2,5,13,16-tetrone (6b). This compound was prepared analogously to a described procedure from the bis((*S*)-*tert*-leucine amide) of pyridine-3,5-dicarboxylic acid (800 mg, 2.0 mmol) and 1,5-dibromo-3-oxapentane (470 mg, 2.0 mmol). The compound was isolated as a yellow powder, which was purified by flash chromatography (column 10 cm × 25 mm diameter, 15 g of Kieselgel Merck 60, 230–240-mesh ASTM) with ethyl acetate (200 mL) as eluent. The material obtained was recrystallized from CH_2Cl_2–diethyl ether (1:1). There was obtained 460 mg (1.03 mmol, 48% yield) of product as a white powder, mp 295 °C dec: IR (KBr) 3300, 1735, 1645, and 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 18 H, $(CH_3)_3C$), 3.77–3.81 (m, 4 H, $CO_2CH_2CH_2O$), 4.23–4.28 + 4.53–4.75 (2 × m, 4 H, CO_2CH_2), 4.78 (d, 2 H, NHCH), 7.11 (d, 2 H, NH), 8.00 (t, 1 H, pyr-4H), and 8.96 (d, 2 H, pyr-2,6H); ^{13}C NMR ($CDCl_3$, CD_3OD) δ 26.2 (q), 35.2 (s), 61.0 (d), 63.3 (t), 69.7 (t), 128.3 (s), 130.9 (d), 152.1 (d), 164.4 (s), and 168.2 (s); $[\alpha]_{578}$ −129.8°, $[\alpha]_{546}$ −153.9°, $[\alpha]_{436}$ −336.5°, $[\alpha]_{365}$ −767.4° (*c* 0.18, DMF); exact mass spectrum, *m/e* calcd for $C_{23}H_{33}N_3O_7$ 463.231, found 463.231; UV (95% ethanol) λ_{max} 258 (ϵ 3700) and 214 nm (ϵ 11 700).

(4*S*,14*S*)-4,14-Di(2-propyl)-5,13-dioxo-6,12-dioxa-3,15,19-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dithione (9). The bridged pyridine 1 (300 mg, 0.69 mmol) and Lawesson reagent[28] (14) (310 mg, 0.76 mmol) were dissolved in 25 mL of dry benzene. The solution was refluxed under a nitrogen atmosphere for 3 h. The solvent was removed under reduced pressure, and the remaining yellow sticky mass was flash chromatographed (column 8 cm × 2.5 cm, 15 g of Kieselgel Merck 60, 230–400-mesh ASTM) with CH_2Cl_2 (100 mL), followed by CH_2Cl_2/ethyl acetate (1:1, 100 mL) as eluents. There was obtained 320 mg (0.69 mmol, 100% yield) of product as a yellow powder, mp 194.3–195.8 °C: IR (KBr) 3180, 1740, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (dd, 12 H, $(CH_3)_2CH$), 1.76 (br s, 6 H, $OCH_2(CH_2)$, CH_2O), 2.06–2.61 (m, 2 H, $(CH_3)_2CH$-), 3.98–4.72 (m, 4 H, CO_2CH_2), 5.10 (dd, 2 H, CSNHCH), 7.23 (br s, 1 H, pyr-4H), 8.38 (br s, 2 H, pyr-2,6H), and 9.21 (d, 2 H, NH); ^{13}C NMR ($CDCl_3$) δ 18.5 (d), 18.9 (d), 25.0 (t), 28.8 (t), 31.3 (d), 64.7 (d), 65.9 (t), 127.9 (d), 136.0 (s), 149.4 (d), 168.2 (s), and 195.0; $[\alpha]_{578}$ −427.5°, $[\alpha]_{546}$ −567.5° (*c* 0.91, CH_2Cl_2); exact mass spectrum, *m/e* calcd for $C_{22}H_{31}N_3O_4S_2$ 465.176, found 465.177; UV (95% ethanol) λ_{max} 372 (ϵ 510), 276 (ϵ 12 200), and 224 nm (ϵ 16 800).

Acknowledgment. We are pleased to acknowledge very productive discussions with Prof. G. Snatzke. This article was prepared during the period that R.M.K. was Michael Guest Professor at the Weizmann Institute of Science.

Supplementary Material Available: Tables A–C (Experimental) with crystal data, final atomic coordinates and equivalent isotropic thermal parameters, and selected interatomic bond distances, bond angles, and torsional angles (13 pages). Ordering information is given on any current masthead page.

(28) Scheibye, S.; Pederson, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

One-Carbon Compounds as Synthetic Intermediates. The Synthesis of Hydropyrimidines and Hydroquinazolines by Sequential Nucleophilic Addition to Diphenyl Cyanocarbonimidate with Concomitant Cyclization

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Diphenyl cyanocarbonimidate (1) undergoes nucleophilic addition with ω-amino esters and amines in a sequential manner to give guanidine derivatives that, for the most part, spontaneously cyclize to give hydropyrimidines or hydroquinazolines. The hydropyrimidines could be dehydrogenated to dihydropyrimidines, and the NCN group could be hydrolyzed to a carbonyl or amine group in the pyrimidine and to an amine group in the quinazoline series. The regiospecificity of the cyclization was determined by a combination of spectroscopic methods and comparison of compounds synthesized by standard routes. The scope of the synthetic route is indicated. Some of the acyclic *N*-cyano-*O*-phenylisoureas formed by the first nucleophilic addition exist as mixtures of isomers, and the barriers to interconversion have been determined by NMR spectroscopy.

One-carbon compounds in which the carbon is divalently bonded to a heteroatom and has two singly bonded electron-withdrawing substituents have found considerable use both as reagents and as synthetic intermediates. Thus 1,1′-carbonyldiimidazole,[2] 1,1′-thiocarbonyldiimidazole,[3] and methyl cyanoformate[4] have been used as reagents or for the introduction of functional groups whereas *N*-arylchloroformimidoyl chlorides[5] and diphenyl and dimethyl cyanocarbonthioimidate[6] have been used as intermediates, particularly in the synthesis of heterocycles. Diphenyl cyanocarbonimidate (1) has also been used in the synthesis of heterocycles,[7] and it has advantages over its sulfur analogues. In many of the cases in which 1 has been used to prepare heterocycles, the cyano group has been involved in the resulting ring system.[8] Thus reaction of

(1) (a) University College London. (b) Sandoz Institute for Medical Research.

(2) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351. See: Fieser, M. *Fiesers' Reagents for Organic Synthesis*; Wiley: New York, 1986; Vol. 12, p 106.

(3) Staab, H. A.; Walther, G. *Justus Liebigs Ann. Chem.* **1962**, *657*, 98. See: Fieser, M. *Fiesers' Reagents for Organic Synthesis*; Wiley: New York, 1986; Vol. 12, p 556.

(4) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

(5) Kühle, E.; Anders, B.; Klauke, E.; Tarnow, H.; Zumach, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 20.

(6) Gomper, R.; Gaeng, M.; Saygin, F. *Tetrahedron Lett.* **1966**, 1885. Gewald, K.; Blauschmidt, P.; Mayer, R. *J. Prakt. Chem.* **1967**, *35*, 97. Wobig, D. *Justus Liebigs Ann. Chem.* **1972**, *764*, 125. Jensen, K. A.; Henrickson, I. *Acta Chem. Scand.* **1968**, *22*, 1107. Wittenbrook, L. S. *J. Heterocycl. Chem.* **1975**, *12*, 37.

(7) (a) Webb, R. L.; Labaw, C. S. *J. Heterocycl. Chem.* **1982**, *19*, 1205. (b) Webb, R. L.; Eggleston, D. S.; Labaw, C. S.; Lewis, J. J.; Wert, K. *Ibid.* **1987**, *24*, 275. (c) Kristinsson, H.; Winkler, T.; Rihs, G.; Fritz, H. *Helv. Chim. Acta* **1985**, *68*, 1155.

(8) Five-membered-ring heterocycles have been prepared with bidentate nucleophiles in which the NCN group is not involved and remains as a ring substituent. See, for example, ref 6, 7.

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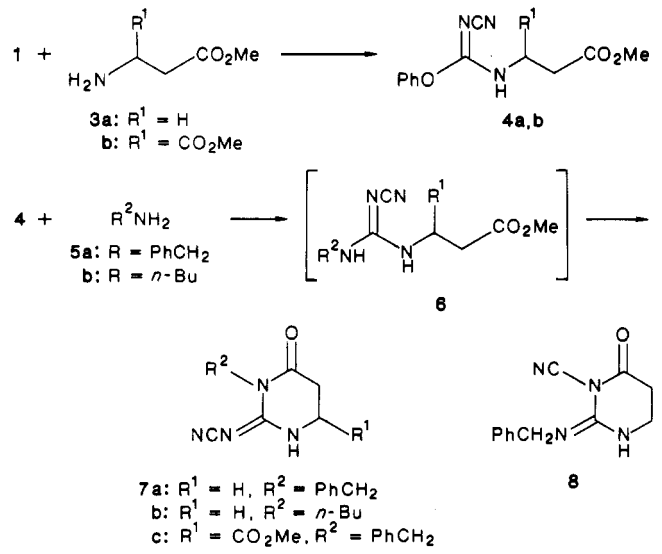
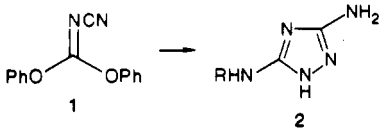
Scheme I



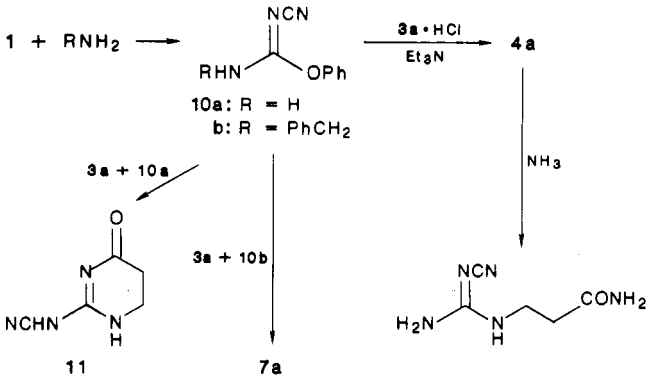
1 with amines followed by hydrazine gave triazoles **2**.[7a,b] That the introduction of the two nucleophiles can be controlled in a sequential manner appeared to provide a means to prepare molecules that could then be cyclized through functional groups on the nucleophiles rather than through the cyano group. We now describe the sequential reaction of **1** with ω-amino esters and amines and the cyclization, usually spontaneous, of the resulting compounds to hydropyrimidines and hydroquinazolines.[9]



Results and Discussion

Synthesis of Hydropyrimidines. Diphenyl cyanocarbonimidate (**1**) was treated with methyl 3-aminopropionate (**3a**) (generated in situ from methyl 3-aminopropionate hydrochloride and triethylamine) in 2-propanol to give **4a** in 72% yield. The IR spectrum of **4a** showed absorptions at 1730 and 1640 cm^{-1}. The ^1H and ^{13}C NMR spectra indicated the presence of two stereomers in the ratio 1.2:1. Heating the sample to 150 °C gave a spectrum attributable to one compound with a small amount of decomposition.[10] Treatment of **4a** with benzylamine (**5a**) in boiling 2-propanol gave, instead of the expected acyclic adduct **6a**, the cyclized product **7a** (Scheme I). The IR spectrum showed bands at 1725 and 1660 cm^{-1}, and the ^1H NMR spectrum is in agreement with a cyclic structure. A question immediately arose regarding the direction of cyclization; reaction of the amine nitrogen with the ester would give **7a**, whereas reaction of the imine nitrogen would give **8**. These compounds differ only in the interchange of substituents between the exocyclic nitrogen and N-3, and with no model compounds on which to rely, distinguishing between them on the basis of spectroscopic properties was not possible. The double bond in either of the two isomers could be endocyclic rather than exocyclic, but its exocyclic position is confirmed from the ^1H NMR spectrum, which shows the protons at C-6 coupled both to those at C-5 and to the proton of N-1. The assignment of structure **7a** to this compound is based on its subsequent conversion to a dihydropyrimidine of known structure (vide infra).

Scheme II



Similarly, treatment of **4a** with 1-aminobutane (**5b**) gave **7b** in 65% yield. Treatment of **4a** with aqueous NH_3 in 2-propanol at room temperature gave the noncyclized compound **9** in which, besides the substitution of PhO by NH_2, the ester group had been replaced by the amide function. Compound **9** probably arises from the expected tetrahydropyrimidine **11** by nucleophilic addition of ammonia on the carbonyl function followed by ring opening, a process with ample precedent.[11] Further support for this suggestion came from experiments in which the order of reaction of the nucleophiles was reversed (Scheme II). Treatment of **1** with ammonia in 2-propanol gave *N*-cyano-*O*-phenylisourea (**10a**) in 85% yield.[12] Treatment of **10a** with methyl 3-aminopropionate hydrochloride and triethylamine gave the *O*-phenylisourea **4a** rather than the desired tetrahydropyrimidine **11**, but treatment of **10a** with pregenerated **3a** gave **11** in 71% yield.[13] We believe that the formation of **4a** in the first case arises from protonation of the NH_2 moiety of **10a** and displacement of ammonia rather than phenoxide (or phenol).

We have assigned the double bond in **11** to an endocyclic position since in the ^1H NMR spectrum of **11** there are two NH signals but no coupling between one of these and the C-6 protons. This is in contrast to the previous derivatives where conjugation with the cyano group is preferred. It is, however, quite possible that proton exchange is occurring between N-1 and the other nitrogens at such a rate that the coupling to the C-6 protons is not observed, the structure with the double bond between C-2 and N-3 appearing particularly favorable.

The order of substitution can also be reversed in the case of methyl 3-aminopropionate and benzylamine. Treatment of **1** with **5a** gave **10b** in 69% yield.[7a,b] Subsequent treatment with **3a**, prepared in situ, gave **7a** but only in 15% yield. The lower yield may reflect diketopiperazine formation or the difficulty of introducing the largest group in the last step, or as in the case with **10a**, it may be due to the in situ mode of generation of **3a**.

Treatment of **1** with dimethyl 2-aminobutanedioate (**3b**) gave **4b** in 62% yield (Scheme I). Treatment of **4b** with benzylamine (**5a**) gave **7c** in quantitative yield. The IR spectrum shows bands at 2190, 1760, 1740, and 1650 cm^{-1}, and the ^1H NMR spectrum again shows coupling between

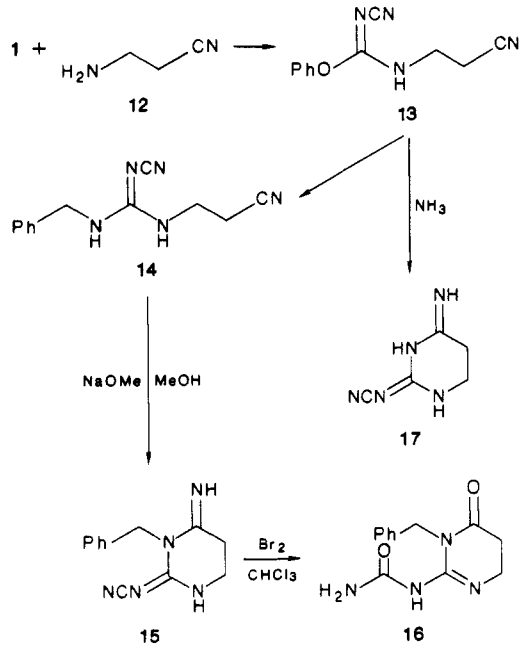
(9) For a preliminary account of part of this work, see: Garratt, P. J.; Hobbs, C. J.; Walpole, C. S. J.; Wrigglesworth, R. *J. Chem. Soc., Chem. Commun.* **1987**, 568.
(10) We thank Dr. H. R. Loosli, Sandoz, Basle, for the initial ^1H NMR spectra of this compound.
(11) Matsumoto, K.; Rapoport, H. *J. Org. Chem.* **1968**, *33*, 552.
(12) Grigat, E.; Pütter, R. *Chem. Ber.* **1965**, *98*, 2619.
(13) Sugino, K.; Kitawaki, R.; Akitani, M. *Chem. Abstr.* **1971**, *74*, P88031x.

Table I. ^1H and ^{13}C NMR Spectral Chemical Shifts of Ring Atoms of Hydropyrimidines[a]

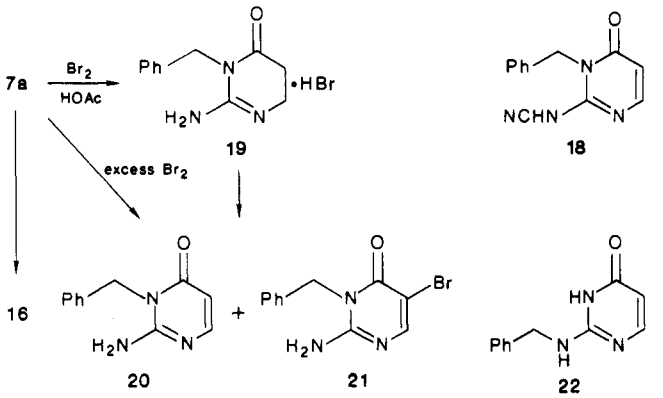
compd	chemical shifts, δ					
	N-1	C-2	N-3	C-4	C-5	C-6
20					5.67	7.58
		156.5		161.9	101.2	155.0
22			6.96		5.56	7.58
		155.0		162.2	103.0	155.9
23					5.89	
		154.1		166.4	96.4	137.9[b]
24	9.0				5.92[b]	
					94.6	139.0
27					5.98	
		153.0			98.5	138.9

[a] All samples dissolved in DMSO-d_6 except those indicated. [b] Samples dissolved in $CDCl_3$.

Scheme III



Scheme IV



the N-1 and C-6 protons, indicating that the double bond is exocyclic. The possibility arises in this case that a five-membered ring can be formed, and indeed, a preference for the formation of five-membered rings has been observed in other cases.[14] The subsequent conversion of **7c** to a tetrahydropyrimidine in good yield supports the six-membered-ring assignment, but the well-known rearrangement of five- to six-membered rings in this area requires further work to afford complete confidence in this structure.[15]

The reaction is not confined to the cyclization of esters. Thus treatment of **1** with 2-cyanoethylamine (**12**) (prepared in situ from the half fumarate salt of **12** and triethylamine) gave **13**, which reacted with benzylamine in boiling 2-propanol to give the *N*-cyanoguanidine **14**, cyclization not having occurred spontaneously in this case (Scheme III). The *N*-cyanoguanidine **14** was, however, readily cyclized with sodium methoxide in methanol to the hexahydropyrimidine **15**. The imine structure for **15** is suggested by the ^1H NMR spectrum, which shows two exchangeable protons with different chemical shifts. Reaction of **15** with bromine in chloroform gave a tetrahydropyrimidine, **16**, identical in all observed respects with a sample that had previously been prepared from **7a** (see Scheme IV). Reaction of **13** with aqueous ammonia gave directly the hexahydropyrimidine **17**.

Synthesis of Dihydropyrimidines. The conversion of the hydropyrimidines described above into dihydropyrimidines was undertaken in the interests of both synthetic utility and the determination of structure. Classically, hexahydro- and tetrahydropyrimidines have been converted into dihydropyrimidines by bromination at C-5 followed by dehydrobromination.[16] When **7a** was treated with bromine in boiling acetic acid, instead of the expected dihydropyrimidine **18**, the hydrobromide **19** was obtained, in which the cyano group had been lost but dehydrogenation had not occurred. The IR spectrum of **19** shows bands at 1728 and 1660 cm^{-1}, and the electronic spectrum shows a maximum at 217 nm, consistent with an acylamino-type acylguanidine.[11] The hydrobromide **19** was then treated with a large excess of bromine in boiling acetic acid for 15 h, and after removal of the solvent, the residue was boiled with pyridine to give 2-amino-3-benzyl-4-oxo-3,4-dihydropyrimidine (**20**) in 48% yield and 2-amino-3-benzyl-5-bromo-4-oxo-3,4-dihydropyrimidine (**21**) in 11% yield (Scheme IV). We then reinvestigated the direct conversion of **7a** into **20** and found that treatment with a 10-fold excess of bromine in boiling acetic acid gave **20** in 72% isolated yield. In order to establish the structure of **20**, the alternative isomer, 2-(benzylamino)-4-oxo-3,4-dihydropyrimidine (**22**), was prepared by a conventional route from 2,4-dichloropyrimidine.[17] The ^1H and ^{13}C NMR spectra of **20** and **22** are compared in Table I.

Treatment of **7a** with bromine in $CHCl_3$ gave the tetrahydropyrimidine **16**, in which hydrolysis of the NCN group had occurred. Presumably hydrolysis of the NCN

(14) Besse, R. J.; Hobbs, C. J.; Seuleiman, A. M., unpublished observations.

(15) See: Mitchell, H. K.; Nyc, J. F. *J. Am. Chem. Soc.* **1947**, *69*, 674.

(16) See: Brown, D. J. The Pyrimidines and Supplements. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1962, 1970, 1985.

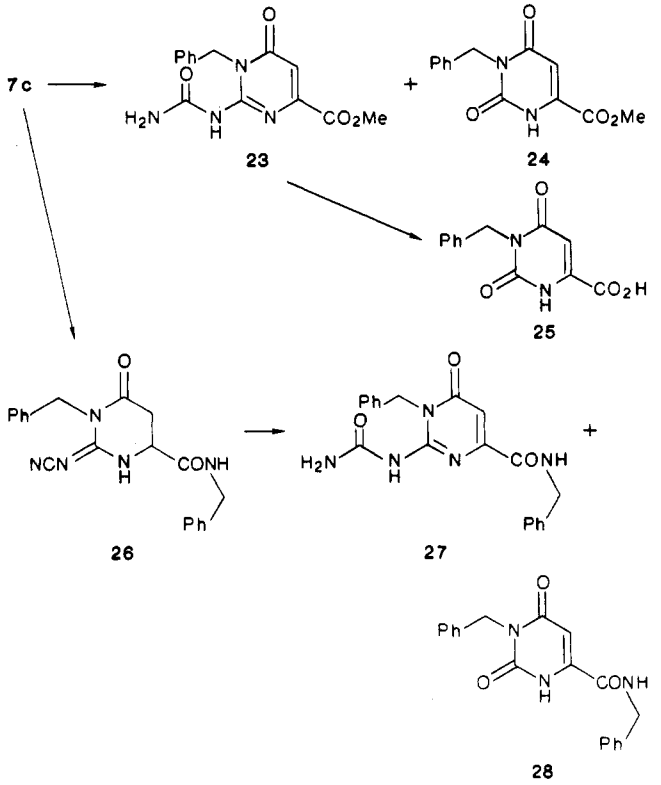
(17) Matsukawa, T.; Shirakawa, K. *Yakugaku Zasshi* **1951**, *71*, 943. These authors prepared **16** by a route different from the one we used, but our melting point is in agreement with that given.

Table II. ^1H and ^{13}C NMR Spectral Chemical Shifts of Ring Atoms of Hydroquinazolines[a]

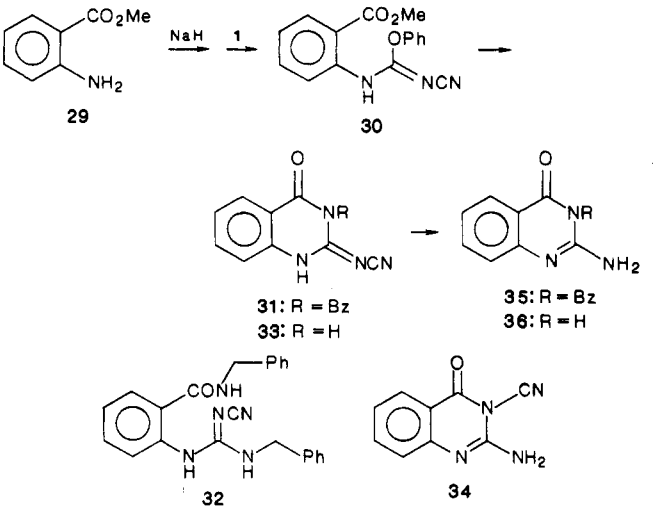
compd	chemical shifts, δ							
	N-1	C-2	N-3	C-4	C-5	C-6	C-7	C-8
31	12.2				8.02	7.37	7.78	7.70
35			10.99		7.87	7.09	7.55	7.19
33	12.18		12.18		7.96	7.34	7.75	7.60
36					7.92		7.59	7.12
		151.9		161.7				
35·HCl					8.04	7.41	7.84	7.49
		151.7		159.4				

[a] Samples dissolved in DMSO-d_6.

Scheme V



Scheme VI



group takes place early in the conversion of **7a** to **20**.

Treatment of **7c** with bromine in boiling acetic acid gave 3-benzyl-6-carbomethoxy-4-oxo-2-ureido-3,4-dihydropyrimidine (**23**) in 61% yield and 3-benzyl-6-carbomethoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (**24**) in 4% yield (Scheme V). Boiling **23** with aqueous NaOH and subsequent acidification gave 3-benzylorotic acid (**25**) in 51% yield. The electronic spectrum of **25** showed the same pH dependence reported by Curran and Angier[18] although the melting point was lower occurring, as reported, with decomposition. Further hydropyrimidines could be derived from **7c**; thus reaction with benzylamine in boiling 2-propanol gave **26** in 49% yield, which could be converted into a mixture of **27** (62%) and **28** (4%) by treatment with bromine in boiling acetic acid. The ^1H and ^{13}C NMR spectra were in accord with the assigned structures.

The synthesis of 3-benzylorotic acid closely resembles the biosynthetic route to orotic acid,[19] both the synthetic and biosynthetic routes involving the connection of 1C, 1N and 1N3C fragments. In our synthesis, a one-carbon entity reacts first with dimethyl 2-aminobutanedioate (1N3C) and then with an amine to form the hexahydropyrimidine whereas the biosynthetic route involves carbon dioxide reacting with ammonia to give a 1N1C fragment, which reacts with 2-aminobutanedioic acid to give the hexahydropyrimidine. It is quite possible that the order of our reactants could be reversed, as was shown for benzylamine and 3-aminopropionate, and benzylamine replaced by ammonia to more closely mimic the biosynthetic pathway.

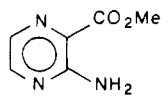
Synthesis of Dihydroquinazolines. The extension of our synthetic procedure to the preparation of dihydroquinazolines was then examined, since the presence of the benzene ring provides an unsaturation that removes the dehydrogenation step required in the dihydropyrimidine synthesis. Methyl anthranilate (**29**) and **1** were dissolved in 2-propanol, and when no reaction occurred after stirring at room temperature for some hours, the mixture was boiled. Even after 16 h, however, only starting materials were present. Presumably the reduced nucleophilicity of the amine function precludes reaction. Consequently, **29** was treated with sodium hydride in dioxane,[20] **1** was added, and the mixture was stirred at room temperature for 16 h, when the *O*-phenylisourea **30** was isolated in 50% yield. Treatment of **30** with benzylamine in boiling 2-propanol gave the 3-benzyltetrahydroquinazoline **31** in 79% yield together with a small amount of the acyclic adduct **32**, in which benzylamine has also displaced the methoxy group (Scheme VI). The ^1H NMR spectrum is consistent with the structure assigned to **31** but does not distinguish whether the C=N bond is endo- or exocyclic. Treatment or **30** with ammonia in 2-propanol at room temperature gave **33** in 84% yield.[21] The formation of this cyclic product is in contrast to the reaction in the pyrimidine series and presumably reflects the greater stability of **33**

(18) Curran, W. V.; Angier, R. B. *J. Org. Chem.* **1966**, *31*, 201.
(19) See: Crosbie, G. W. In *The Nucleic Acids*; Chargaff, E., Davidson, J. N., Eds.; Academic Press: New York, 1960; Vol. 3, p 323.
(20) Major, R. T.; Peterson, L. H. *J. Org. Chem.* **1957**, *22*, 579.
(21) Skowrońska-Serafinova, B.; Urbański, T. *Rocz. Chem.* **1952**, *26*, 51; *Chem. Abstr.* **1953**, *47*, 7507i.

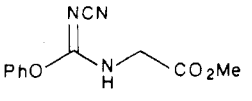
conferred by the benzene ring unsaturation. Structure **33** is preferred for this product although cyclization by the alternative mode to give **34** has not been excluded.

The CN groups in both **31** and **33** can be hydrolyzed with HCl, the product from **31** requiring treatment with NaOH in DMSO to release the free base from the hydrochloride salt. The dihydroquinazoline **35**[22] was obtained in 81% yield and the dihydroquinazoline **36**[23] in 63% yield by this method. Compound **35** had a somewhat lower melting point than that reported[22] and analyzed for a partial hydrate despite extensive drying. The ^{1}H NMR spectra of the hydroquinazolines are given in Table II.

Attempted Synthesis of Hydropteridines. Methyl 3-aminopyrazine-2-carboxylate (**37**) was treated with **1** in an attempt to extend the synthetic method to hydropteridines. No reaction occurred, and so **37** was first treated with nBuLi and then with **1**, but only alkylated pyrazine products were isolated. Replacement of nBuLi by LDA gave similar products. Presumably the anion formed by proton abstraction is delocalized into the ring and reaction at the exocyclic nitrogen does not occur. In an attempt to activate the amino group, **37** was treated with hexamethyldisilazane and a trace of trimethylsilyl chloride. Compound **37** dissolved but only starting materials were recovered when the solution was treated with **1**.



37



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NMR Spectra of Acyclic and Cyclic *N*-Cyano Derivatives. As was mentioned in connection with compound **4a**, some of the asymmetrically substituted derivatives of **1** show the presence of two isomers in the room temperature ^{1}H and ^{13}C NMR spectra. There is a considerable variation in behavior, however, depending on the pattern of substitution. Thus **4a** and **4b** both show the presence of two isomers at room temperature; when the samples are warmed, the NMR signals broaden and coalesce; and at higher temperatures, a spectrum for a single compound is observed. The process is reversible, and the initial relative ratio of isomers is reestablished. Similar behavior was observed for the glycine derivative **38**.[9] Compounds **9**, **10a**, **30**, and **32** show well-resolved signals in the NMR spectrum for only one isomer at room temperature, and the coalescence temperatures are presumably considerably lower. The presence of barriers between imine nitrogen isomers of this type is well-known,[24a] and considerable discussion has ensued as to whether the interconversion represents a rotation around the C=N bond or nitrogen inversion. In guanidines, particularly in those compounds with an electron-withdrawing group on the double-bond nitrogen, dipolar structures are considered to be important, reducing the bond order of the C=N bond and increasing that of the C–N bond, rotation around the latter becoming rate determining.[24b] The rates of exchange for some of the compounds described here were calculated by the method of Gutowsky and Holm,[25] and the values of ΔG were calculated from the Eyring equation,[26] a unit transmission coefficient (κ) being assumed. No correction was made for the unequal populations of isomers, but such corrections are small.[27] The barriers to rotation are collected in Table III.

Table III. Rotational Barriers in *O*-Phenylisoureas[a]

compd	T_c, K	$\Delta\nu$, Hz	k_1, s^{-1}	ΔG, kcal mol^{-1}
4a	323	57	127	15.8
4b	333	66.5	148	16.2
38	343	60	133	16.8

[a] Calculated from coalescence of the NC*H* proton signals. Calculations based on the coalescence of other signals gave closely similar values.

An examination of the structures suggests that compounds with different heteroatom substituents on the carbon of the imine bond show the larger interconversional barrier, with the steric bulk of the substituent having a secondary effect.

Cyclic *N*-cyanoimines are likely to have lower barriers to interconversion than the acyclic systems.[24b] Small amounts of a second isomer can be observed in the ^{13}C NMR spectrum of compound **7a**, but this is probably an isomer in which the double bond has shifted position.

Conclusion. We have shown that the 1C, 1N, 1N3C route to 1,3-diazacyclohexane rings is viable using diphenyl cyanocarbonimidate as the 1C synthon. A variety of hydropyrimidines can be prepared, but the full scope of the reaction has not yet been explored. The method can accept benzannelation to give hydroquinazolines, but we were unable to find conditions where 1,4-diazabenzannelation was acceptable and were consequently unable to prepare hydropteridines. The order of substitution does not seem very important except in those cases, such as with ammonia, where the first substituent can be displaced preferentially to the phenoxide anion. The extension of the synthesis to other heterocycles and to nucleosides is under investigation.

Experimental Section

^{1}H NMR spectra were recorded on Varian VXR-400, XL-200, or JEOL PMX-60 spectrometers and are reported in δ units with Me_4Si as internal standard. ^{13}C NMR spectra were recorded on Varian VXR-400 or XL-200 spectrometers and are reported in δ units with Me_4Si as internal standard. Mass spectra were obtained on a VG-7070F spectrometer. IR spectra were obtained on Perkin-Elmer PE983 or PE781 spectrophotometers as KBr disks. Electronic spectra were recorded on a Perkin-Elmer λ5 spectrophotometer in methanol, spectra under acidic or basic conditions being taken by addition of one drop of 0.1 M HCl or 0.1 M NaOH. Melting points were recorded on a Büchi oil bath apparatus and are uncorrected. Flash chromatography was performed by using Woelm silica (32–63 μm) as the stationary phase.

Preparation of 4a. A slurry of diphenyl cyanocarbonimidate (**1**) (9.60 g, 40 mmol) in 2-propanol (250 mL) was added to a solution of methyl 3-aminopropionate hydrochloride (5.6 g, 40 mmol) and Et_3N (8.0 mL, 58 mmol) in 2-propanol (180 mL). The mixture was stirred at room temperature for 90 min, by which time a solution was formed. The solution was cooled to 4 °C for 15 h and the precipitated white crystalline solid collected by filtration and dried in vacuo at 40 °C as **4a** (7.10 g, 29 mmol, 72%). This material was used for further reactions, but a sample was recrystallized from 2-propanol: mp 112–112.5 °C; mass spectrum, *m/e* 248 (M^+ + 1), 91; ^{1}H NMR see discussion; ^{13}C NMR (DMSO-d_6) δ 171.3, 162.6, 159.6, 151.6, 151.2, 130.3, 129.5, 126.3, 126.2, 121.7, 119.8, 114.6, 114.2, 51.5, 38.4, 38.0, 33.5, 32.5; IR 3180,

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2920, 2185, 1730, 1640 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.18; H, 5.42; N, 16.79.

Preparation of 7a and 7b. Benzylamine (2.88 g, 26.9 mmol) was added to a stirred solution of **4a** (6.00 g, 24.0 mmol) in 2-propanol (125 mL), and the solution was then heated to reflux for 3 h. The solution was cooled (4 °C, 15 h) and the resulting white precipitate removed by filtration and air-dried as **7a** (3.40 g, 14.9 mmol, 61%). This material was used for further reactions, but a sample was recrystallized from 2-propanol: mp 200–202 °C; mass spectrum, *m/e* 229 ($M^+ + 1$), 228 (M^+), 91; ^{1}H NMR ($CDCl_3$) δ 7.99 (br s, 1 H), 7.24–7.37 (m, 5 H), 5.02 (s, 2 H), 3.48 (dt, 2 H), 2.76 (t, 2 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 159.2, 136.6, 128.4, 128.3, 127.5, 115.8, 44.6, 35.9, 31.1; IR 3440, 2180, 1725, 1660, 1505 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.26; N, 24.56. Found: C, 63.01; H, 5.35; N, 24.65.

Treatment of **4a** (1.07 g, 4.3 mmol) with 1-aminobutane (0.341 g, 4.7 mmol) in 2-propanol (40 mL) in the same manner gave, after reduction of volume (to one-fourth) and cooling, **7b** (0.55 g, 2.8 mmol, 65%): recrystallized from water, mp 166–168 °C; mass spectrum, *m/e* 195 ($M^+ + 1$), 194 (M^+), 55; ^{1}H NMR ($CDCl_3$) δ 8.0 (br s, 1 H), 3.79 (t, 2 H), 3.48 (dt, 2 H), 2.72 (t, 2 H), 1.50 (m, 2 H), 1.28 (m, 2 H), 0.90 (t, 3 H); ^{13}C NMR (DMSO-d_6) δ 168.2, 158.8, 115.7, 40.9, 35.7, 30.4, 29.7, 19.5, 13.7; IR 3220, 3175, 2960, 2930, 2180, 1715, 1620, 1500 cm^{-1}. Anal. Calcd for $C_9H_{14}N_4O$: C, 55.65; H, 7.26; N, 28.84. Found: C, 55.61; H, 7.36; N, 28.63.

Reaction of 4a with Ammonia. Preparation of 9. The *O*-phenylisourea **4a** (1.20 g, 4.86 mmol) was added to aqueous ammonia (0.880 SG, 10 mL) and 2-propanol (30 mL) and the mixture stirred for 15 h. The solvent was removed by evaporation, the resulting white solid triturated with $CHCl_3$ (10 mL), and the residue removed by filtration, washed with $CHCl_3$, and dried in vacuo. Recrystallization from ethanol gave **9** (0.719 g, 4.64 mmol, 95%): mp 191–192.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.40 (br s, 1 H), 7.0–6.6 (m, 3 H), 6.93 (br s, 1 H), 3.23 (q, 2 H), 2.25 (t, 2 H); ^{13}C NMR (DMSO-d_6) δ 172.7, 161.2, 118.3, 36.9, 34.7; IR 3345, 3190, 2182, 2158, 1668, 1613, 1553, 1446 cm^{-1}. Anal. Calcd for $C_5H_9N_5O$: C, 38.70; H, 5.84; N, 45.14. Found: C, 38.56; H, 6.00; N, 44.85.

Preparation of *N*-Cyano-*O*-phenylisourea (10a). Aqueous ammonia (0.880 SG, 2.0 mL) and **1** (2.50, 10.4 mmol) were stirred together in 2-propanol (25 mL) at room temperature for 5 min. The solvent was removed under reduced pressure and the residue triturated with ether. The residue was removed by filtration, washed with ether, and dried. A second crop was obtained from the mother liquors by the same process. The combined material was identified as **10a** (1.437 g, 8.9 mmol, 85%). This material was used for further reactions, but a sample was recrystallized from methanol/water: mp 152–153 °C (lit.[12] mp 158 °C); mass spectrum, *m/e* 162 ($M^+ + 1$), 94; ^{1}H NMR (DMSO-d_6) δ 8.60 (br d, 2 H), 7.38 (t, 2 H), 7.24 (t, 1 H), 7.15 (d, 2 H); ^{13}C NMR (DMSO-d_6) δ 164.3, 151.0, 129.5, 126.1, 121.6, 114.9; IR 3353, 3182, 2202, 1675, 1653, 1598, 1560, 1492 cm^{-1}. Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.74; H, 4.40; N, 26.18.

Reaction of 10a with 3a. a. With in Situ Generation of 3a. Triethylamine (0.138 g, 1.37 mmol) and **3a**·HCl (0.173 g, 1.24 mmol) were stirred in 2-propanol (8 mL) for 5 min, **10a** (0.200 g, 1.24 mmol) was then added, and the resulting solution was heated to reflux for 6 h. On standing at room temperature over 2 days, a white crystalline precipitate formed, which was collected by filtration. A second crop was obtained by reduction of the mother liquors and again allowing the solution to stand at room temperature. The combined crops were recrystallized from methanol/water to give **4a** (0.136 g, 0.54 mmol, 44%): mp 112–112.5 °C, identical in all observed respects with an authentic sample.

b. With Pregeneration of 3a. Preparation of 11. Diethylamine (3.56 g, 48.7 mmol) was added to **3a**·HCl (5.00 g, 35.8 mmol) in benzene (100 mL) with stirring. Dry ether (250 mL) was added and the resulting white precipitate of diethylamine hydrochloride collected by filtration. The solvent was removed from the filtrate by evaporation at 30 °C to give a colorless oil (1.92 g). Compound **10a** (0.500 g, 3.11 mmol) was added to a solution of the above oil (0.314 g) in 2-propanol (5 mL), and the mixture was stirred at room temperature for 6 h. The resulting white precipitate was removed by filtration, and two more crops were obtained from the mother liquors by a similar procedure. The combined material was recrystallized from water as **11** (0.297 g, 2.15 mmol, 71%): mp >250 °C (lit.[13] mp 264 °C); mass spectrum, *m/e* 138 (M^+); ^{1}H NMR (DMSO-d_6) δ 10.85 (br s, 1 H), 8.84 (br s, 1 H), 3.39 (t, 2 H), 2.55 (t, 2 H); ^{13}C NMR (DMSO-d_6) δ 169.4, 158.4, 116.0, 36.7, 29.7; IR 3195, 2200, 1727, 1713, 1676, 1537, 1374, 1326, 1275 cm^{-1}; UV 238 (ϵ 15 800), 214 nm (14 700). Anal. Calcd for $C_5H_6N_4O$: C, 43.48; H, 4.38; N, 40.56. Found: C, 44.00; H, 4.68; N, 40.85.

Reaction of 10b with 3a. Alternative Preparation of 7a. Compound **3a**·HCl (0.058 g, 0.42 mmol) was added to a solution of Et_3N (0.044 g, 0.44 mmol) in 2-propanol (1 mL) and the mixture stirred for 5 min at room temperature. Compound **10b** (0.100 g, 0.40 mmol), prepared by the method of Webb et al.,[8b] was then added and the solution heated to reflux for 12 h. On cooling, a white crystalline precipitate formed, which was separated by filtration and dried in vacuo as **7a** (0.014 g, 0.06 mmol, 15%), identical in all observed respects with the previous sample.

Reaction of 1 with Dimethyl (*S*)-2-Aminobutanedioate (3b). Diethylamine (2.05 g, 28.1 mmol) was added to a stirred solution of (*S*)-**3b**·HCl (4.00 g, 20.3 mmol) in benzene (60 mL). Ether (130 mL) was added and the resulting precipitate of Et_2NH·HCl removed by filtration. The filtrate was evaporated in vacuo to give a yellow oil (2.00 g). The oil was dissolved in 2-propanol (125 mL), and **1** (3.10 g, 12.9 mmol) was added with stirring. After addition, stirring was maintained for 15 h, and the volume was then reduced to one-half in vacuo and the solution cooled to 4 °C for 72 h. The white crystalline precipitate was collected and air-dired as **4b** (2.35 g, 7.7 mmol, 62%). This material was used for further reactions, but a sample was recrystallized from ether: mp 61–62 °C; $[\alpha]^{26}_D$ (MeOH) −26.3°; mass spectrum, *m/e* 306 ($M^+ + 1$), 94; ^{1}H NMR (DMSO-d_6) δ 9.19 (br s), 7.50–7.43 (m), 7.31 (m), 7.23 (d), 7.13 (d), 4.91 (t, J = 6.75 Hz), 4.75 (t, J = 6.6 Hz), 3.75 (s), 3.71 (s), 3.67 (s), 3.64 (s), 3.03 (m), 2.95 (dd, J = 16.7, 5.1 Hz), 2.85 (dd, J = 16.8, 8.1 Hz); ^{13}C NMR (DMSO-d_6) δ 170.5, 170.2, 170.1, 169.7, 162.4, 159.8, 151.9, 151.1, 130.4, 129.7, 126.6, 126.2, 121.6, 119.3, 114.1, 113.4, 52.9, 52.8, 52.0, 51.7, 35.0, 34.6; IR 3255, 3175, 2958, 2195, 1755, 1745, 1650 cm^{-1}. Anal. Calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 55.09; H, 4.91; N, 13.59.

Reaction of 4b with Benzylamine. Preparation of 7c. Benzylamine (1.03 g, 9.63 mmol) was added to a solution of **4b** (2.68 g, 8.79 mmol) in 2-propanol (30 mL). The solution was heated to reflux for 90 min and was then allowed to cool and stand at room temperature for 72 h. The resulting white crystalline precipitate was removed by filtration as **7c** (2.50 g, 8.75 mmol, 99%). This material was used for subsequent reactions, but a sample was recrystallized from 2-propanol: mp 171–173 °C; mass spectrum, *m/e* 286 (M^+), 94; ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1 H), 7.41–7.30 (m, 5 H), 4.70 (s, 2 H), 4.44 (dd, 1 H), 3.66 (s, 3 H), 2.89 (ddd, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.2, 169.3, 162.4, 134.7, 128.9, 128.7, 128.3, 115.4, 55.1, 52.4, 43.4, 35.0; IR 3150, 3025, 2945, 2840, 2190, 1760, 1740, 1650, 1487 cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.74; H, 4.95; N, 19.57. Found: C, 58.76; H, 4.94; N, 19.50.

Preparation of *N*-Cyano-*N'*-(2-cyanoethyl)-*O*-phenylisourea (13). 3-Aminopropionitrile hemifumarate (**12**) (3.20 g, 0.025 mol) was suspended in 2-propanol (100 mL) containing triethylamine (2.5 mL) and the mixture stirred vigorously. Compound **1** (6.00 g, 0.025 mol) in 2-propanol (100 mL) was added and the resulting mixture stirred for 16 h. The resulting precipitate was removed by filtration and dried in vacuo at 50 °C to give **13** (4.02 g, 0.019 mol, 75%): mp 127–128 °C; ^{1}H NMR δ 8.19 (br t, 1 H), 7.06–7.69 (m, 5 H), 3.48–3.93 (m, 2 H), 2.71 (t, J = 7 Hz, 2 H); IR (Nujol) 2225, 2190, 1655, 1640 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.68; H, 4.67; N, 26.17. Found: C, 61.23; H, 4.67; N, 26.08.

Preparation of *N*-Benzyl-*N'*-cyano-*N''*-(2-cyanoethyl)-guanidine (14). Benzylamine (1.25 mL, 0.011 mol) and **13** (2.14 g, 0.01 mol) were added to 2-propanol (60 mL), and the mixture was heated to reflux for 5 h. The mixture was cooled and the solvent removed in vacuo. The resulting residue was triturated with methanol and the crystalline solid removed by filtration and dried at 50 °C in vacuo to give **14** (1.68 g, 0.007 mol, 74%): mp 121–122 °C; ^{1}H NMR (DMSO-d_6) δ 7.74 (t, J = 6 Hz, 1 H), 7.40 (m, 6 H), 4.32 (d, J = 6 Hz, 2 H), 3.35 (m, 2 H), 2.67 (t, J = 6.5 Hz, 2 H); IR (Nujol) 3340, 3280, 2250, 2175 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_5$: C, 63.43; H, 5.72; N, 30.84. Found: C, 63.25; H, 5.81; N, 30.75.

Preparation of 3-Benzyl-2-(cyanoimino)-4-iminohexahydropyrimidine (15). Sodium methoxide (5 mL, 1 M in methanol) and **14** (1.13 g, 0.005 mol) were added to methanol (5 mL), and the mixture was stirred for 16 h. A precipitate formed, which was removed by filtration, washed with a little methanol, and dried at 60 °C in vacuo to give **15** (0.655 g, 0.003 mol, 57%): mp 159–160 °C; mass spectrum, *m/e* 227 (M^+); ^1H NMR (DMSO-d_6) δ 8.75 (s, 1 H), 8.6 (br s, 1 H), 7.34–7.17 (m, 5 H), 5.09 (s, 2 H), 3.32 (m, 2 H), 2.77 (t, 2 H); IR (Nujol) 3300, 3205, 2180, 1645 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_5$: C, 63.43; H, 5.72; N, 30.84. Found: C, 63.00; H, 5.96; N, 30.67.

Reaction of 15 with Bromine in Chloroform. Formation of 16. Compound **15** (0.023 g, 0.10 mmol) was suspended in $CHCl_3$ (5 mL), and a solution of bromine in $CHCl_3$ (0.11 mL, 1 M, 0.11 mmol) was added. The mixture was stirred at room temperature until the bromine color disappeared. A further portion of the bromine solution (0.11 mL) was added and the mixture stirred for 20 h. The solvent was removed by evaporation, and the pale yellow residue was recrystallized from ethanol to give **16** (0.005 g, 0.02 mmol, 20%), identical in all respects with a previously prepared sample (see below).

Preparation of 2-(Cyanoimino)-4-iminohexahydropyrimidine (17). Compound **13** (0.856 g, 4.0 mmol) was added to a solution of ammonia (20 mL, 0.880 SG) and the mixture stirred at room temperature for 16 h. The solvent was removed by evaporation and the resulting residue recrystallized from methanol and dried at 80 °C in vacuo to give **17** (0.269 g, 2.0 mmol, 49%): mp 169–170 °C; mass spectrum, *m/e* 137 (M^+); ^1H NMR (DMSO-d_6) δ 8.36 (s, 1 H), 8.08 (s, 1 H), 7.88 (br s, 1 H), 3.18 (m, 2 H), 2.42 (t, 2 H). Anal. Calcd for $C_5H_7N_5$: C, 43.79; H, 5.11; N, 51.09. Found: C, 43.77; H, 5.21; N, 50.96.

Reaction of 7a with Bromine. Preparation of 2-Amino-3-benzyl-4-oxo-3,4,5,6-tetrahydropyrimidine Hydrobromide (19). Bromine (1.34 g, 8.39 mmol) was added to a stirred solution of **7a** (1.60 g, 7.02 mmol) in glacial acetic acid (48 mL). The solution was heated to reflux for 20 min, when the orange color discharged, and was then cooled to 4 °C, when the acetic acid froze. The mixture was then allowed to warm to room temperature and the white crystalline precipitate removed by filtration. A second crop was obtained from the mother liquors by the same procedure, and the two crops were combined as **19** (1.03 g, 3.6 mmol, 51%). This material was used for subsequent experiments, but a sample was recrystallized from 2-propanol: mp 230–231 °C; mass spectrum, *m/e* 204 (M^+ – Br), 80; ^1H NMR (DMSO-d_6) δ 9.22 (br s, 1 H), 8.55 (br s, 2 H), 7.39–7.06 (m, 5 H), 5.05 (s, 2 H), 3.57 (t, 2 H), 2.89 (t, 2 H); ^{13}C NMR (DMSO-d_6) δ 167.7, 154.8, 135.2, 128.5, 127.4, 126.5, 43.3, 34.9, 30.3; IR 3440, 2975, 1728, 1660, 1552 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_3OBr$: C, 45.72; H, 4.97; N, 14.38; Br, 28.12. Found: C, 45.85; H, 4.83; N, 14.47; Br, 28.22.

Preparation of 2-Amino-3-benzyl-4-oxo-3,4-dihydropyrimidine (20). From the Hydrobromide 19. Bromine (0.8 mL, 15.5 mmol) in glacial acetic acid (10 mL) was added to the hydrobromide **19** (0.400 g, 1.41 mmol), and the resulting solution was heated to reflux for 15 h. The orange color discharged over this period, and the solvent was then removed in vacuo at 40 °C. Pyridine (5 mL) was added to the residue and the mixture heated to reflux for 45 min. The pyridine was removed by evaporation in vacuo, and the residual brown oil was purified by flash chromatography, eluting with $CHCl_3$ to give **20** (0.136 g, 0.68 mmol, 48%) and **21** (0.043 g, 0.15 mmol, 11%). Compound **20** was recrystallized from $CHCl_3$, Et_2O, mp 170–173 °C; mass spectrum, *m/e* 201.0907 ($C_{11}H_{11}N_3O$ requires 201.0902), 201 (M^+), 91; ^1H NMR (DMSO-d_6) δ 7.58 (d, 1 H), 7.34–7.14 (m, 5 H), 5.67 (d, 1 H), 5.15 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 161.9, 156.5, 155.0, 136.0, 128.4, 127.1, 126.7, 101.2, 43.1; IR 3378, 3185, 3062, 1662, 1630, 1570, 1527, 1504 cm^{-1}; UV (MeOH) 288 (ϵ 9600), (pH 13) 288, (pH 1) 256 nm.

Compound **21**: ^1H NMR ($CDCl_3$) δ 7.9 (s, 1 H), 7.3 (m, 5 H), 5.2 (s, 2 H).

From the Hexahydropyrimidine 7a. A solution of **7a** (0.204 g, 0.895 mmol) and bromine (1.141 g, 8.85 mmol) in glacial acetic acid (10 mL) was heated to reflux for 3 h, when the brown solution had become pale yellow. The solvent was removed by evaporation, and pyridine (25 mL) was added. The mixture was heated to reflux for 5 min and the precipitate removed by filtration. The solvent was removed by evaporation and the resulting yellow oil purified by flash chromatography to give **20** (0.130 g, 0.65 mmol, 72%), identical in all observed respects with that synthesized above.

Preparation of 3-Benzyl-2-ureido-4-oxo-3,4,5,6-tetrahydropyrimidine (16). The hexahydropyrimidine **7a** (0.100 g, 0.440 mmol) and bromine (0.080 g, 0.5 mmol) were added to $CHCl_3$ (5 mL), and the mixture was heated to reflux for 5 min. The solution was allowed to cool and the resultant precipitate removed by filtration as **16** (0.074 g, 0.301 mmol, 68%): mp 185–186 °C; mass spectrum, *m/e* 246 (M^+), 91; ^1H NMR (DMSO-d_6) δ 7.36–7.32 (m, 5 H), 5.13 (s, 2 H), 3.71 (br s, 2 H), 2.87 (t, 2 H); IR 3285, 3222, 3157, 3058, 1734, 1713, 1658, 1551 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 44.05; H, 4.62; N, 17.12. Found: C, 43.69; H, 4.71; N, 16.68.

Preparation of 3-Benzyl-6-(methoxycarbonyl)-2-ureido-4-oxo-3,4-dihydropyrimidine (23). Bromine (0.573 g, 3.56 mmol) in glacial acetic acid (25 mL) was added to **7c** (0.500 g, 1.75 mmol) and the mixture heated to reflux for 10 min, during which time the orange color was discharged. The solution was cooled, water (25 mL) was added, and the mixture was then cooled to 4 °C. The light yellow crystalline precipitate that formed was removed by filtration and dried in vacuo as **23** (0.324 g, 1.07 mmol, 61%). This material was used for subsequent reactions, but a sample was recrystallized from ethanol: mp 165–167 °C; mass spectrum, *m/e* 302 (M^+), 91; ^1H NMR ($CDCl_3$) δ 11.40 (br s, 1 H), 7.41–7.31 (m, 5 H), 5.89 (s, 1 H), 5.51 (br s, 1 H), 5.22 (br s, 1 H), 4.82 (s, 2 H), 3.82 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 163.6, 162.3, 154.1, 137.9, 135.2, 128.7, 128.5, 128.1, 96.4, 42.8; IR 3480, 3330, 1750, 1678, 1665, 1618, 1570 cm^{-1}; UV (MeOH) 313, (pH 13) 282 and 384, (pH 1) 314 nm. Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N, 18.53. Found: C, 55.51; H, 4.72; N, 19.00.

The solvent was removed from the filtrate to give a residual yellow oil, which was chromatographed on silica, eluting with CH_2Cl_2 to give **24** (0.018 g, 0.07 mmol, 4%): mp 206 °C; mass spectrum, *m/e* 260.0809 ($C_{13}H_{12}N_2O_4$ requires 260.0797), 260 (M^+), 91; ^1H NMR ($CDCl_3$) δ 9.0 (s, 1 H), 7.35–7.32 (m, 5 H), 5.92 (s, 1 H), 4.75 (s, 2 H), 3.80 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 164.9, 162.7, 154.4, 139.0, 135.7, 128.5, 127.5, 127.3, 94.6, 51.6; IR 3275, 1775, 1732, 1697, 1667, 1405, 1342, 1333 cm^{-1}; UV 251 (ϵ 9700), 298 (12 500), (pH 1) 254 and 355 (pH 14) 251 and 298 nm.

Preparation of 3-Benzylorotic Acid (25). A solution of **23** (0.197 g, 0.65 mmol) in 2 M NaOH (20 mL) was heated to reflux for 3 h. The solution was cooled and neutralized with concentrated HCl and the mixture extracted with ether (3 × 25 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed by evaporation to give **25**, which was recrystallized from water (0.082 g, 0.33 mmol, 51%): mp 218–219 °C dec (lit.[18] mp 226–227 °C dec); mass spectrum, *m/e* 246.0633 ($C_{12}H_{10}N_2O_4$ requires 246.0641), 247 (M^+ + 1, 13), 246 (M^+, 90), 132, 106 (100); ^1H NMR (DMSO-d_6) δ 11.28 (s, 1 H), 7.24 (m, 5 H), 6.12 (s, 1 H), 4.91 (s, 2 H); IR 3146, 1725, 1653, 1495, 1440 cm^{-1}; UV (0.1 M NaOH) 299 (ϵ 7500), (0.1 M HCl), 282 nm (10 000).

Reaction of 7c with Benzylamine. Preparation of 3-Benzyl-6-(benzylcarbamoyl)-2-(cyanoimino)-4-oxohexahydropyrimidine (26). Benzylamine (0.103 g, 0.96 mmol) and **7c** (0.250 g, 0.87 mmol) were dissolved in 2-propanol (10 mL), and the solution was heated to reflux for 24 h. The solution was cooled, and the resulting white crystals were removed by filtration. A second crop was obtained from the mother liquors and the combined material collected as **26** (0.153 g, 0.425 mmol, 49%): mp 239 °C dec; ^1H NMR (DMSO-d_6) δ 9.86 (s, 1 H), 8.54 (t, 1 H), 7.37–7.25 (m, 10 H), 4.62 (d, 2 H), 4.60 (t, 1 H), 4.29 (m, 2 H), 2.82 (d, 2 H); ^{13}C NMR (DMSO-d_6) δ 174.0, 167.6, 161.9, 138.9, 135.7, 128.3, 128.2, 127.2, 127.1, 126.7, 115.4, 55.2, 42.2, 42.0, 35.2; IR 3283, 3129, 3030, 2194, 1751, 1668, 1488 cm^{-1}.

Reaction of 26 with Bromine. Preparation of 3-Benzyl-6-(benzylcarbamoyl)-2-ureido-4-oxo-3,4-dihydropyrimidine (27). Bromine (0.050 g, 0.31 mmol) and **20** (0.102 g, 0.28 mmol) were added to glacial acetic acid (5 mL), and the mixture was heated to reflux for 1 min. The solvent was removed by evaporation in vacuo to give a pale yellow residue, which was separated into two components by flash chromatography, eluting with CH_2Cl_2/methanol, 20:1.

Compound **27** (0.066 g, 0.204 mmol, 62%): recrystallized from ethanol, mp 192–194 °C dec; mass spectrum, *m/e* 378 (M^+ + 1), 91; ^1H NMR (DMSO-d_6) δ 8.98 (t, 1 H), 7.34–7.28 (m, 10 H), 7.12

(br s, 1 H), 6.84 (br s, 1 H), 5.98 (s, 1 H), 4.76 (s, 2 H), 4.39 (d, 2 H); ^{13}C NMR (DMSO-d_6) δ 165.0, 163.3, 162.8, 153.0, 138.9, 136.0, 128.5, 128.4, 127.5, 127.5, 127.4, 127.0, 98.5, 42.2, 41.9; IR 3488, 3370, 1747, 1664, 1638, 1585, 1575 cm^{-1}; UV 318 (ϵ 24 000), (pH 1) 318, (pH 14) 376 nm. Anal. Calcd for $C_{20}H_{19}N_5O_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.54; H, 5.17; N, 18.58.

Compound **28** (0.004 g, 0.012 mmol, 4%): mp 228–230 °C dec; mass spectrum, *m/e* 335 (M$^+$), 106; ^{1}H NMR ($CDCl_3$) δ 10.63 (br s, 1 H), 8.88 (m, 1 H), 7.31–7.21 (m, 10 H), 5.92 (s, 1 H), 4.58 (s, 2 H), 4.33 (d, 2 H); IR 3374, 3261, 1796, 1721, 1681, 1634 cm^{-1}; UV 250 (ϵ 10 400), 299 (16 800), (pH 1) 250 and 299, (pH 13) 250 and 352 nm. Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.04; H, 5.11; N, 12.53. Found: C, 67.81; H, 5.12; N, 12.49.

Preparation of *N*-(2-Carbomethoxyphenyl)-*N'*-cyano-*O*-phenylisourea (30). Methyl anthranilate (5.00 g, 37.0 mmol) in dioxane (35 mL) was added dropwise to a stirred suspension of sodium hydride (1.04 g, 43.3 mmol) in dioxane (40 mL) under N_2 over 10 min. Compound **1** (7.95 g, 33.4 mmol) was then added to the mixture, which was stirred for 15 h. Water (50 mL) was then added, the mixture was extracted with CH_2Cl_2 (3 × 60 mL), and the combined extracts were washed with water (150 mL) and dried (Mg_2SO_4). The solvent was removed in vacuo, the waxy residue triturated with ether, and the undissolved solid removed by filtration. A second crop was obtained from the mother liquors, and the two were combined as **30** (4.90 g, 16.6 mmol, 50%). This material was used for further experiments, but a sample was recrystallized from methanol: mp 141–142 °C; mass spectrum, *m/e* 295 (M$^+$), 94; ^{1}H NMR ($CDCl_3$) δ 11.4 (br s, 1 H), 8.33 (d, 1 H), 8.07 (dd, 1 H), 7.61–7.21 (m, 7 H), 3.89 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.0, 150.4, 138.3, 134.4, 131.2, 130.1, 127.3, 124.2, 121.3, 120.9, 116.6, 113.3, 52.7; IR 3109, 2195, 1978, 1621, 1604, 1586 cm^{-1}. Anal. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.32; H, 4.58; N, 13.96.

Reaction of 30 with Benzylamine. Preparation of 3-Benzyl-2-(cyanoimino)-4-oxo-1,2,3,4-tetrahydroquinazoline (31). A solution of **30** (0.150 g, 0.51 mmol) and benzylamine (0.057 g, 0.53 mmol) in 2-propanol (2 mL) was heated to reflux for 2 h. After cooling, the precipitated white solid was removed by filtration, washed with 2-propanol, and dried in vacuo to give **31** (0.111 g, 0.40 mmol, 79%): recrystallized from dioxane, mp >260 °C; mass spectrum, *m/e* 276 (M$^+$), 91; ^{1}H NMR (DMSO-d_6) δ 12.2 (br s, 1 H), 8.02 (d, 1 H), 7.78 (m, 1 H), 7.70 (d, 1 H), 7.37 (t, 1 H), 7.33–7.29 (m, 4 H), 7.26 (m, 1 H), 5.21 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 160.0, 153.4, 138.3, 136.1, 135.4, 128.2, 127.2, 124.4, 116.5, 114.5, 114.2, 45.1; IR (KBr) 2985, 2210, 2179, 1699, 1635, 1588 cm^{-1}. Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.37; H, 4.67; N, 20.22.

Reaction of 30 with Ammonia. Preparation of 2-(Cyanoimino)-4-oxo-1,2,3,4-tetrahydroquinazoline (33). The *O*-phenylisourea **30** (0.700 g, 2.37 mmol) was added to a saturated solution of NH_3 in 2-propanol (15 mL) and the mixture stirred for 1 h at room temperature. The solvent was removed in vacuo, the resulting white residual solid triturated with ether (5 mL), and the solid collected by filtration, washed with ether, and dried to give **33** (0.337 g, 1.99 mmol, 84%): recrystallized from water, ethanol, mp 307–309 °C (lit.[21] mp 306–307 °C); mass spectrum, *m/e* 186 (M$^+$); ^{1}H NMR (DMSO-d_6) 12.18 (br s, 2 H), 7.96 (dd, 1 H), 7.75 (dt, 1 H), 7.60 (d, 1 H), 7.34 (t, 1 H); IR (KBr) 3460, 3140, 3002, 2839, 2205, 1697, 1660 cm^{-1}. Anal. Calcd for $C_9H_6N_4O$: C, 58.06; H, 3.25; N, 30.09. Found: C, 58.01; H, 3.28; N, 29.85.

Preparation of 2-Amino-3-benzyl-4-oxo-3,4-dihydroquinazoline (35). A solution of **31** (0.600 g, 2.18 mmol) in a mixture of concentrated HCl (50 mL) and DMSO (28 mL) was heated to reflux for 6 h. The cooled solution was neutralized with 8 M NaOH and the resulting white precipitate collected by filtration, washed with water, and dried in vacuo as **35**·HCl (0.505 g, 1.75 mmol, 81%). Recrystallization from ethanol gave **35**·HCl: mp >250 °C; mass spectrum, *m/e* 251 (M$^+$ – HCl), 91; ^{1}H NMR (DMSO-d_6) δ 8.92 (br s, 2 H), 8.04 (d, 1 H), 7.84 (t, 1 H), 7.49 (d, 1 H), 7.41 (t, 1 H), 7.34–7.28 (m, 5 H), 5.31 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 159.4, 157.1, 138.0, 136.3, 134.4, 128.6, 127.6, 125.1, 117.0, 114.4, 44.8; IR (KBr) 3439, 3104, 2756, 1706, 1654, 1595, 1542 cm^{-1}. Anal. Calcd for $C_{15}H_{14}ClN_3O$: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.62; H, 4.63; N, 14.67.

The salt **35**·HCl (0.050 g, 0.175 mmol) was added to 2 M NaOH (10 mL), and the mixture was heated to reflux. DMSO was then added dropwise at this temperature until all the solid dissolved, and the resulting solution was then heated at reflux for 1 min. On cooling, a white precipitate formed that increased on addition of water (10 mL). The precipitate was collected by filtration, washed with water, and air-dried. Recrystallization from toluene gave **35** (0.032 g, 0.13 mmol, 73%): mp 195–196 °C (lit.[22] mp 202–204 °C); mass spectrum, *m/e* 251 (M$^+$), 91; ^{1}H NMR (DMSO-d_6) 7.92 (d, 1 H), 7.59 (t, 1 H), 7.33–7.19 (m, 6 H), 7.12 (t, 1 H), 6.99 (s, 2 H), 5.28 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 161.7, 151.9, 136.1, 128.5, 127.2, 126.7, 123.1, 122.0, 115.8, 44.0; IR (KBr) 3517, 3443, 3378, 3333, 3069, 1683, 1628, 1610, 1563 cm^{-1}.

Preparation of 2-Amino-4-oxo-3,4-dihydroquinazoline (36). A solution of **33** (0.215 g, 1.16 mmol) in concentrated HCl (10 mL) was heated to reflux for 6 h. The solution was allowed to cool and was then neutralized with 10 M NaOH. The resulting white precipitate was collected by filtration and washed with water. The solid was then dissolved in the minimum of 2 M NaOH, and dry CO_2 was then bubbled through the solution. The resulting white precipitate was collected by filtration, washed with water, and dried in vacuo as **36** (0.118 g, 0.74 mmol, 63%): mp >250 °C (lit.[28] mp 312 °C dec); mass spectrum, *m/e* 161.058 24 ($C_8H_7N_3O$ requires 161.058 91); ^{1}H NMR (DMSO-d_6) δ 10.99 (br s, 1 H), 7.87 (dd, 1 H), 7.55 (dt, 1 H), 7.19 (d, 1 H), 7.09 (t, 1 H), 6.37 (br s, 2 H); IR (KBr) 3400, 3184, 3063, 1685, 1653, 1609, 1574 cm^{-1}.

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Registry No. **1**, 79463-77-7; **3a**, 4138-35-6; **3a**·HCl, 3196-73-4; **3b**·HCl, 32213-95-9; **4a**, 111970-99-1; **4b**, 111971-01-8; **7a**, 111971-03-0; **7b**, 118438-54-3; **7c**, 111971-05-2; **9**, 118438-55-4; **10a**, 3277-47-2; **10b**, 110821-27-7; **11**, 31036-23-4; **12**, 2079-89-2; **13**, 111971-00-7; **14**, 118438-56-5; **15**, 111971-04-1; **16**, 118438-57-6; **17**, 71655-85-1; **19**, 118438-58-7; **20**, 111971-06-3; **21**, 118438-59-8; **22**, 111971-07-4; **23**, 111971-08-5; **24**, 111971-09-6; **25**, 5971-86-8; **26**, 118438-60-1; **27**, 118438-61-2; **28**, 118438-62-3; **29**, 134-20-3; **30**, 118438-63-4; **31**, 118438-64-5; **33**, 112656-43-6; **35**, 102242-07-9; **35**·HCl, 118438-65-6; **36**, 20198-19-0; **38**, 111971-02-9; benzylamine, 100-46-9; 1-aminobutane, 109-73-9.

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