# Synthesis of Imidazo[5,4-*d*][1,3]thiazines: X-Ray Structure of *N*-Methyl-*N'*-[5-(methylamino)-3-nonylimidazo[5,4-*d*][1,3]thiazin-7(3*H*)-ylidene]thiourea



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*N*-Alkyl-*N'*-[5-(alkylamino)-3-alkylimidazo[5,4-*d*][1,3]thiazin-7(3*H*)-ylidene]thioureas were obtained by the reaction of 1-substituted 5-amino-4-cyanoimidazoles with alkyl isothiocyanates. The structure of this heterocyclic system was confirmed by single crystal X-ray diffraction analysis.

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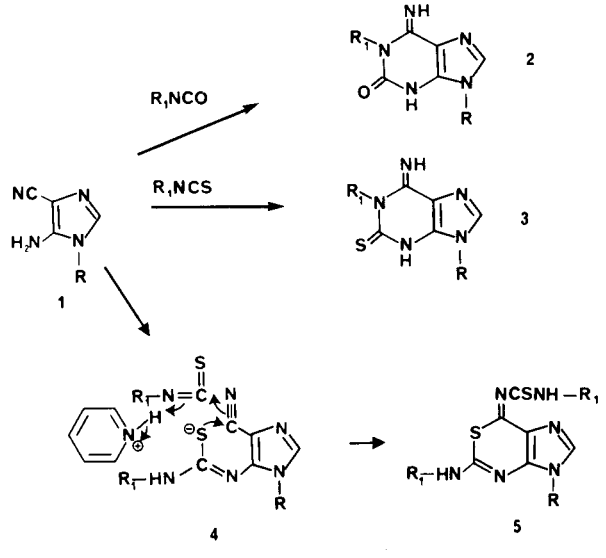
Since the isolation of 1-methylisoguanosine (**2a**) from several marine sources - the sponge *Tedania Digitata*, the dorid nudibranch *Anisodoris Nobilis*, and the coral *Madracis Mirabilis* [1,2,3] - various synthetic modifications have been reported [4,5].

In view of the potent pharmacological properties of 1-methyl-9-ribosylisoguanine, we were interested in the medicinal chemistry of analogs of this natural lead [4].

We previously reported that the reaction of 1-substituted 4-amino-5-cyanoimidazoles with isothiocyanates resulted in 7-substituted 2-thioxopurines [6]. In this paper we wish to report the reaction of the isomeric 1-substituted 5-amino-4-cyanoimidazoles **1** with alkyl isothiocyanates, which display a different chemistry by forming imidazo-[5,4-*d*][1,3]thiazines **5** (Scheme I, Table I).

Scheme I




Recently [3] we prepared 1,9-disubstituted-isoguanines **2** from the reaction of 1-substituted 5-amino-4-cyanoimidazoles **1** with alkyl isocyanates. Using the same method, we reacted **1** with alkyl isothiocyanates in the hope of obtaining 1,9-disubstituted 2-thioxopurines **3**. The present note reports the unexpected isolation of imidazo-[5,4-*d*][1,3]thiazines **5**.

Table I

| Compound **5** | | R | $R_1$ |
|---|---|---|---|
| **a** | [3] | ribofuranosyl | methyl |
| **b** | [6] | H | methyl |
| **c** | | methyl | methyl |
| **d** | | 2-ethoxyethyl | methyl |
| **e** | | 2-(cyclohexylthio)ethyl | methyl |
| **f** | | 3-[4-(*p*-chlorobenzyl)piperazinyl]propyl | methyl |
| **g** | | 2-(ethylthio)ethyl | methyl |
| **h** | | 2-(*p*-chlorophenyl)thioethyl | methyl |
| **i** | | 2-methoxyethyl | methyl |
| **j** | | nonyl | methyl |
| **k** | | benzyl | methyl |
| **l** | | *p*-chlorobenzyl | methyl |
| **m** | | methyl | allyl |
| **n** | | methyl | ethyl |
| **o** | | benzyloxy | methyl |
| **p** | | 2-(*N*,*N*-dimethylamino)ethyl | methyl |

The starting materials **1c-p** were known, except for **1d** which was obtained by the alkylation of 4(5)-amino-5(4)-cyanoimidazole with 2-bromoethyl ethyl ether. Both isomers were isolated and the site of attachment was determined by comparison of the $^{13}C$ nmr spectrum in DMSO-$d_6$ of both isomers with the carbon signals of the heterocycle of 5-amino-4-cyano-1-(2',3'-*O*-isopropylidene-5'-*O*-acetyl-β-D-ribofuranosyl)imidazole [7]; (**1p**-AcO-AICNR, δ 87.44, 116.68, 130.14, 147.44; compound **1d**, δ 90.65, 117.01, 132.81, 147.26). This strongly suggested that the

site of attachment is identical. Treatment of **1c-p** with alkyl isothiocyanates in pyridine gave as major products yellow crystalline materials, which proved not to be the anticipated purines **3**.

The elemental analysis indicated the addition of two moles of alkyl isothiocyanate. The nmr spectra of the products showed the presence of two non-equivalent alkylamino groups. The uv spectra in 0.1*N* hydrochloric acid displayed two strong absorptions at 378-376 nm and 282-270 nm. This suggested the presence of a highly conjugated system. On this basis we assumed the sulfur atom to be part of a heterocyclic ring-structure. The reaction probably involves an initial formation of a thiocarbamate pyridinium salt **4** followed by intramolecular nucleophilic addition to the nitrile group. The resulting imine then added another mole of isothiocyanate to form *N*-alkyl-*N'*-[5-(alkylamino)-3-alkyl-imidazo[5,4-*d*] [1,3]thiazin-7(3*H*)-ylidene]thioureas **5**. This mechanism is similar to the reported reactions of cyclic *o*-aminonitriles with carbon disulfide in pyridine [8,9] and the reaction of 5-amino-4-cyano-1-(β-D-ribofuranosyl)imidazole **(1a)** with phenyl isothiocyanate in DMF [10]. Our results differ from those in which 5-amino-4-cyano-1-(β-D-ribofuranosyl)imidazole **(1a)** is reacted with methyl isothiocyanate in pyridine and where the isolated product is reported to be *N'*-methyl-2-mercaptopurine **(3a)** [11].

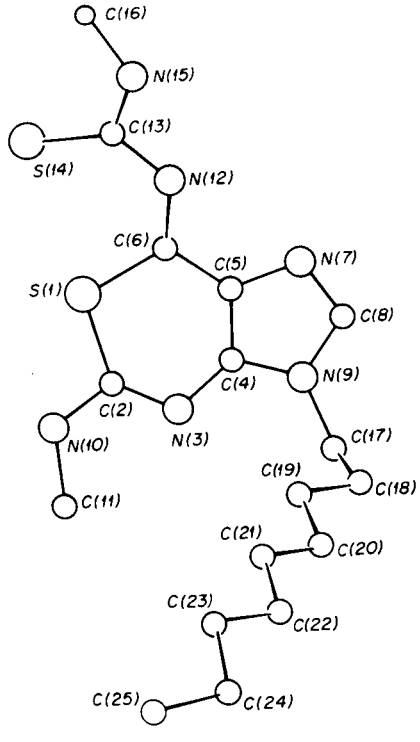



Figure 1

Perspective view of one of the independent molecules of *N*-methyl-*N'*-[5-(methylamino)-3-nonylimidazo[5,4-*d*] [1,3]thiazin-7(3*H*)-ylidine]thiourea with the crystallographic numbering scheme. No hydrogen atoms are shown.

In order to establish unequivocally the direction of ring closure of 1-substituted 5-amino-4-cyanoimidazoles **1** with isothiocyanates, a representative product, **5j**, obtained from the reaction of **1j** with methyl isothiocyanate was subjected to a single crystal X-ray analysis. The result is shown in Figure 1. The X-ray analysis establishes the molecular constitution of this reaction product. The sulfur atom has indeed been incorporated into the ring.

Table II

Fractional Atomic Coordinates (x10⁴) for the Non-Hydrogen Atoms, with Estimated Standard Deviations in Parentheses

| Atom | x/a | y/b | z/c |
|---|---|---|---|
| S(1) | 9400(1) | 2230(2) | 4898(1) |
| C(2) | 9602(5) | 1806(7) | 5786(4) |
| N(3) | 9002(4) | 1586(6) | 6238(3) |
| C(4) | 8152(5) | 1769(7) | 6017(4) |
| C(5) | 7773(5) | 2150(8) | 5386(4) |
| C(6) | 8276(5) | 2491(7) | 4823(4) |
| N(7) | 6841(4) | 2201(6) | 5422(4) |
| C(8) | 6696(5) | 1865(8) | 6046(4) |
| N(9) | 7468(4) | 1607(6) | 6535(3) |
| N(10) | 10477(4) | 1671(6) | 5953(4) |
| C(11) | 10777(6) | 1267(8) | 6639(5) |
| N(12) | 7931(4) | 2996(6) | 4305(3) |
| C(13) | 8300(5) | 3265(8) | 3688(4) |
| S(14) | 8944(1) | 2418(2) | 3250(1) |
| N(15) | 7991(4) | 4118(6) | 3399(3) |
| C(16) | 8131(6) | 4388(8) | 2668(4) |
| C(17) | 7552(6) | 1323(9) | 7186(4) |
| C(18) | 8101(11) | 2934(17) | 7929(6) |
| C(19) | 9244(12) | 4198(18) | 8079(7) |
| C(20) | 9929(12) | 5664(19) | 8929(7) |
| C(21) | 11069(11) | 6863(17) | 9079(8) |
| C(22) | 11783(12) | 8100(24) | 9934(9) |
| C(23) | 12917(14) | 9273(22) | 10038(11) |
| C(24) | 13617(16) | 10516(35) | 11050(17) |
| C(25) | 14632(22) | 11528(34) | 11184(17) |
| S(1') | 4678(1) | 2549(2) | 5487(1) |
| C(2') | 4561(4) | 2672(8) | 4532(4) |
| N(3') | 3878(4) | 2932(6) | 4110(3) |
| C(4') | 3157(5) | 3060(8) | 4433(4) |
| C(5') | 2948(4) | 2885(7) | 5121(4) |
| C(6') | 3572(5) | 2643(8) | 5706(4) |
| N(7') | 2091(4) | 3114(6) | 5171(4) |
| C(8') | 1798(5) | 3380(8) | 4522(5) |
| N(9') | 2419(4) | 3368(6) | 4055(3) |
| N(10') | 5300(4) | 2494(7) | 4255(4) |
| C(11') | 5373(6) | 2671(10) | 3487(4) |

Table II (continued)

| Atom | x/a | y/b | z/c |
|---|---|---|---|
| N(12') | 3358(4) | 2456(6) | 6324(3) |
| C(13') | 4064(5) | 2454(9) | 6957(5) |
| S(14') | 5420(2) | 3827(4) | 7439(2) |
| N(15') | 3481(5) | 1212(8) | 7184(4) |
| C(16') | 4040(9) | 989(11) | 7878(6) |
| C(17') | 2338(6) | 3716(9) | 3316(5) |
| C(18') | 1832(11) | 2247(14) | 2501(10) |
| C(19') | 839(13) | 1154(21) | 2293(10) |
| C(20') | 295(19) | −186(29) | 1216(15) |
| C(21') | −90(23) | −1230(35) | 1111(18) |
| C(22') | −167(22) | −2650(35) | 312(17) |
| C(23') | −295(26) | −4112(40) | 251(21) |
| C(24') | −306(29) | −4043(45) | 803(22) |
| C(25') | −405(40) | −5111(61) | 774(29) |

Table III

Interatomic Distances (Å) and Valency Angles (degrees) with Estimated Standard Deviations in Parentheses

a) Bond lengths

| | Unprimed | Primed |
|---|---|---|
| S(1)-C(2) | 1.783(8) | 1.755(8) |
| S(1)-C(6) | 1.776(7) | 1.789(7) |
| C(2)-N(3) | 1.310(9) | 1.307(9) |
| C(2)-N(10) | 1.342(9) | 1.348(9) |
| N(3)-C(4) | 1.346(9) | 1.348(9) |
| C(4)-C(5) | 1.398(10) | 1.384(10) |
| C(4)-N(9) | 1.358(9) | 1.369(9) |
| C(5)-C(6) | 1.405(10) | 1.411(10) |
| C(5)-N(7) | 1.410(9) | 1.397(9) |
| C(6)-N(12) | 1.304(9) | 1.264(10) |
| N(7)-C(8) | 1.298(10) | 1.313(11) |
| C(8)-N(9) | 1.381(10) | 1.369(10) |
| N(9)-C(17) | 1.462(10) | 1.475(10) |
| N(10)-C(11) | 1.460(10) | 1.475(11) |
| N(12)-C(13) | 1.378(9) | 1.391(10) |
| C(13)-S(14) | 1.702(8) | 1.658(8) |
| C(13)-N(15) | 1.305(10) | 1.368(11) |
| N(15)-C(16) | 1.461(10) | 1.492(14) |
| C(17)-C(18) | 1.482(15) | 1.491(19) |
| C(18)-C(19) | 1.47(2) | 1.24(2) |
| C(19)-C(20) | 1.51(2) | 1.78(3) |
| C(20)-C(21) | 1.45(2) | 1.52(4) |
| C(21)-C(22) | 1.46(2) | 1.45(5) |
| C(22)-C(23) | 1.47(3) | 1.73(5) |
| C(23)-C(24) | 1.67(4) | 1.03(6) |
| C(24)-C(25) | 1.28(4) | 1.33(7) |

Table III (continued)

b) Valency angles

| | Unprimed | Primed |
|---|---|---|
| C(2)-S(1)-C(6) | 104.1(3) | 105.1(3) |
| S(1)-C(2)-N(3) | 128.2(6) | 127.3(5) |
| S(1)-C(2)-N(10) | 111.1(5) | 111.8(5) |
| N(3)-C(2)-N(10) | 120.6(7) | 120.9(7) |
| C(2)-N(3)-C(4) | 115.3(6) | 116.1(6) |
| C(3)-C(4)-C(5) | 132.2(6) | 132.4(7) |
| C(3)-C(4)-N(9) | 122.1(6) | 121.2(6) |
| C(5)-C(4)-N(9) | 105.7(6) | 106.3(6) |
| C(4)-C(5)-C(6) | 124.7(6) | 124.2(6) |
| C(4)-C(5)-N(7) | 109.7(6) | 109.3(6) |
| C(6)-C(5)-N(7) | 125.6(7) | 126.3(7) |
| S(1)-C(6)-C(5) | 115.2(5) | 114.5(5) |
| S(1)-C(6)-N(12) | 124.2(5) | 122.0(6) |
| C(5)-C(6)-N(12) | 120.6(6) | 123.5(6) |
| C(5)-N(7)-C(8) | 104.2(6) | 105.0(6) |
| N(7)-C(8)-N(9) | 113.5(6) | 112.6(7) |
| C(4)-N(9)-C(8) | 106.9(6) | 106.7(6) |
| C(4)-N(9)-C(17) | 127.6(6) | 127.3(6) |
| C(8)-N(9)-C(17) | 125.4(6) | 125.9(6) |
| C(2)-N(10)-C(11) | 120.7(6) | 119.4(7) |
| C(6)-N(12)-C(13) | 126.4(6) | 122.9(6) |
| N(12)-C(13)-S(14) | 125.8(6) | 126.2(6) |
| N(12)-C(13)-N(15) | 112.0(6) | 110.9(7) |
| S(14)-C(13)-N(15) | 121.8(6) | 122.7(7) |
| C(13)-N(15)-C(16) | 123.8(6) | 121.6(8) |
| N(9)-C(17)-C(18) | 110.5(8) | 116.5(9) |
| C(17)-C(18)-C(19) | 115(1) | 115(2) |
| C(18)-C(19)-C(20) | 117(1) | 108(2) |
| C(19)-C(20)-C(21) | 116(1) | 97(2) |
| C(20)-C(21)-C(22) | 116(1) | 117(3) |
| C(21)-C(22)-C(23) | 113(1) | 117(3) |
| C(22)-C(23)-C(24) | 106(2) | 117(4) |
| C(23)-C(24)-C(25) | 109(2) | 118(5) |

There are two independent molecules which make up this crystal; both display disorder in the nonyl unit though it is much more pronounced in the primed molecule. The molecular parameters are generally similar for the two molecules with the largest differences being near the termini of the nonyl tails, in the N(3)-C(4)-C(5)-C(6) torsion angle (unprimed −2.3(9), primed 5.7(8)°) and around the C(12)-C(13) bond (C(6)-N(12)-C(13)-S(14) unprimed 22.6(8), primed 46.7(8)°).

The purine-like skeleton of this molecule is quite planar with the unprimed molecule displaying more planarity. In the primed molecule the sulfur atom lies furthest from the plane (0.062 Å) while in the unprimed molecule it is one of two atoms furthest from the plane (0.042 Å).

Table IV

Selected Torsion Angles (degrees)
with Estimated Standard Deviations in Parentheses

| | Unprimed | Primed |
|---|---|---|
| C(6)-S(1)-C(2)-N(3) | 5.9(8) | 5.6(7) |
| C(6)-S(1)-C(2)-N(10) | −176.8(7) | −175.5(6) |
| C(2)-S(1)-C(6)-C(5) | −6.4(7) | −3.5(6) |
| C(2)-S(1)-C(6)-N(12) | 172.5(8) | 174.5(7) |
| S(1)-C(2)-N(3)-C(4) | −3.1(6) | −2.5(5) |
| N(10)-C(2)-N(3)-C(4) | 179.9(8) | 178.8(7) |
| S(1)-C(2)-N(10)-C(11) | −177.9(7) | −176.1(6) |
| N(3)-C(2)-N(10)-C(11) | −0.4(9) | 2.8(7) |
| C(2)-N(3)-C(4)-C(5) | 0.5(11) | −3.9(9) |
| C(2)-N(3)-C(4)-N(9) | −178.5(9) | 178.6(7) |
| N(3)-C(4)-C(5)-C(6) | −2.3(9) | 5.7(8) |
| N(3)-C(4)-C(5)-N(7) | −179.8(9) | −178.8(8) |
| N(9)-C(4)-C(5)-C(6) | 176.8(9) | −176.5(7) |
| N(9)-C(4)-C(5)-N(7) | 0.7(8) | −1.0(6) |
| N(3)-C(4)-N(9)-C(8) | −179.8(7) | 178.5(6) |
| N(3)-C(4)-N(9)-C(17) | 3.5(9) | −4.6(8) |
| C(5)-C(4)-N(9)-C(8) | 1.0(8) | 0.3(6) |
| C(5)-C(4)-N(9)-C(17) | −175.7(8) | 177.3(7) |
| C(4)-C(5)-C(6)-S(1) | 5.7(7) | −0.8(6) |
| C(4)-C(5)-C(6)-N(12) | −173.3(9) | −178.7(8) |
| N(7)-C(5)-C(6)-S(1) | −177.2(7) | −175.5(6) |
| N(7)-C(5)-C(6)-N(12) | 3.8(9) | 6.6(8) |
| C(4)-C(5)-N(7)-C(8) | 0.0(8) | 1.2(7) |
| C(6)-C(5)-N(7)-C(8) | −177.4(8) | 176.6(7) |
| S(1)-C(6)-N(12)-C(13) | 5.5(8) | 11.5(7) |
| C(5)-C(6)-N(12)-C(13) | −175.7(9) | −170.7(8) |
| C(5)-N(7)-C(8)-N(9) | 0.6(8) | −1.1(7) |
| N(7)-C(8)-N(9)-C(4) | −1.0(7) | 0.5(6) |
| N(7)-C(8)-N(9)-C(17) | 175.8(8) | −176.5(7) |
| C(4)-N(9)-C(17)-C(18) | 97.6(11) | 75.5(10) |
| C(8)-N(9)-C(17)-C(18) | −78.6(11) | −108.1(10) |
| C(6)-N(12)-C(13)-S(14) | 22.6(8) | 46.7(8) |
| C(6)-N(12)-C(13)-N(15) | −165.9(9) | −137.5(8) |
| N(12)-C(13)-N(15)-C(16) | −171.2(8) | −177.3(8) |
| S(14)-C(13)-N(15)-C(16) | 0.6(8) | −1.4(8) |

While the mean intra-annular angle in the six membered ring is 120°, the angles range from 104°, at S(1), to the substantially opened 132°, at C(4). In a related compound with a nitrogen instead of the sulfur in the ring, 6-methyl-7-nonyl-2-thioxopurine [6] the mean angle is also 120° but the range is much smaller, only 118° to 122°. The 5-membered ring is normal with the endocyclic angle at the substituted N(9) larger (107°) than that at the unsubstituted N(7) (~104.5°) and the C(8) angle being the largest ring angle (113°).

The methyl amino group at C(2) is coplanar with the six membered ring. The =NC(=S)NH - side chain adopts slightly different conformations relative to the purine-like skeleton in the two independent molecules; in the unprimed molecule the plane of this substituent makes 26° angle with the ring plane, in the primed molecule this angle is 55°.

The nonyl group is essentially syn-clinal to the ring plane. The N(9)-C(17)-C(18)-C(19) is also syn-clinal, with the rest of the group being all trans in the more well defined (unprimed) molecule. This orientation is very similar to that adopted by 6-methyl-7-nonyl-2-thioxopurine [6].

## EXPERIMENTAL

Melting points were determined on a Buchi oil bath apparatus and are uncorrected. The nmr spectra were measured in deuteriochloroform or DMSO-$d_6$ with TMS as internal standard; the instrument used was the Brucker WM 250 spectrometer. Ultraviolet spectra were obtained using a Cary 118-C and Perkin Elmer Model 320 UV/VIS spectrometer. Silica gel (600-200 mesh) purchased from Davison Chemical, Baltimore Md. was used for all column chromatographic separations. Elemental analyses were performed by Micro Tech Laboratories, Skokie, Ill.

*N*-Methyl-*N'*-[5-(methylamino)-3-methylimidazo[5,4-*d*] [1,3]thiazin-7(3*H*)ylidene]thiourea (**5c**).

To a stirred solution of 5-amino-1-methylimidazole-4-carbonitrile (**1c**), [12] (3.66 g, 30 mmoles) in pyridine (50 ml) was added methyl isothiocyanate (7.3 g, 100 mmoles). The mixture was refluxed for two hours, and then evaporated to dryness. Addition of methanol gave a yellow solid which was collected by filtration. The residual solid was dissolved in hot DMF. After cooling and addition of ether the title compound **5c** was obtained, 3.5 g (43%) mp 203-204°; nmr (DMSO-$d_6$): δ 9.45 (q, 1H, J = 4 Hz, $NHCH_3$), 8.47 (q, 1H, J = 4 Hz, $NHCH_3$), 7.77 (s, 1H, CH) 3.60 (s, 3H, $CH_3$), 2.95 (d, 3H, J = 4 Hz, $CH_3NH$), 2.90 (d, 3H, J = 4 Hz, $CH_3NH$); uv (0.1*N* hydrochloric acid) λ max 282 nm (ε 12600), 377 nm (ε 8200); (0.1*N* sodium hydroxide): 228 nm (ε 12900), 254 nm (ε 9600) 277 (ε 6800), 321 (ε 8300).

*Anal.* Calcd. for $C_9H_{12}N_6S_2$: C, 40.30; H, 4.51; N, 31.33; S, 23.86. Found: C, 40.48; H, 4.61; N, 31.54; S, 23.61.

5-Amino-1-(2-ethoxyethyl)-4-cyanoimidazole (**1d**) and the Isomeric 4-Amino-1-(2-ethoxyethyl)-5-cyanoimidazole.

A suspension of 10.8 g (0.1 mole) of 4(5)-amino 5(4)-cyanoimidazole (**1b**), 13.8 g (0.1 mole) of potassium carbonate and 15.3 g (0.1 mole) of 2-bromoethyl ethyl ether in 30 ml of DMF and 50 ml of THF was heated to reflux for 4 hours. The solvent was removed under reduced pressure and the mixture purified by column chromatography on silica gel. Compound **1d** was eluted with 5% ethanol in methylene chloride (3.4 g, 19%) mp 140-142°; nmr (DMSO-$d_6$): δ 7.13 (s, 1H, CH), 6.15 (s, 2H, $NH_2$), 3.95 (t, 2H, J = 5 Hz, $CH_2$, 3.55 (t, 2H, J = 5 Hz, $CH_2$), 3.40 (q, 2H, J = 8 Hz, $CH_2$), 1.05 (t, 3H, J = 8 Hz, $CH_3$).

*Anal.* Calcd. for $C_8H_{12}N_4O$: C, 53.32; H, 6.71; N, 31.09. Found: C, 53.36; H, 6.76; N, 31.04.

The second product isolated gave 4.3 g (23%) mp 112-114° of the isomer 4-amino-1-(2-ethoxyethyl)-5-cyanoimidazole; nmr (DMSO-$d_6$): δ 7.45 (s, 1H, CH), 5.87 (s, 2H, $NH_2$), 4.00 (t, 2H, J = 5 Hz, $CH_2$), 3.60 (t, 2H, J = 5 Hz, $CH_2$), 3.40 (q, 2H, J = 8 Hz, $CH_2$), 1.10 (t, 3H, J = 8 Hz, $CH_3$).

*Anal.* Calcd. for $C_8H_{12}N_4O$: C, 53.32; H, 6.71; N, 31.09. Found: C, 53.67; H, 6.69; N, 31.20.

*N*-Methyl-*N'*-[5-(methylamino)-3-(2-ethoxyethyl)imidazo[5,4-*d*] [1,3]thiazin-7(3*H*)-ylidene]thiourea (**5d**).

A mixture of 5-amino-1-(2-ethoxyethyl)imidazole-4-carbonitrile (**1d**), (0.18 g, 1 mmole) and methyl isothiocyanate (0.73 g, 10 mmoles) in pyridine (3 ml) was refluxed for one hour. The mixture was evaporated *in vacuo*. The residue was purified by chromatography on silica gel, and the fractions containing the product were concentrated and recrystallized from ethanol to give 0.20 g (61%) of **5d**, mp 168-169°; nmr (DMSO-$d_6$): δ 9.42 (q, 1H, J = 5 Hz, $NHCH_3$), 8.48 (q, 1H, J = 5 Hz, $NHCH_3$), 7.74 (s, 1H, CH), 4.16 (t, 2H, J = 5 Hz), 3.69 (t, 2H, J = 5 Hz, $CH_2$), 3.45 (q, 2H, 6 Hz, $CH_2$), 2.93 (d, 3H, J = 5 Hz, $CH_3NH$), 2.87 (d, 3H, J = 5 Hz, $CH_3NH$), 1.06 (t, 3H, J = 6 Hz, $CH_3$); uv (0.1*N* hydrochloric acid): λ max 282 nm (ε 16300), 377 nm (δ 11700); (0.1*N* sodium hydroxide): 225 nm (ε 23700), 255 nm (ε 12400) 278 nm (ε 8500), 322 nm (ε 12400).

*Anal.* Calcd. for $C_{12}H_{18}N_6S_2O$: C, 44.15; H, 5.56; N, 25.74; S, 19.64. Found: C, 43.94; H, 5.43; N, 25.52; S, 19.71.

*N*-Methyl-*N'*-[5-(methylamino)-3-(2-cyclohexylthioethyl)imidazo[5,4-*d*]-[1,3]thiazin-7(3*H*)-ylidene]thiourea (**5e**).

A mixture of 5-amino-1-(2-cyclohexylthioethyl)imidazole-4-carbonitrile (**1e**), [6] (5.0 g, 20 mmoles) in pyridine (50 ml) was treated with methyl isothiocyanate (6.0 g, 80 mmoles) at 100° for one hour. The resulting mixture was poured with stirring into water (0.5 l). The precipitate was collected, washed with water, and dried. This material was purified on a silica gel column eluting with methylene chloride-ethanol (95:5). The appropriate fractions were combined, evaporated to dryness, and recrystallized twice from methylene chloride-ether to give pure **5e**, yield 2.0 g (25%), mp 195-196°; nmr (DMSO-$d_6$): δ 9.43 (q, 1H, J = 5 Hz, $NHCH_3$), 8.50 (q, 1H, J = 5 Hz, $NHCH_3$), 7.81 (s, 1H, CH), 4.16 (t, 2H, J = 5 Hz, $CH_2$), 2.93 (d, 3H, J = 5 Hz, $CH_3NH$), 2.88 (d, 3H, J = 5 Hz, $CH_3NH$), 2.74 (m, 3H, $CH_2$), 1.93 (m, 2H, $CH_2$), 1.66 (m, 2H, $CH_2$), 1.57-1.23 (m, 6H, $CH_2$); uv (0.1*N* hydrochloric acid): λ max 271 nm (ε 15900), 377 nm (ε 12000); (0.1*N* sodium hydroxide): 229 nm (ε 8600), 258 nm (ε 8300), 308 nm (ε 8100), 370 nm (ε 3600).

*Anal.* Calcd. for $C_{16}H_{24}N_6S_3$: C, 48.48; H, 6.10; N, 21.20; S, 24.22. Found: C, 48.78, H, 6.19; N, 21.30; S, 24.29.

*N*-Methyl-*N'*-[5-(methylamino)-3-[3-(4-*p*-chlorobenzyl)piperazine-1-yl)-propyl]imidazo[5,4-*d*] [1,3]thiazin-7(3*H*)-ylidene]thiourea (**5f**).

A solution of 5-amino-1-[3-(4-(*p*-chlorobenzyl)piperazine-1-yl)propyl]-imidazole-4-carbonitrile (**1f**), [6] (1.0 g, 3 mmoles) in pyridine (25 ml) was treated with methyl isothiocyanate (3.0 g, 40 mmoles) at 100° for 90 min. The solvent was evaporated and the residue treated with water. The resulting solid was removed by filtration and purified on a silica gel column eluting with methylene chloride-ethanol-ammonium hydroxide (90:9:1). The fractions containing the desired product were combined, concentrated and recrystallized from methylene chloride and ether to give 0.8 g of **5f** (52%), mp 205-206°; nmr (DMSO-$d_6$): δ 9.41 (q, 1H, J = 5 Hz, $NHCH_3$), 8.45 (q, 1H, J = 5 Hz, $NHCH_3$), 7.76 (s, 1H, CH), 7.33 (m, 4H, arom), 4.02 (t, 2H, J = 6 Hz, $CH_2$), 3.43 (s, 2H, $CH_2$, 2.93 (d, 3H, J = 5 Hz, $CH_3NH$), 2.86 (d, 3H, J = 5 Hz, $CH_3NH$), 2.34-2.25 (m, 10H, $CH_2$), 1.89 (t, 2H, J = 6 Hz, $CH_2$); uv (0.1*N* hydrochloric acid): λ max 280 nm (ε 16300) 376 nm (ε 12200); (0.1*N* sodium hydroxide): 254 nm (ε 40100), 276 nm (ε 27000), 321 nm (ε 41500).

*Anal.* Calcd. for $C_{22}H_{29}ClN_8S_2$: C, 52.31; H, 5.79; Cl, 7.02; N, 22.18; S, 12.70. Found: C, 52.13; H, 5.66; Cl, 6.98; N, 22.12; S, 12.73.

*N*-Methyl-*N'*-[5-methylamino)-3-(2-ethylthioethyl)imidazo[5,4-*d*] [1,3]-thiazin-7(3*H*)-ylidene]thiourea (**5g**).

A solution of 5-amino-1-(2-ethylthioethyl)imidazole-4-carbonitrile (**1g**), [6] (1.96 g, 10 mmoles) in pyridine (25 ml) was treated with methyl isocyanate (3.0 g, 40 mmoles) at 100° for two hours. After cooling, the mixture was poured into water and filtered. The product was purified on a silica gel column eluting with methylene chloride-ethanol (95:5). The appropriate fractions were combined and evaporated to dryness. Recrystallization from methylene chloride and ether gave pure **5g**, 1.5 g (44%) mp 188-190°; nmr (DMSO-$d_6$): δ 9.43 (q, 1H, J = 5 Hz, $NHCH_3$), 8.49 (q, 1H, J = 5 Hz, $NHCH_3$), 7.81 (s, 1H, CH), 4.18 (t, 2H, J = 6 Hz, $CH_2$), 2.93 (d, 3H, J = 5 Hz, $CH_3NH$), 2.87 (d, 3H, J = 5 Hz, $CH_3NH$), 2.9-2.8 (m, 2H, $CH_2$), 2.54 (q, 2H, J = 5 Hz, $CH_2$), 1.78 (t, 3H, J = 6 Hz, $CH_3$); uv (0.1*N* hydrochloric acid): λ max 279 nm (ε 13200), 378 nm (ε 9400); (0.1*N* sodium hydroxide): 226 nm (ε 36000); 255 nm (ε 20900); 277 nm (ε 14500); 322 nm (ε 22500).

*Anal.* Calcd. for $C_{12}H_{18}N_6S_3O$: C, 42.10; H, 5.30; N, 24.55; S, 28.05. Found: C, 41.90; H, 5.19; N, 24.42; S, 28.19.

*N*-Methyl-*N'*-[5-(methylamino)-3-[2-(*p*-chlorophenyl)thioethyl]imidazo-[5,4-*d*] 1,3]thiazin-7(3*H*)-ylidene]thiourea (**5h**).

A solution of 5-amino-1-[2-(*p*-chlorophenyl)thioethyl]imidazole-4-carbonitrile (**1h**), [6] (2.0 g, 7 mmoles) in pyridine (25 ml) was treated with methyl isothiocyanate (3.0 g, 40 mmoles) at 100° for two hours. Water was added, and after one hour the crystalline material was filtered. The precipitate was dissolved in methylene chloride-ethanol (1:1) and applied to a silica gel column and eluted with methylene chloride-ethanol (95:5). The appropriate fractions were combined, evaporated, and recrystallized twice from ethanol to give 1.5 g of **5h** (49%), mp 186-189°; nmr (DMSO-$d_6$): δ 9.42 (q, 1H, J = 5 Hz, $NHCH_3$), 8.48 (q, 1H, J = 5 Hz, $NHCH_3$), 7.78 (s, 1H, CH), 7.38 (m, 4H, arom), 4.21 (t, 2H, J = 4 Hz, $CH_2$), 3.44 (t, 2H, J = 4 Hz, $CH_2$), 2.93 (d, 3H, J = 5 Hz, $CH_3NH$), 2.79 (d, 3H, J = 5 Hz, $CH_3NH$); uv (0.1*N* hydrochloric acid): λ max 257 nm (ε 8500); 386 nm (ε 4800); (0.1*N* sodium hydroxide): 228 nm (ε 7000), 255 nm (ε 7800), 322 nm (ε 4200).

*Anal.* Calcd. for $C_{16}H_{17}ClN_6S_3$: C, 45.22; H, 4.03; Cl, 8.34; N, 19.77; S, 22.63. Found: C, 45.26; H, 4.00; Cl, 8.63; N, 19.77; S, 22.91.

*N*-Methyl-*N'*-[5-(methylamino)-3-(2-methoxyethyl)imidazo[5,4-*d*] [1,3]-thiazin-7(3*H*)-ylidene]thiourea (**5i**).

A solution of 5-amino-1-(2-methoxyethyl)imidazole-4-carbonitrile (**1i**), [6] (3.3 g, 20 mmoles) in pyridine (25 ml) and methyl isothiocyanate (6.0 g, 80 mmoles) was heated under reflux with stirring for two hours. The solution was evaporated to dryness and the product was purified over silica gel. Recrystallization from methanol gave 0.9 g (14%) of analytical pure **5i**, mp 184-185°; nmr (deuteriochloroform): δ 7.65 (s, 1H, CH), 7.45 (br q, 1H, $NHCH_3$), 5.47 (br q, 1H, $NHCH_3$), 4.20 (t, 2H, J = 5 Hz, $CH_2$), 3.68 (t, 2H, J = 5 Hz, $CH_2$), 3.35 (s, 3H, $CH_3O$), 3.20 (d, 3H, J = 5 Hz, $CH_3NH$), 3.08 (d, 3H, J = 5 Hz, $CH_3NH$); uv (0.1*N* hydrochloric acid): λ max 280 nm (ε 18800), 378 nm (ε 13300); (0.1*N* sodium hydroxide): 255 nm (ε 13300), 277 nm (ε 9200), 320 nm (ε 13500).

*Anal.* Calcd. for $C_{11}H_{16}N_6S_2O$: C, 42.29; H, 5.16; N, 26.90; S, 20.53. Found: C, 42.30; H, 5.19; N, 26.51; S, 20.59.

*N*-Methyl-*N'*-[5-(methylamino)-3-nonylimidazo[5,4-*d*] [1,3]thiazin-7(3*H*)-ylidene]thiourea (**5j**).

A solution of 5-amino-1-nonylimidazole-4-carbonitrile (**1j**), [6] (0.23 g, 1 mmole) in pyridine (3 ml) was treated with methyl isothiocyanate (3.65 g, 50 mmoles) at 100° for 90 minutes. The product was evaporated to a foam, dissolved in methylene chloride, and applied to a silica gel column. The column was eluted with methylene chloride containing 2% ethanol. The fraction containing the product were combined and evaporated. The residue was crystallized from methylene chloride and ether to give 0.3 g of **5j** (79%), mp 182-183°; nmr (deuteriochloroform): δ 7.52 (s, 1H, CH), 7.40 (br q, 1H, $NHCH_3$), 5.40 (br q, 1H, $NHCH_3$), 4.02 (t, 2H, J = 7 Hz, $CH_2$), 3.18 (d, 3H, J = 5 Hz, $CH_3NH$), 3.10 (d, 3H, J = 5 Hz, $CH_3NH$), 1.85 (m, 2H, $CH_2$), 1.30 (m, 12H, $(CH_2)_6$), 0.80 (t, 3H, J = 6 Hz, $CH_3$); ms: (70 ev, ei scanned to 85°) m/e 381 ($M^+$), 307 (m − $CH_3NCS$), 276 (100); uv (0.1*N* hydrochloric acid): λ max 222 nm (ε 35000) 279 nm (ε 15000), 378 nm (ε 11700); (0.1*N* sodium hydroxide): 226 nm (ε 10400), 263 nm (ε 9700), 310 nm (ε 10000), 400 nm (ε 8200).

*Anal.* Calcd. for $C_{17}H_{28}N_6S_2$: C, 53.66; H, 7.42; N, 22.09; S, 16.82. Found: C, 53.65; H, 7.42; N, 21.96; S, 16.82.

*N*-Methyl-*N'*-[5-(methylamino)-3-benzylimidazo[5,4-*d*] [1,3]thiazin-7(3*H*)-ylidene]thiourea (**5k**).

A solution of 5-amino-1-benzylimidazole-4-carbonitrile (**1k**), [6] (1.98 g, 10 mmoles) and methyl isothiocyanate (2.93 g, 40 mmoles) in pyridine (30

ml) was heated under reflux with stirring for 3 hours, the solution was evaporated to dryness and recrystallized from ethanol and ether to give **5k**, 1.1 g (32%), mp 201-202°; nmr (DMSO-$d_6$): δ 9.43 (q, 1H, J = 4 Hz, $NHCH_3$), 8.50 (q, 1H, J = 4 Hz, $NHCH_3$), 7.92 (s, 1H, CH), 7.4-7.2 (m, 5H, arom) 5.22 (s, 2H, $CH_2$), 2.93 (d, 3H, J = 4 Hz, $CH_3NH$), 2.87 (d, 3H, J = 4 Hz, $CH_3NH$); uv (0.1*N* hydrochloric acid): λ max 280 nm (ε 14600), 378 nm (ε 10500); (0.1*N* sodium hydroxide): 230 nm (ε 11400), 257 nm (ε 10000), 277 nm (ε 7100), 323 nm (ε 11000).

*Anal.* Calcd. for $C_{15}H_{16}N_6S_2$: C, 52.32; H, 4.68; N, 24.41; S, 18.59. Found: C, 52.26; H, 4.71; N, 24.28; S, 18.80.

*N*-Methyl-*N'*-[5-(methylamino)-3-(4-chlorobenzyl)imidazo[5,4-*d*][1,3]-thiazin-7(3*H*)-ylidene]thiourea (**5l**).

A mixture of 5-amino-1-(4-chlorobenzyl)imidazole-4-carbonitrile (**1l**), [6] 2.3 g (10 mmoles), methyl isothiocyanate (2.92 g, 40 mmoles) and pyridine (25 ml) was refluxed for one hour. The pyridine was removed by distillation and the residue recrystallized from ethanol and ether to give 1.3 g (35%) of **5l**, mp 196-197°; nmr (DMSO-$d_6$): δ 9.45 (q, 1H, J = 5 Hz, $NHCH_3$), 8.52 (q, 1H, J = 5 Hz, $NHCH_3$), 7.92 (s, 1H, CH), 7.4 (m, 4H, arom), 5.23 (s, 2H, $CH_2$), 2.93 (d, 3H, J = 5 Hz, $CH_3NH$), 2.87 (d, 3H, J = 5 Hz, $CH_3NH$); uv (0.1*N* hydrochloric acid): λ max 221 nm (ε 27500); 278 nm (ε 9300) 377 nm (ε 7200); (0.1*N* sodium hydroxide): insoluble.

*Anal.* Calcd. for $C_{15}H_{15}ClN_6S_2$: C, 47.55; H, 3.99; Cl, 9.36; N, 22.18; S, 16.92. Found: C, 47.57; H, 4.04; Cl, 9.61; N, 21.99; S, 16.92.

*N*-Allyl-*N'*-[5-(allylamino)-3-methylimidazo[5,4-*d*][1,3]thiazin-7(3*H*)-ylidene]thiourea (**5m**).

A mixture of 5-amino-1-methylimidazo-4-carbonitrile (**1c**), [12] (2.44 g, 20 mmoles) and allyl isothiocyanate (5.91 g, 60 mmoles) in pyridine (20 ml) was refluxed for two hours. The reaction mixture was concentrated *in vacuo* to a resin which was purified by chromatography on silica gel using methylene chloride and ethanol (95:5) to give 0.5 g (10%) of **5m** as a yellow crystalline solid, mp 149-150°; nmr (DMSO-$d_6$): δ 9.65 (t, 1H, J = 4 Hz, $NHCH_2$) 8.73 (t, 1H, J = 4 Hz, $NHCH_2$), 7.76 (s, 1H, CH), 5.8-6.0 (m, 2H, 2 CH=$CH_2$), 5.2-5.3 (m, 4H, 2 $CH_2$-N) ($CH_2$-$N)_2$) 4.15 (t, 2H, J = 4 Hz, $CH_2$=CH), 4.02 (t, 2H, J = 4 Hz, $CH_2$=CH), 3.57 (s, 3H, $CH_3$); uv (0.1*N* hydrochloric acid): λ max 274 nm (ε 12400) 376 nm (ε 8600); (0.1*N* sodium hydroxide): 225 nm (ε 30500), 256 (ε 15500), 275 nm (ε 10300), 321 nm (ε 15000).

*Anal.* Calcd. for $C_{13}H_{16}N_6S_2$: C, 48.72; H, 5.03; N, 26.23; S, 20.01. Found: C, 48.86; H, 5.02; N, 26.52; S, 19.80.

*N*-Ethyl-*N'*-[5-(ethylamino)-3-methylimidazo[5,4-*d*][1,3]thiazin-7(3*H*)-ylidene]thiourea (**5n**).

A mixture of 5-amino-1-methylimidazole-4-carbonitrile (**1c**), [12] (2.44 g, 20 mmoles) and ethyl isothiocyanate (5.22 g, 60 mmoles) in pyridine (20 ml) was refluxed for one hour. The mixture was evaporated *in vacuo*. The residue was purified by chromatography using silica gel, eluting with methylene chloride and ethanol (95:5). The fractions containing the required product were combined and the yellow crystalline product was recrystallized from methanol and ether to give 1.3 g (22%) of **5n**, mp 208-210°; nmr (DMSO-$d_6$): δ 9.47 (t, 1H, J = 5 Hz, $NHCH_2$), 8.52 (t, 1H, J = 5 Hz, $NHCH_2$) 7.74 (s, 1H, CH), 3.50 (s, 3H, $CH_3$), 3.3-3.5 (m, 4H, 2 $CH_2CH_3$), 1.1-1.2, (m, 6H, 2 $CH_3CH_2$); uv (0.1*N* hydrochloric acid): λ max uv (0.1*N* hydrochloric acid): 272 nm (ε 13200), 362 nm (ε 9200); (0.1*N* sodium hydroxide): 253 nm (ε 17600), 277 nm (ε 12000), 322 nm (ε 12500), 388 nm (ε 36000).

*Anal.* Calcd. for $C_{11}H_{16}N_6S_2$: C, 44.59; H, 5.44; N, 28.37; S, 21.60. Found: C, 44.48; H, 5.41; N, 28.47; S, 21.28.

*N*-Methyl-*N'*-5-(methylamino)-3-benzyloxyimidazo[5,4-*d*][1,3]thiazin-7(3*H*)-ylidene]thiourea (**5o**).

A solution of 5-amino-1-benzyloxyimidazole-4-carbonitrile (**5o**), [13] (2.1 g, 10 mmoles) and methyl isothiocyanate (2.92 g, 40 mmoles) in pyridine (20 ml) was refluxed for two hours. The solvent was removed *in vacuo* and the precipitate digested with methylene chloride, filtered, and transferred to a silica gel column. Elution with methylene chloride and ethanol (98:2) gave pure **5o** (0.52 g, 14%), mp 200-201°; nmr (DMSO-$d_6$): δ 9.50 (br q, 1H, $NHCH_3$), 8.67 (br q, 1H, $NHCH_3$), 7.78 (s, 1H, CH), 7.45 (m, 5H, arom), 5.35 (s, 2H, $CH_2O$), 2.92 (s, 6H, 2 $CH_3NH$); uv (sample is insoluble in 0.1*N* hydrochloric acid and 0.1*N* sodium hydroxide).

*Anal.* Calcd. for $C_{15}H_{16}N_6OS_2$: C, 49.98; H, 4.47; N, 23.31; S, 17.79. Found: C, 50.35; H, 4.48; N, 23.59; S, 17.76.

*N*-Methyl-*N'*-[5-(methylamino)-3-*N*,*N*-dimethylaminoethylimidazo-[5,4-*d*][1,3]thiazine 7(3*H*)-ylidene]thiourea Hemihydrate (**5p**).

A solution of 5-amino-1-*N*,*N*-dimethylaminoethylimidazole-4-carbonitrile (**1p**), [6] (1.79 g, 10 mmoles) and methyl isothiocyanate (3.65 g, 50 mmoles) in pyridine (25 ml) was refluxed for two hours. The solvent was removed *in vacuo* and the residue was chromatographed over silica gel using 10% ethanol in methylene chloride to give **5p** (0.7 g, 22%), mp 175-177°; nmr (DMSO-$d_6$): δ 9.42 (q, 1H, J = 4 Hz, $NHCH_3$), 8.50 (q, 1H, J = 4 Hz, $NHCH_3$), 7.80 (s, 1H, CH), 4.10 (t, 2H, J = 5 Hz, $CH_2$), 2.95 (d, 3H, J = 4 Hz, $CH_3NH$), 2.87 (d, 3H, J = 4 Hz, $NHCH_3$), 2.62 (t, 2H, J = 5 Hz, $CH_2$), 2.20 (s, 6H, $N(CH_3)_2$; uv (hydrochloric acid): λ max 281 nm (ε 12400), 376 nm (ε 8500); (0.1*N* sodium hydroxide): 255 nm (ε 14400) 276 nm (ε 10000) 322 nm (ε 15700).

*Anal.* Calcd. for $C_{12}H_{19}N_7S_2 \cdot \frac{1}{2}H_2O$: C, 43.09; H, 6.02; N, 29.31; S, 19.17. Found: C, 42.88; H, 5.86; N, 28.96; S, 18.99.

Crystallography.

Crystal data were the following: $C_{17}H_{28}N_6S_2$, $M$ = 380.6, Triclinic, $a$ = 14.736(3), $b$ = 9.892(3), $c$ = 18.186(3) Å, α = 106.22(2), β = 101.45(1), γ = 117.38(2)°, V = 2088(1) Å$^3$, $D_c$ = 1.211 g cm$^{-3}$, Z = 4, F(000) = 816. Cu-Kα radiation (λ = 1.5418 Å), μ = 23.2 cm$^{-1}$. Space group P$\bar{1}$ ($C_i^1$) by structure refinement. Specimen: 0.10 x 0.20 x 0.65 mm.

Crystallographic Measurements and Structure Analysis.

A hemisphere of data to θ = 65° was collected on a Syntex P2$_1$ automated diffractometer using variable speed, θ/2θ scans. Of the 5383 reflections collected, 3543 reflections with I ≥ 2σ(I) were corrected for Lorentz and polarization effects and used in the structure solution and refinement. An empirical absorption correction was made to these data based on ψ scan information. The structure was solved by direct phasing methods (MULTAN80) [14]. The asymmetric unit comprises two independent molecules. There is some disorder apparent at the end of the nonyl chain in the unprimed molecule. Disorder is much more pronounced in the nonyl chain of the other molecule. The six terminal atoms were included with large isotropic temperature factors. Hydrogen atoms were not included. Full-matrix least-squares of all non-hydrogen atoms brought the R values to 0.118.

Table II lists the non-hydrogen atomic positional parameters, Table III lists bond lengths and valency angles and Table IV lists selected torsion angles.

Supplementary Materials.

Listings of final thermal parameters and torsion angles can be obtained from the Authors.

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