5-Aryl-7-(N-arylcarbamoyl)-4,6-dioxo-2,3,3a,4,5,6-hexahydrooxa(thia)zolo-[2,3-c]pyrimidines and 3-(N-Arylcarbamoyl)-2,4-dihydroxyquinolines from 2-Methyloxa(thia)zoline and Aryl Isocyanates

R. Richter* and H. Ulrich

The Upjohn Company, D. S. Gilmore Research Laboratories, North Haven, Connecticut 06473

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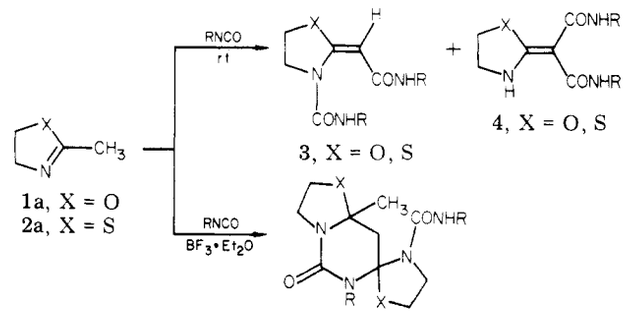
Two structurally different heterocyclic products, 5-aryl-7-(*N*-arylcarbamoyl)-4,6-dioxo-2,3,3a,4,5,6-hexahydrooxazolo- and -thiazolo[2,3-*c*]pyrimidines (**8**) and 3-(*N*-arylcarbamoyl)-2,4-dihydroxyquinolines (**10**), are obtained in low yield on heating 2-methyloxazoline (**1a**) or 2-methylthiazoline (**2a**) with aryl isocyanates to approximately 150 °C. The structures of both heterocyclic products were confirmed by independent synthesis of compounds **10** (by base-catalyzed addition of aryl isocyanate to 2,4-dihydroxyquinoline) and 1-(2-chloroethyl)-3-phenyl-5-(*N*-phenylcarbamoyl)barbituric acid (**11**), a degradation product of **8a** (R = C_6H_5).

The usefulness of certain cyclic imino ethers such as 2-substituted oxazolines and oxazines as building blocks with "latent functionality" in the synthesis of a variety of organic molecules (carboxylic acids, lactones, aldehydes, alcohols, and thiirans) has been demonstrated in recent years.[1-3] 2-Alkyloxazolines (**1**) were found to be especially accessible to modifications (i.e., homologation) at the 2-alkyl group,[1] and alkylation reactions on **1** received considerable attention in connection with the synthesis of chiral products.[3]

Acylations of 2-alkyloxazolines (**1**) and thiazolines (**2**), especially those involving isocyanates, were also investigated and were found to yield a variety of products depending upon the reaction conditions:[4-6] C- and/or N-acylated products **3** and **4** (see Scheme I) were obtained on reacting **1** and **2** with excess aryl isocyanates at room or only moderately elevated temperatures. Boron trifluoride etherate catalyzed reactions of the same components produced tricyclic adducts which were found to be spiro[oxazoline-oxazolopyrimidines] **5a** and the corresponding thiazoline derivatives **5b**. We now wish to report the synthesis of two other heterocyclic ring systems which are formed in the reaction of **1** and **2** with aryl isocyanates at elevated temperature.

When 2-methyloxazoline (**1a**) is heated with 4 equiv of phenyl isocyanate at 140–150 °C for 16 h, a highly colored product mixture is formed from which 5-aryl-7-(*N*-phenylcarbamoyl)-4,6-dioxo-2,3,3a,4,5,6-hexahydrooxazolo[2,3-*c*]pyrimidine (**8a**) was isolated as a pale yellow, high-melting solid in 24% yield. Further workup of the reaction mixture with methanol–acetone yielded various amounts of *N,N'*-diphenylurea and *N,N',N''*-triphenylbiuret but no other products containing the structural elements of **1a**. When **1a** or 2-methylthiazoline (**2a**) was treated under similar conditions with certain substituted phenyl isocyanates, several other differently substituted oxazolo- and thiazolo[2,3-*c*]pyrimidines (**8a–e**) were obtained in low yield (see Scheme II and Table I).

Scheme I



A different series of products (**10c–f**) were obtained from **1a** and **2a** with certain other aryl isocyanates on changing the imino ether to isocyanate ratio in the reaction mixture, while leaving the reaction temperature at approximately 150 °C. Changing the reaction duration did not alter the nature of the product but did in some cases affect the yield of the respective product. The compounds, equally high melting and isolated by trituration of the crude reaction mixture with acetone–methanol, were found to be 3-(*N*-arylcarbamoyl)-2,4-dihydroxyquinolines (**10**). Byproducts here were also varying amounts of *N,N'*-diarylureas and *N,N',N''*-triarylbiurets. In cases where both type **8** and **10** compounds would be formed from a particular isocyanate (i.e., **8b** and **10f** or **8e** and **10e**), the pyrimidines **8** were obtained when relatively large amounts of aryl isocyanates were used (imino (thio)ether to isocyanate ratio approximately 1:10). With certain other isocyanates, however, we were able to synthesize only oxa(thia)zolo[2,3-*c*]pyrimidines **8** or quinoline derivatives **10** regardless of the molar ratio of the reagents (see Table I). Heating of *m*-chlorophenyl isocyanate with **1a** failed to give either of the expected products; only large amounts of *N,N'*-bis(*m*-chlorophenyl)urea could be isolated in this case. In all these reactions, extensive decomposition and/or polymerization (in which the isocyanate could possibly act as catalyst[6b]) of the cyclic imino (thio)ethers seem to be the cause for the low yields of heterocycles. The reaction of **2a** with *m*-tolyl isocyanate to give the quinoline **10** was expected to lead to the 2- or 4-thioxo derivative but produced the sulfur-free 2,4-dioxo derivative **10f** instead.

Proof for the structure of the oxa(thia)zolo[2,3-*c*]pyrimidine derivatives **8** was obtained by independent synthesis of a degradation product. Treatment of **8a** with hydrogen chloride in chloroform leads to oxazoline ring cleavage and formation of 1-(2-chloroethyl)-3-phenyl-5-

(1) A. I. Meyers and E. D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, **15**, 270 (1976), and papers cited therein; A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
(2) A. I. Meyers, "Heterocycles in Organic Synthesis", Wiley, New York, 1974.
(3) A. I. Meyers, *Acc. Chem. Res.*, 11, 375 (1978).
(4) R. Richter and H. Ulrich, *Justus Liebigs Ann. Chem.*, **743**, 10 (1971).
(5) R. Richter and H. Ulrich, *Chem. Ber.*, **106**, 1501 (1973).
(6) (a) A. Nehring and W. Seeliger, *Justus Liebigs Ann. Chem.*, **698**, 167 (1966); (b) W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nering, W. Thier, and H. Hellmann, *Angew. Chem., Int. Ed. Engl.*, **5**, 875 (1966).

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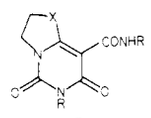
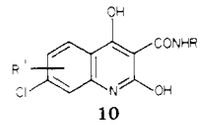
Table I. Products from Reactions of 2-Methyloxa(thia)zoline (1a and 2a) and 2,4-Dihydroxyquinoline with Aryl Isocyanates[a]



8

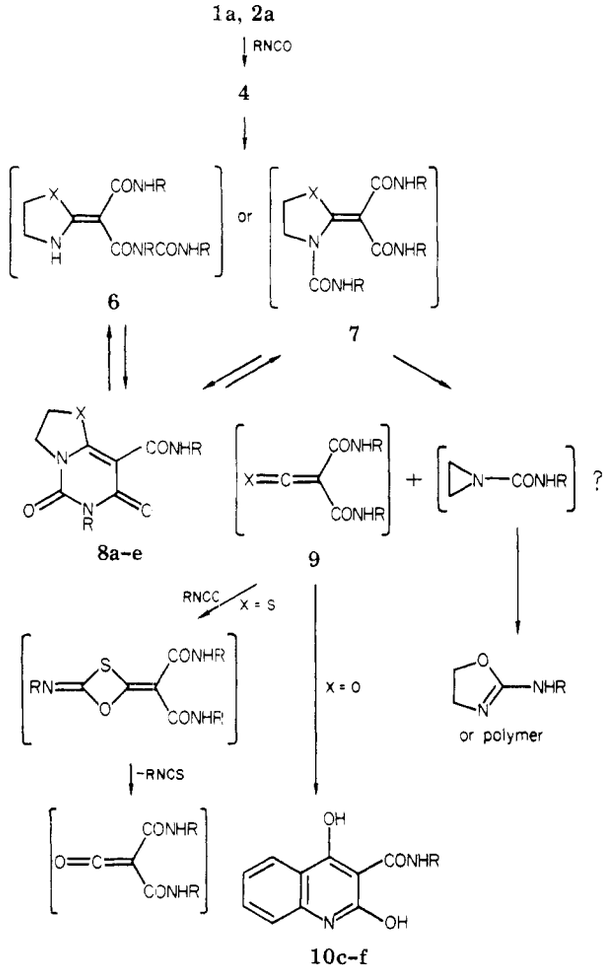


10

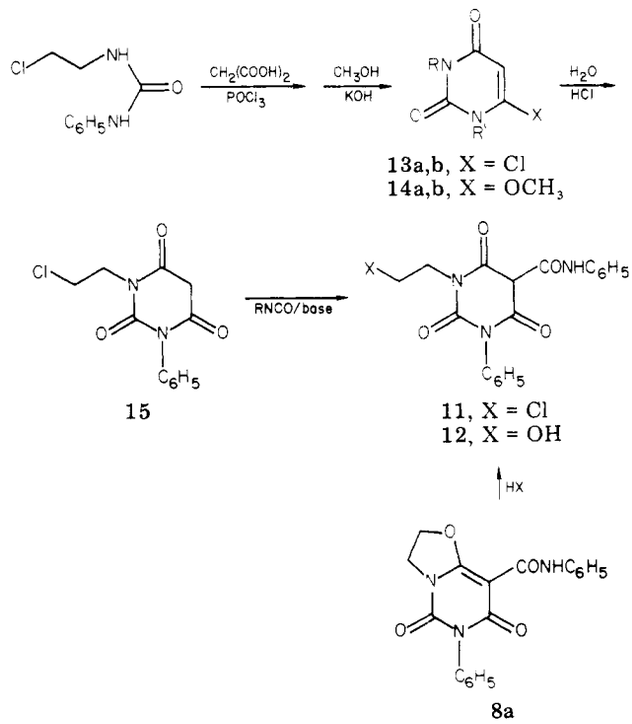
compd	R	R′	X	method[b]	molar ratio[c]	reaction duration, h	temp, °C	yield, %	mp, °C
8a	C_6H_5		O	A	1:4[d]	16	140-145	24	>300
8b	$C_6H_4CH_3$-*p*		O	A	1:10[d]	4.5	155	12	>300
8c	C_6H_5		S	A	1:5[e]	22	145	16	>300
8d	$C_6H_4CH_3$-*p*		S	A	1:5[e]	22	145	21	288
8e	$C_6H_4CH_3$-*m*		S	A	1:10[e]	4.5	145	37	278
10a	C_6H_5	H		B		0.25	170	91	305
10b	$C_6H_4CH_3$-*m*	H		B		0.25	170	72	286
10c	C_6H_4Cl-*m*	7-Cl		B		0.25	175	68	>320
10c	C_6H_4Cl-*m*	7-Cl		A	1:4[d]	23	145	14	>320
10d	C_6H_4F-*m*	7-F		A	1:4[d]	23	145-150	<5	>320
10e	$C_6H_4CH_3$-*m*	7-CH_3		A	1:5[e]	16	160	<5	280-282
10f	$C_6H_4CH_3$-*p*	6-CH_3		A	1:5[d]	18	160	<5	308-310

[a] Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds. [b] Method A: from **1a** or **2a** and excess aryl isocyanate. Method B: from 2,4-dihydroxyquinoline and excess aryl isocyanate. [c] Ratio of **1a** or **2a** to RN=C=O. [d] **1a** used. [e] **2a** used.

Scheme II



Scheme III



a, R = CH_2CH_2Cl, R′ = C_6H_5; **b**, R = C_6H_5, R′ = CH_2CH_2Cl.

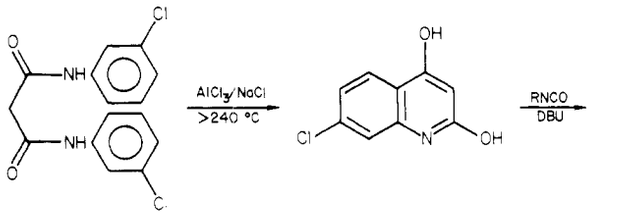
(*N*-phenylcarbamoyl)barbituric acid (**11**). Heating of **8a** in 10% methanolic potassium hydroxide gives the 1-(2-hydroxyethyl) derivative of the barbituric acid (**12**) instead of **11**.

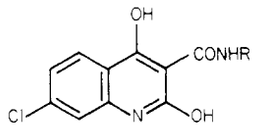
Compound **11** was independently synthesized by the sequence outlined in Scheme III from *N*-(2-chloroethyl)-*N*′-phenylurea and malonic acid. The condensation in the presence of phosphoryl chloride gives directly a chlorouracil for which we were unable to determine the exact substituent positions. This reaction probably involves the initial formation of 1-(2-chloroethyl)-3-phenyl barbiturate (**15**) which is converted to **13a** or **13b** by excess phosphoryl chloride. We were unable to synthesize **15** by a direct route in analogy to a published procedure for the preparation of 1,3-dimethylbarbituric acid.[7] Subsequent conversion of the chlorouracil into **15** proceeds best via the corresponding methoxyuracil, **14a** or **14b**, which is obtained on methanol–potassium hydroxide treatment of **13**, even in the presence of considerable amounts of water. Exchange of the methoxy group by OH in **14** in concentrated

(7) W. Pfleiderer and K. H. Schündehütte, *Justus Liebigs Ann. Chem.*, 612, 158 (1958).

hydrochloric acid yielded the barbiturate **15**. Base-catalyzed addition of phenyl isocyanate to **15** gave **11** in the final step.

The structure of the quinolines (**10**) was also verified by independent synthesis. Treatment of malondianilides with $AlCl_3/NaCl$ at elevated temperature leads to formation of 2,4-dihydroxyquinolines[8] which are subsequently converted to **10** on heating with an aryl isocyanate in the presence



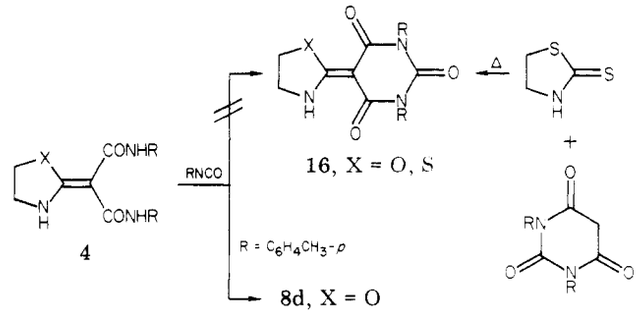


10c

of catalytic amounts of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU). Since cyclization of **1a** and **2a** with 3-substituted aryl isocyanates could lead to either 5- or 7-substituted quinolines, this synthesis also helped in establishing the position of the substituent on the carbocyclic part of the quinoline nucleus. Thus the synthesis of **10c** from malonbis(3-chloroanilide) as starting material established the mode of quinoline ring closure in the oxazoline and thiazoline–isocyanate reactions.

The formation of two entirely different heterocyclic structures from the same starting materials by only slight variations of the reaction conditions indicates that the reactions proceed via a common intermediate. In Scheme II we are presenting one possible pathway leading to both products. The acyclic 3:1 adducts **7**, previously proposed as intermediates of **4**,[4] or **6** can be envisioned as intermediates in the cyclization of **8**. On the other hand, thermal degradation of **4**, **6**, or **7** could alternatively lead to a (thio)ketene intermediate **9** which would itself stabilize by intramolecular cyclization to give **10**. These quinolines contain only the two carbon atoms of C-3 and C-4 from the imine components **1a** and **2a**. Related cyclizations, via ketene intermediates, leading to quinoline derivatives have been reported.[9,10] No evidence could be obtained for the loss of aziridine or a *N*-carbamoylaziridine on cleavage of the oxa(thia)zolidines **4**, **6**, and **7**.[11] The loss of sulfur in the thioketene **9** (X = S) is likely to take place prior to cyclization, possibly via a (2 + 2) cycloadduct as labile intermediate as indicated in Scheme II. A similar sequence, involving the formation of 4-anilinopyrrolo[2,3-*b*]quinolines, has been invoked for a C=O to C=NR exchange with aryl isocyanate.[9] Several related ring closures leading also to oxazolo- and thiazolo[2,3-*c*]pyrimidines have been observed in reactions of benzoyl and thiobenzoyl isocyanate with **1** and **2**.[12]

Initially we could not rule out a reaction of the acyclic adducts of type **4** (which are stable up to 180 °C) with aryl isocyanates to produce compounds of type **16**. The independent synthesis of the degradation product of **8a** eliminated **16** as another possible product. When **4a** (R = $C_6H_4CH_3$-*p*) was heated with excess *p*-tolyl isocyanate at 145 °C for 17 h, the oxazolopyrimidine **8d** was obtained in 17% yield. In addition to the evidence described above, we synthesized the (thiazolidin-2-yl)barbituric acid derivative **16a** (X = S, R = C_6H_5) from 1,3-dimethylbarbituric acid and 2-mercaptothiazoline on heating to 240–255 °C.[13]



The initial assumption that the preferred formation of quinolines **10** in mixtures containing less aryl isocyanate was somehow associated with a depletion of the isocyanate supply during the reaction proved not to be true. The reaction of **1a** with *p*-tolyl isocyanate was monitored by IR spectroscopy, and it was found that mixtures of the reagents in molar ratios of 1:5 and 1:10 still contained residual isocyanate after 22 h. A visible difference between both mixtures was the formation of considerable amounts of solid products in the 1:5 mixture early during the reaction (2 h).

We also established that oxazolopyrimidines **8** are not precursors of the quinolines **10** since heating of **8d** with excess *p*-tolyl isocyanate at 150–155 °C for 17 h does not lead to formation of **10f** (70% of **8d** recovered).

Experimental Section[14]

General Procedure for the Preparation of 5-Aryl-7-(*N*-arylcarbamoyl)-4,6-dioxo-2,3,3a,4,5,6-hexahydrooxazolo- and -thiazolo[2,3-*c*]pyrimidines (8a–e) and 3-(*N*-Arylcarbamoyl)-2,4-dihydroxyquinolines (10c–f) from 1a, 2a, and Aryl Isocyanates. A mixture of aryl isocyanate and 2-methyloxazoline (**1a**) or 2-methylthiazoline (**2a**) was kept from 4.5 to 23 h at a temperature near 150 °C (for individual molar ratios of reagents and reaction conditions see Table I). During the reaction the mixtures turned yellow and later orange and became highly viscous toward the end. In several cases, initially formed solid products redissolved during heating. The cooled melts were treated with an acetone–methanol mixture which resulted in a partial conversion of the glassy reaction products into crystalline solids while large amounts of colored and often fluorescent byproducts were dissolved. The crude solids, which were collected by filtration and washed with acetone–methanol consisted mostly of a mixture of product (**8** or **10**) and varying amounts of *N,N'*-diarylurea and *N,N',N''*-triarylbiuret. Treatment with boiling methanol (if necessary several times) dissolved the ureas and biurets almost entirely. Final purification of the remaining crude products **8** or **10** was best achieved by recrystallization from DMF–methanol.

The amounts of products isolated by this method probably do not truly reflect the actual yields since repeating recrystallization for the isolation of analytically pure samples led unavoidably to losses of material. Yields, melting points, and analytical data are given in Table I.

(8) E. Ziegler, R. Wolf, and T. Kappe, *Monatsh. Chem.*, **96**, 418 (1965); *Chem. Abstr.*, **63**, 5636 (1965).
(9) R. Richter and H. Ulrich, *J. Org. Chem.*, **38**, 2614 (1973).
(10) H. M. Blatter and H. Lukaszewski, *Tetrahedron Lett.*, 855 (1964).
(11) It seems likely that any *N*-ethylene-*N'*-phenylurea formed would be polymerized under the reaction conditions. See also Y. Iwakura and A. Nabeya, *Nippon Taishitsugaku Zasshi*, **77**, 773 (1956); *Chem. Abstr.*, **52**, 9028 (1958).
(12) O. Tsuge and S. Kanemasa, *Tetrahedron*, **28**, 4737 (1972).
(13) For related reactions of isothioamide derivatives with active methylene compounds see: K. Hardtke, *Angew. Chem.*, **76**, 781 (1964).
(14) Melting points were taken with a Fisher-Johns melting point apparatus; elemental analyses were by Galbraith Laboratories, Knoxville, TN; IR spectra were determined by using a Beckman Acculab 4 and a Perkin-Elmer 267 spectrophotometer.

1-(2-Chloroethyl)-3-phenyl-4-chlorouracil (13a) or 3-(2-Chloroethyl)-1-phenyl-4-chlorouracil (13b). A solution of 4.1 g (0.04 mol) of malonic acid, 8.0 g (0.04 mol) of *N*-(2-chloroethyl)-*N'*-phenylurea, and 25 g (0.16 mol) of phosphoryl chloride in 50 mL of chloroform was kept for 7 h at 75–80 °C during which time hydrogen chloride was given off. After the reaction the dark brown solution was concentrated at reduced pressure, and the residue was decomposed with ice. The resulting aqueous solution was extracted with chloroform, the extracts were, after drying over sodium sulfate, evaporated, and the dark residue was taken up in hot methanol. Crystals which separate on cooling were collected by filtration and dried: 2.35 g (30%); mp 183–184 °C (methanol); colorless needles; IR ($CHCl_3$) 1715 and 1665 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{10}Cl_2N_2O_2$: C, 50.55; H, 3.54; N, 9.82; Cl, 24.87. Found: C, 50.58; H, 3.52; N, 9.70; Cl, 24.67.

1-(2-Chloroethyl)-3-phenyl-4-methoxyuracil (14a) or 3-(2-chloroethyl)-1-phenyl-4-methoxyuracil (14b) was prepared by heating a suspension of 1.50 g (0.005 mol) of **13a** or **13b** in a mixture of 20 mL of methanol, 5 mL of a 5% methanolic potassium hydroxide solution, and 5 mL of water to reflux until most of the solid had dissolved (potassium chloride was formed during the process). Diluting the reaction mixture with water caused separation of colorless crystals of **14** (1.03 g, 68%), which were collected by filtration after cooling of the mixture to room temperature: mp 173–174 °C dec (methanol); colorless needles; IR ($CHCl_3$) 1715 and 1655 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{13}ClN_2O_3$: C, 55.63; H, 4.67; N, 9.98; Cl, 12.63. Found: C, 55.87; H, 4.79; N, 9.91; Cl, 12.83.

1-(2-Chloroethyl)-3-phenylbarbituric Acid (15). When a suspension of 0.7 g (0.0025 mol) of **14a** or **14b** and 3 mL of concentrated hydrochloric acid was stirred at room temperature for 15 min, a colorless to pale yellow solution was obtained. Dilution with water caused the separation of a gummy material, which was, after decanting off the aqueous solution, dissolved in hot methanol, and the solution was diluted gradually with water until crystallization started. The product (0.43 g, 65%) was once more crystallized for analysis from methanol–water to yield fine, colorless needles: mp 117–120 °C; IR ($CHCl_3$) 1710 (sh) and 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{11}ClN_2O_3$: C, 54.05; H, 4.15; N, 10.50. Found: C, 54.14; H, 4.21; N, 10.38.

1-(2-Chloroethyl)-3-phenyl-5-(*N*-phenylcarbamoyl)-barbituric Acid (11). (a) From 15. A mixture of 0.20 g (0.52 mmol) of **15** and 0.80 g (6.6 mmol) of phenyl isocyanate containing 1 drop of triethylamine was kept for 5 min at 80 °C. Colorless crystals started to form in the solution during the reaction, and more were precipitating after cooling and diluting with approximately 5–10 mL of methanol (to destroy excess isocyanate). Filtration afforded 0.20 g (69%) of **11**, which was recrystallized for analysis from chloroform–methanol to give fine, colorless needles: mp 189–190 °C; IR ($CHCl_3$) 1720 and 1650 (vs) cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{16}ClN_3O_4$: C, 59.15; H, 4.18; N, 10.89; Cl, 9.19. Found: C, 59.29; H, 4.20; N, 10.70; Cl, 9.06.

(b) From 8a. When a stream of dry HCl gas was passed into a suspension of 0.50 g (1.43 mmol) of **8a** in 20 mL of chloroform at 30–40 °C, a clear yellow solution was obtained within 10 min (at this time IR indicated completion of the ring opening). Removal of solvent left a crystalline residue which was taken up in methanol and filtered off; 0.55 g (quantitative) of **11** was isolated, which was identical in IR comparison and mixture melting point with the material prepared above. A less pure product was obtained on ring opening with concentrated hydrochloric acid.

1-(2-Hydroxyethyl)-3-phenyl-5-(*N*-phenylcarbamoyl)-barbituric acid (12) was formed on heating a suspension of **8a** (1.0 g, 2.86 mmol) in 10% methanolic potassium hydroxide solution (20 mL) to reflux until a clear yellow solution was obtained (approximately 10 min). Removal of solvent in vacuo left a semisolid residue which was taken up in water. Acidification of the solution by dropwise addition of concentrated hydrochloric acid led to precipitation of a pale yellow solid which was isolated by filtration (1.04 g, quantitative). A sample was recrystallized for analysis from methanol: mp 204–205 °C; pale yellow needles; IR ($CHCl_3$) 1705 (sh), 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{17}N_3O_5$: C, 62.12; H, 4.66; N, 11.44. Found: C, 62.23; H, 4.59; N, 11.30.

General Procedure for the Preparation of 2-(*N*-Arylcarbamoyl)-2,4-dihydroxyquinolines (10b) from 2,4-Dihydroxyquinolines and Aryl Isocyanate. 2,4-Dihydroxyquinolines bearing substituents in the 6 and 7 position were prepared by following a literature procedure.[8] Mixtures of 1.0 g of 2,4-dihydroxyquinoline and 10 mL of aryl isocyanate were kept at 170 °C for 5 min after which approximately 100 mg of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) was added. Conversion of the starting materials was indicated by partial dissolution of the quinoline followed by precipitation of reaction product. More DBU (100 mg) was added after 5 min. The mixtures were allowed to cool to room temperature after a 15-min total reaction duration. The crude products were filtered off and washed with methanol; recrystallization of samples for analysis was usually from DMF–methanol. Yields, melting points, and analytical data are shown in Table I.

1,3-Diphenyl-2,4,6-trioxo-5,5-(thiazolidine-2,2-diyl)perhydropyrimidine (16, X = S). A mixture of 1.40 g (5 mmol) of 1,3-diphenylbarbituric acid and 1.20 g (0.01 mol) of 2-mercaptothiazoline was kept at 240–245 °C for 5 min. Hydrogen sulfide was given off during the reaction. After the yellow melt was cooled to room temperature, methanol was added which transformed the glassy product into a pale yellow crystalline powder. Filtration and drying of the residue gave 1.12 g (61%) of **16**: mp >300 °C (chloroform–methanol); pale yellow powder; IR ($CHCl_3$) 1715, 1645, and 1625 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{15}N_3SO_3$: C, 62.46; H, 4.14; N, 11.50. Found: C, 62.35; H, 4.37; N, 11.36.

Registry No. **1a**, 1120-64-5; **2a**, 2346-00-1; **8a**, 71901-57-0; **8b**, 71886-04-9; **8c**, 71886-05-0; **8d**, 71886-06-1; **8e**, 71886-07-2; **10a**, 16798-54-2; **10b**, 71886-08-3; **10c**, 71886-09-4; **10d**, 71886-10-7; **10e**, 71886-11-8; **10f**, 71886-12-9; **11**, 71886-13-0; **12**, 71886-14-1; **13a**, 71886-15-2; **13b**, 71886-16-3; **14a**, 71886-17-4; **14b**, 71886-18-5; **15**, 71886-19-6; **16** (X = S), 71886-21-0; malonic acid, 141-82-2; *N*-(2-chloroethyl)-*N'*-phenylurea, 7144-13-0; 2,4-dihydroxyquinoline, 52851-41-9; 7-chloro-2,4-dihydroxyquinoline, 1677-35-6; 7-fluoro-2,4-dihydroxyquinoline, 71886-20-9; 7-methyl-2,4-dihydroxyquinoline, 1677-43-6; 6-methyl-2,4-dihydroxyquinoline, 1677-44-7; 1,3-diphenylbarbituric acid, 7391-60-8; 2-mercaptothiazoline, 96-53-7; phenyl isocyanate, 103-71-9; *p*-methylphenyl isocyanate, 622-58-2; *m*-methylphenyl isocyanate, 621-29-4; *m*-chlorophenyl isocyanate, 2909-38-8; *m*-fluorophenyl isocyanate, 404-71-7.