of the 4-methylthio analogue **(23)** (2.5 g; 12.7 mmoles) of the desired product, butanol (10 ml) and 2-aminoethanol (5 ml) was refluxed

for 10 hrs to yield, after being allowed to cool, 1.7 g (64%) of a crystalline product, m.p. 270 °C (water).

$C_{10}H_{15}N_3O_2$ (209.2). Calc'd C 57.40, H 7.23, N 20.08. Found C 57.58, H 7.32, N 19.58%.

UV (EtOH), λ_{max} (log ε): ~200 (~4.3), 278 (3.98).

4-(2-Chloroethylamino)-1,6-dimethyl-2(1H)-pyrimidinone hydrochloride (**25** · HCl, $R^1 = R^6 = Me$, $R^5 = H$)

The corresponding 4-(2-hydroxyethylamino) derivative **(24)** (1.5 g; 8.2 mmoles) was refluxed for 15 min with thionyl chloride (10 ml), the excess reagent was distilled off and the residue triturated with ether to yield 1.6 g (82%) of a crystalline product, m.p. 282 °C (MeOH), after a change in the crystal structure had taken place between 200—220 °C.

$C_8H_{13}Cl_2N_3O$ (238.1). Calc'd C 40.35, H 5.50, Cl (total) 29.78. Found C 40.33, H 6.00 Cl (total) 29.91%.

6,7-Dimethyl-2,3-dihydro-5(6H)-imidazo[1,2-c]pyrimidinone hydrochloride (**26**, $R^1 = R^6 = Me$, $R^5 = H$)

The above hydrochloride was kept for 1 hr at 220 °C to yield, under evolution of hydrogen chloride, 0.8 g (99%) of a crystalline product, m.p. 282 °C (methanol-ether) without any prior change of the crystal structure.

$C_8H_{12}ClN_3O$ (201.6). Calc'd C 47.65, H 6.00, ionic Cl 17.58. Found C 48.08, H 6.15, ionic Cl 17.75%.

UV (EtOH), λ_{max} (log ε): 216 (3.88), 292 (4.14).

2,3,7,8,9,10-Hexahydro-5(6H)-imidazo[1,2-c]quinazolinone (**26**, $R^1 = H$, $R^5 + R^6 = -(CH_2)_4-$)

24 (R^1, R^5 and R^6 as for the title compound) (1.45 g; 6.7 mmoles) was refluxed for 15 min with thionyl chloride (10 ml), the excess reagent was distilled off and the residue was triturated with 5% aqueous $NaHCO_3$ solution to yield **25** (R^1, R^5 and R^6 as above) in crystalline form. This product was dried over P_2O_5 and kept for 1 1/2 hrs at 170 °C. During this period the starting material, which was insoluble in water and contained no ionic Cl, turned into a new compound (the hydrochloride of the title compound), soluble in water and containing ionic chlorine; the transformation, of course, did not affect the weight of the product. After being allowed to cool, the hydrochloride was treated with ethereal (35 ml) diazomethane. The solvent was distilled off (caution!) and the residue was crystallized from chloroform-petroleum ether. 1.0 g (78%) of the desired product was obtained, m.p. 241 °C.

$C_{10}H_{13}N_3O$ (191.2). Calc'd C 62.81, H 6.85, N 21.98. Found C 62.45, H 6.83, N 22.40%.

UV (EtOH), λ_{max} (log ε): 224 (3.94), 287 (3.86).

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Summary

The syntheses of a series of isocytosines **(7, 8, 17, 18)** and imidazo[1,2-*a*]pyrimidinones **(10, 19, 20)** containing fixed tautomeric structures is described. Starting with 4-thiouracils **(22)** some new cytosines **(24)** and imidazo[1,2-*c*]pyrimidinones **(26)** have been obtained.

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