Synthesis of Quinazoline Nucleosides from Ribose and Anthranilonitrile. Application of Phase-Transfer Catalysis in Nucleoside Synthesis

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Condensation of anthranilonitrile with ribose gave *N*-(β-D-ribopyranosyl)anthranilonitrile (**1**) in 88% yield. It is converted to the triacetyl derivative **2**, a compound which was synthesized from anthranilonitrile and 1-chloro-2,3,4-tri-*O*-acetyl-D-ribopyranose by phase-transfer catalysis. *N*-(2′,3′,5′-tri-*O*-acetyl-D-ribofuranosyl)anthranilonitrile (**3**) was also prepared by phase-transfer catalysis from anthranilonitrile and 1-chloro-2,3,5-tri-*O*-acetyl-D-ribofuranose. Treatment of **3** with methanolic NH_3 gave **1**. Reaction of **2** with NaH and PhNCS gave 1-(2′,3′,4′-tri-*O*-acetyl-β-D-ribopyranosyl)-2-thio-3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline (**5a**). Treatment of **5a** with ethanolic NH_3 gave 1-(β-D-ribopyranosyl)-2-thio-4-amino-1,2,3,4-tetrahydroquinazoline (**10**) and 1-(β-D-ribopyranosyl)-2-anilino-4-imino-1,4-dihydroquinazoline (**11**). Reaction of **2** with NaH and CH_3NCS gave 1-(2′,3′,4′-tri-*O*-acetyl-β-D-ribopyranosyl)-2-thio-3-methyl-4-imino-1,2,3,4-tetrahydroquinazoline (**5b**). Treatment of **5b** with methanolic NH_3 gave the corresponding deblocked nucleoside **15**. The structures of the sugar moieties were confirmed by ^1H NMR spectroscopy and of the aglycons by acid hydrolysis of the nucleosides to the corresponding quinazolines.

Enaminonitriles and *o*-aminonitriles are versatile starting materials for the synthesis of a wide array of heterocyclic ring systems.[1] The combination of an electrophilic cyano group proximate to a nucleophilic amino function in aminonitriles often results in a one-step addition–cyclization reaction of electrophiles to give pyrimidines and pyrimidine analogues. The imidazole and pyrazole ring systems can be formed by the photochemical rearrangement of these versatile starting materials.[2] The facile conversion of aminonitrile derivatives to heterocyclic systems which are analogues of biomolecules prompted our investigation of the synthesis of potential antitumor and antiviral agents by this route. Here we report the formation of a ribose adduct of anthranilonitrile (*o*-aminobenzonitrile) and its subsequent cyclization to quinazoline ribosides. These quinazolines may exhibit antiviral or antitumor activity since N^1-β-D-ribofuranosyl-2,4-quinazolinedione possesses in vitro antiviral activity.[3,4]

Results and Discussion

The direct condensation of ribose and anthranilonitrile to *N*-ribosylanthranilonitrile (**1**) proceeds in 88% yield in refluxing benzene using acetic acid as catalyst (Scheme I). Presumably the reaction proceeds from the Schiff base, formed by the reaction of the open-chain tautomer of ribose with the amino group of anthranilonitrile. The tri-*O*-acetyl derivative **2** was formed on treatment of **1** with excess acetic anhydride and pyridine for 7 h. A mixture of the triacetyl and 2′,3′-diacetyl derivatives was formed when shorter (2 h) reaction times were used (see Experimental Section).

The structure of the *N*-ribosylanthranilonitrile adduct was established as **1** by the independent synthesis of triacetate **2** in the reaction of 1-chloro-2,3,4-tri-*O*-acetyl-D-ribopyranose[5] with anthranilonitrile (Scheme I). An isomeric β-D-ribofuranoside triacetate (**3**) was obtained in 86% yield by the reaction of the *o*-aminonitrile with 1-chloro-2,3,5-tri-*O*-acetyl-D-ribofuranose.[6] Both of these syntheses proceed under conditions of phase-transfer catalysis by the displacement of the chloro group with the anion of the *o*-aminonitrile.[7] The successful alkylation of amines[7] by phase-transfer catalysis prompted our use of this technique for the synthesis of **2** and **3**. We are currently investigating the possibility of using this novel nucleoside synthesis for the direct formation of known antitumor agents by the condensation of the corresponding aglycon anion with ribosyl halides.

The pyranose ring structure in **1** and **2** was established by the independent synthesis of **2** starting from 1-chloro-2,3,4-tri-*O*-acetylribopyranose. The possibility that an undetected rearrangement to the furanoside took place during the course of the synthesis was eliminated by the synthesis of the isomeric ribofuranosyl triacetate starting from a 1-chloro-2,3,5-tri-*O*-acetylribofuranose. The β configuration was assigned to **2** and **3** on the basis of the method of synthesis used in which the β anomer is formed as a result of the neighboring group participation of the 2′-acetyl group.[8] This configurational assignment is consistent with the ^1H NMR spectrum of **1** in which the anomeric proton at δ 4.83 is a doublet with $J = 9$ Hz. An $H_{1'}$–$H_{2'}$ coupling constant of 8–11 Hz would be expected for the anti-periplanar relationship of H-1′ and H-2′ in **1**.[9,10] $H_{1'}$–$H_{2'}$ coupling constants of 7–9 Hz were reported recently for structurally related nucleoside ribopyranosides.[11,12] The coupling constant of 2.5 Hz for $H_{1'}$–$H_{2'}$ is consistent with the assignment of the β configuration to the ribofuranoside **3**.[9-12]

The ^1H NMR spectrum of **2** indicated it to be predominantly in the 1C conformation with an axial 1′-cyanoanilino grouping. Decoupling experiments established that the chemical shift of H-2′ (δ 5.70) was greater than that of H-1′ (δ 5.33) and that $J_{1',2'} \simeq 1$ Hz. The downfield shift of H-2′ relative to H-1′ is consistent with the 1C conformation in which the equatorial H-2′ is shielded by the aromatic aglycon. Similar anisotropic effects of aromatic aglycons on the chemical shifts of 2′-acetoxyl groups have been reported.[13] The nonbonded interaction between the gauche 2′-acetoxyl and 1′-cyanoanilino groupings must shift the conformational equilibrium in favor of 1C in the triacetate. It is not obvious why this interaction is greater than that of the 1,3-diaxial acetoxyl groupings in 1C. This interaction is diminished when the acetoxyls are cleaved and C1 is the predominant conformation in **1**.

Deacetylation of the tri-*O*-acetylribofuranose **3** with methanolic ammonia at room temperature resulted in its conversion to **1**. This rearrangement, which undoubtedly proceeds via the open-chain Schiff base, demonstrates that the β-pyranoside is the thermodynamically stable isomer. This is consistent with the observation that the β-pyranoside form of ribose is the predominant isomer in aqueous solution.[14,15]

We anticipated that the conversion of the ribosylanthranilonitrile **1** to quinazoline derivatives would proceed unexceptionally along the synthetic routes devised for the conversion of *o*-aminonitriles to quinazolines.[1,16] Surprisingly it was not possible to cyclize **1** or **2** to a quinazoline nucleoside with phenyl isocyanate,[17] phenyl isothiocyanate,[16] methyl isothiocyanate,[16] thiourea,[17] formamide,[18] potassium *O*-ethyl

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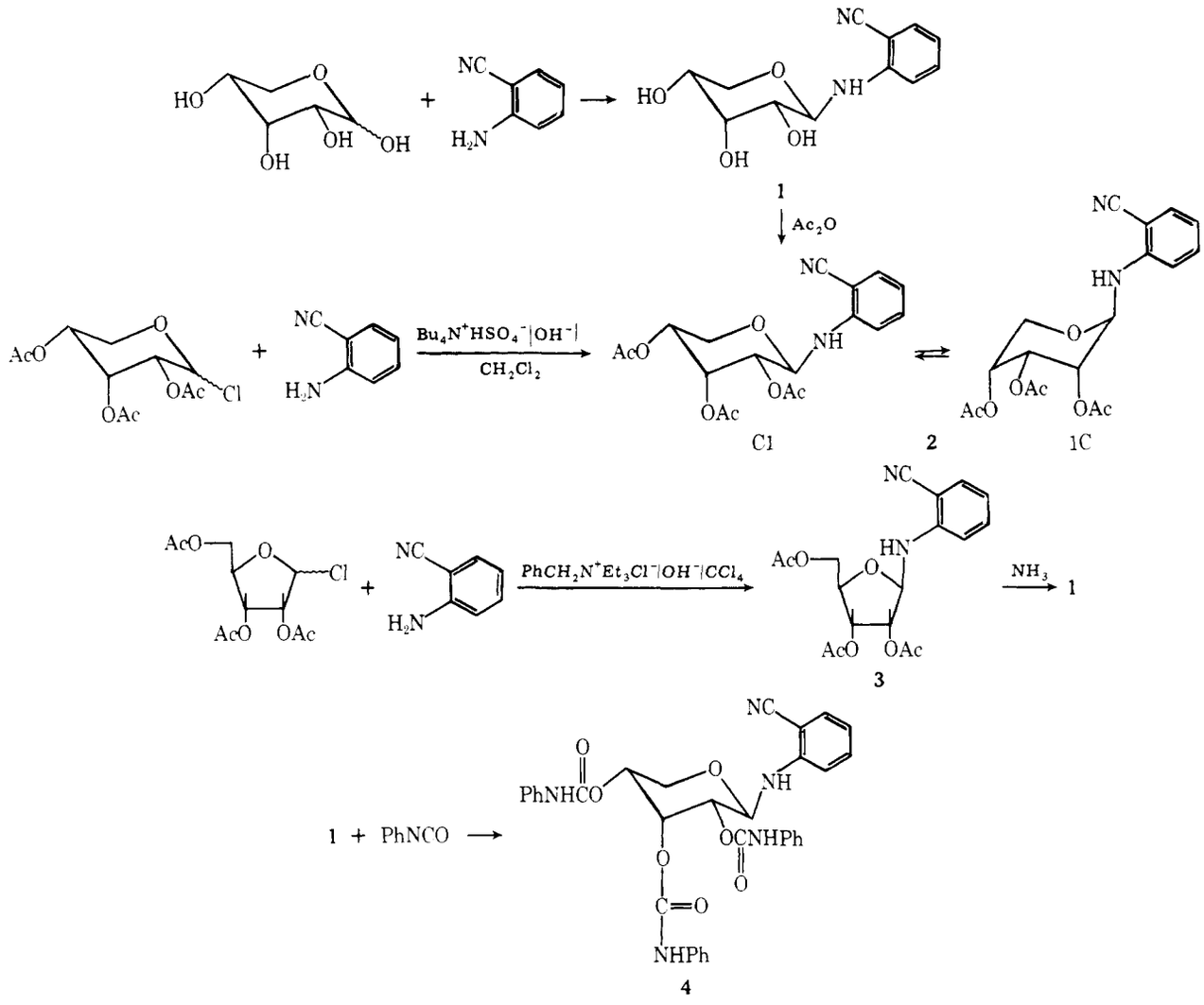
Scheme I



dithiocarbonate,[19] or potassium thiocyanate. Several of these procedures gave modest yields of anthranilonitrile or heterocycles derived from it, thus demonstrating that the cleavage of the ribose moiety was a predominant reaction pathway. The tricarbamate **4** was the product of the reaction of **1** with phenyl isocyanate in pyridine.[16] Reaction of the triacetate **2** with phenyl isocyanate under the same reaction conditions gave no adduct of **2** but only resulted in the formation of diphenylurea from traces of moisture present.[20]

The low reactivity of *N*-ribosylanthranilonitrile was unexpected in view of the previous reports of the reaction of anthranilonitrile and *N*-methylanthranilonitrile with these reagents.[16] The lack of reactivity of ribosylanthranilonitrile is probably due to the diminished nucleophilicity of the amino function as a consequence of (1) the steric bulk of the ribose ring and (2) the electrophilic character of the masked aldehyde carbon atom at C-1′ of the pyranose ring.

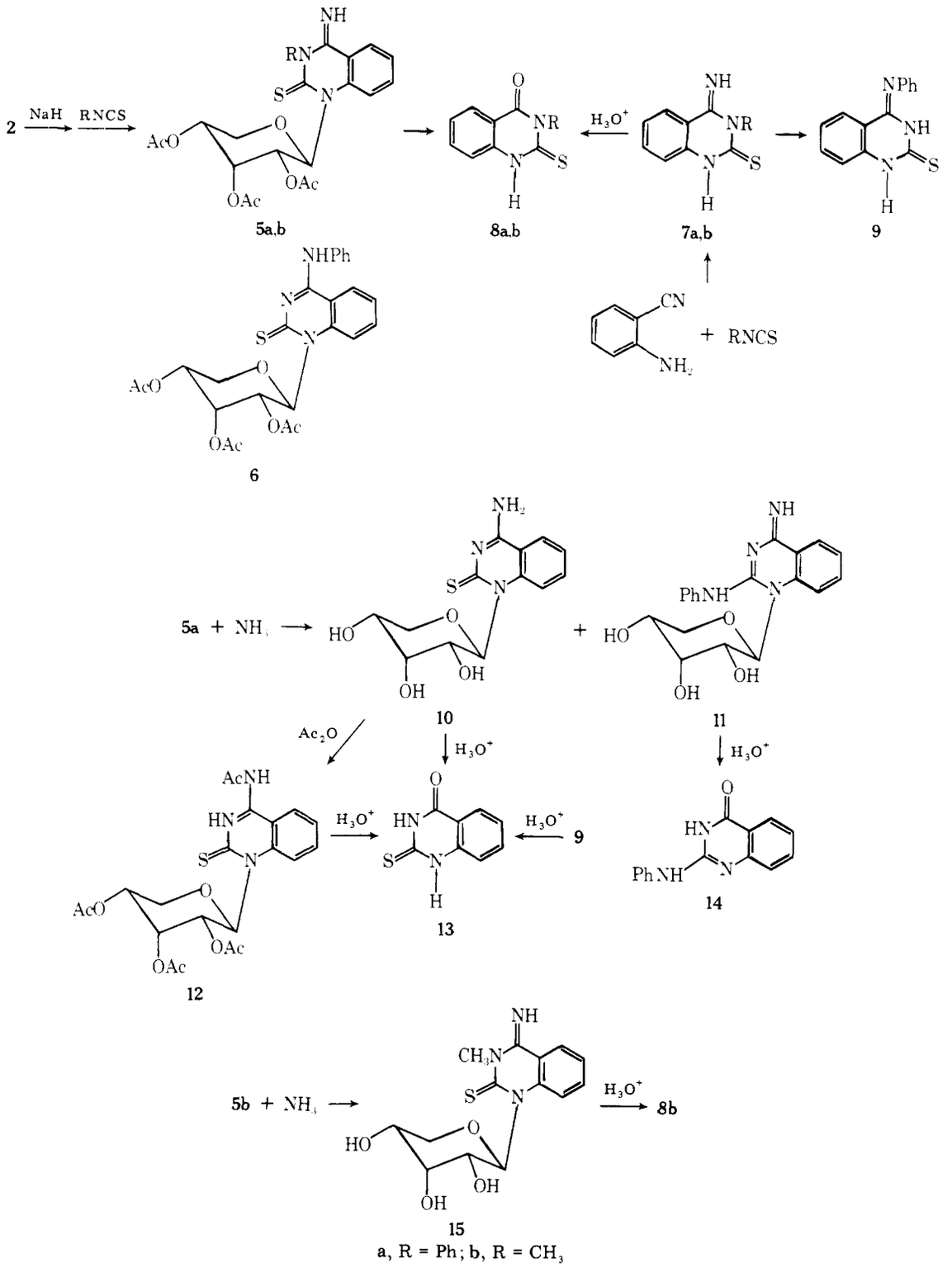
It was possible to increase the nucleophilicity of ribosylanthranilonitrile by conversion of the N–H grouping to the anilide anion with sodium hydride in dimethyl sulfoxide.[21] Thus, reaction of the anion of **2** with phenyl isothiocyanate resulted in the formation of the quinazoline nucleoside **5a** in 94% yield (Scheme II). It was established that **5a** and not **6** was the structure of the reaction product by the close similarity of the UV spectra of **5a** and **7a**. In addition, acid hydrolysis of **5a** gave **8a**, the identity of which was established by its independent synthesis from anthranilonitrile and phenyl isothiocyanate.[16]

Methyl isothiocyanate was added to the anion of **2** in a similar fashion to give **5b** in 73% yield. The structure of the aglycon portion of **5b** was proved by UV spectral comparison with an authentic sample of **7b** and the acid hydrolysis of **7b** and **5b** to the same compound (**8b**).[22]

It was surprising to find that **5a** and **5b** reacted by quite different pathways on treatment with methanolic ammonia. These reaction pathways also differ from that reported for the corresponding 1-methyl analogue (1-methyl-2-thio-3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline) with sodium methoxide.[16] The rearranged structures **10** and **11** were obtained in roughly equal amounts on treatment of **5a** with methanolic ammonia. It proved difficult to separate these products by fractional crystallization and chromatographic techniques. However, if the reaction was allowed to proceed in ethanolic ammonia, the thioquinazoline (**10**) precipitated from the reaction mixture in 40% yield. Fractional crystallization of the filtrate yielded a pure sample of the 2-anilino derivative (**11**). The structure of **10** was suggested initially by its ^{1}H NMR spectrum which exhibited only four protons in the aromatic region. The assigned structure is consistent with the formation of a tetracetyl derivative (**12**). Compound **12** was characterized by a ^{1}H NMR spectrum with four singlets for the methyl groupings and an IR spectrum with an amide band at 1630 cm^{-1}. The structures of **10** and **12** were proved by their acid hydrolysis to **13**, an authentic sample of which was prepared by the acid hydrolysis of **9**.[16]

The structure of the 2-anilino derivative **11** was suggested

Scheme II

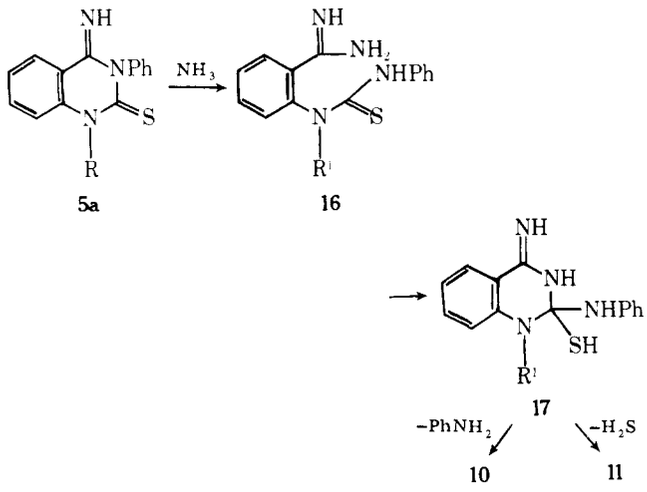


on the basis of mass spectral molecular weight determination using chemical ionization with methane. Its structure was proved by the absence of sulfur and by acid hydrolysis to **14**, an authentic sample of which was prepared by the condensation of *N*-phenylurea and methyl anthranilate.[23]

In contrast to the aminolysis of **5a**, the treatment of **5b** with methanolic ammonia resulted in the formation of **15** by the simple cleavage of the *O*-acetyl groups. Structure **15** was assigned on the basis of spectral data and the acid hydrolysis product which was identical with an authentic sample of **8b**.[22] The $H_{1'}$–$H_{2'}$ coupling constants in **5a**, **10**, **11**, **12**, and **15** are 9.5–10 Hz, a result consistent with the assigned β-ribopyranose structures. The 1C conformer of these structures would be of much higher energy than the C1 conformer because of the large nonbonded interactions between the substituents on the C-2 position of the quinazoline ring and the axial hydrogens at the 3′ and 5′ positions in 1C.

The Dimroth rearrangement[25] of **5a** to **10** and **11** is initiated by the attack of NH_3 at the 4 position of the quinazoline ring with the formation of intermediate **15** (Scheme III).[16,25] Cyclization of **16** yields **17**, an intermediate which can eliminate aniline or H_2S to give **10** or **11**, respectively. The alternative

Scheme III



R = tri-*O*-acetylribosyl; R¹ = ribosyl

mechanisms proposed for the rearrangement of this quinazoline ring system are incompatible with our observation of the formation of **10** and **11** from **5a**. In one proposal, it was suggested that the rearrangement is initiated by anion formation at the 1 position,[26] a pathway which is not possible with the N-1 alkyl substituent present in **5a**. In the other mechanistic postulate the initial attack of the basic reagent is at the C-2 thione,[16] but it is not possible to form **11** from **5a** by this route.

Initially it was surprising that the *N*-phenylquinazoline **5a** rearranged to **10** and **11** while the *N*-methyl derivative **5b** did not. These results can be understood if the rate-limiting step is the nucleophilic addition to the imino group. The reactivity of the imino group in **5b** to nucleophiles is decreased by the electron-releasing methyl group. In contrast, the reactivity of the imino group in **5a** is increased because the phenyl group will delocalize the electron pair on N-3 and the imino function will then be more susceptible to nucleophilic attack.

Conclusions

Novel quinazoline nucleosides may be prepared readily and in good yield by the addition of electrophiles to the *o*-aminonitrile adduct of ribose. The ribose moiety decreases the nucleophilicity of the amino function of the *o*-aminonitrile, but this can be overcome by the generation of the anilide anion with NaH. β-Pyranosides were synthesized in the present study starting from the adduct (**1**) formed in high yield by the direct condensation of ribose and anthranilonitrile. The synthetic procedures used for the preparation of quinazoline ribopyranose nucleosides can also be applied to the ribofuranose series now that we devised a convenient synthesis of *N*-(2′,3′,5′-tri-*O*-acetyl-D-ribofuranosyl)anthranilonitrile (**3**) by phase-transfer catalysis.

Experimental Section

General Procedures. The following instruments were used for spectral measurements: Unicam SP-800A (UV), Perkin-Elmer 137 (IR), Varian T-60A or HA-100 (NMR), Hitachi Perkin-Elmer RMU-6E or Finnigan 4000 equipped for chemical ionization with methane or isobutane (mass spectra). Analytical TLC was performed on Eastman chromatogram sheets coated with silica gel, and preparative TLC was done on Fisher Scientific Co. TLC plates coated with a 1000-μm layer of silica gel GF. Column chromatography was performed on J. T. Baker Co. 60–200 mesh silica gel. Melting points were determined on a Mel-Temp in capillaries and are uncorrected. Elemental analyses were perfomred by Instranal Analyses, Rensselaer, N.Y.

***N*-(β-D-Ribopyranosyl)anthranilonitrile (1).** Ribose (11.3 g, 0.076 mol) was suspended in a solution of anthranilonitrile (8.9 g, 0.076 mol), 0.5 mL of acetic acid, and 150 mL of dry benzene, and the mixture was heated at reflux for 24 h while stirring vigorously. After 24 h no more water was collected in the Dean-Stark trap. The solution was cooled to room temperature, and the precipitate was filtered. The precipitate was heated to reflux in 70 mL of absolute ethanol with stirring for 30 min, cooled, and filtered to give 14.3 g of **1**. The combined benzene and ethanol filtrates were evaporated to 40 mL, and three additional crops of **1** were obtained to give a total yield of 16.65 g (88%). The product was purified by crystallization from ethanol: mp 194–195 °C; NMR (Me_2SO-d_6–D_2O) δ 4.83 (d, 1, J = 9.0 Hz, H-1′); IR (Nujol) 3370 (s, N–H, O–H), 2225 (s, C≡N), 1604 (s, C=C) cm^{-1}; UV max (CH_3OH) 320 nm (ε 4.36×10^3), 248 (1.02×10^4), 219 (2.26×10^4); mass spectrum, *m/e* 250 (molecular ion).

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.69; N, 11.19. Found: C, 57.72; H, 5.64; N, 11.20.

***N*-(2′,3′,4′-Tri-*O*-acetyl-D-ribopyranosyl)anthranilonitrile (2). (a) By Acetylation of 1.** Compound **1** (2.5 g, 0.01 mol) was added to a stirred mixture of 20 mL of acetic anhydride and 20 mL of pyridine which had been cooled to 0–5 °C. The mixture was stirred at 0–5 °C for 3 h and at room temperature for 7 h. The excess reagents were removed using a rotary evaporator, and 80 mL of ice cold water was added to the residue. The mixture was stirred vigorously for 30 min, and the white precipitate which formed was filtered, dried, and crystallized from ethanol to give 3.4 g (91%) of **2**: mp 140–141 °C; NMR (Me_2SO-d_6) δ 5.70 (m, 1, H-2′), 5.04 (d, 1, $J \simeq 1$ Hz, H-1′), 2.18 (s, 3, CH_3), 2.03 (s, 3, CH_3), 1.98 (s, 3, CH_3); IR (Nujol) 3350 (m, NH), 2225 (m, C≡N), 1755 (s, C=O), 1615 (s, C=C) cm^{-1}; UV max (methanol) 218 nm (ε 2.65×10^4), 247 (1.06×10^4), 316 (4.63×10^3); mass spectrum, *m/e* 376 (molecular ion).

Anal. Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.32; N, 7.44. Found: C, 57.08; H, 5.31; N, 7.31.

When the same reaction was allowed to proceed for 2 h at 0–5 °C, the triacetyl derivative **2** (2.1 g) was obtained on crystallization from absolute ethanol. The 2′,4′-*O*-diacetyl derivative of **1** was eluted with ethanol from a silica gel column as a gum: NMR ($CDCl_3$) δ 2.05 (s, 3, CH_3), 2.07 (s, 3, CH_3); mass spectrum, *m/e* 334 (molecular ion). It would be expected that the axial hydroxyl group at C-3′ in **1** would be the least reactive of the three hydroxyl groups,[27] and this was the basis for its structural assignment as the C-2′, C-4′ diacetate. This diacetyl derivative was converted to **2** by reaction with acetic anhydride and pyridine at room temperature for 7 h.

(b) By Condensation of Anthranilonitrile with 1-Chloro-2,3,4-tri-*O*-acetyl-D-ribopyranose. A mixture of tetrabutylammonium hydrogen sulfate (3.39 g, 0.01 mol), NaOH (0.8 g, 0.02 mol), and anthranilonitrile (1.18 g, 0.01 mol) in 15 mL of H_2O was stirred at room temperature for 1 h. Then 45 mL of CH_2Cl_2 was added followed by 15 mL of a CH_2Cl_2 solution of 1-chloro-2,3,4-tri-*O*-acetylribopyranose (freshly prepared from 3.18 g, 0.01 mol, of 1,2,3,4-tetra-*O*-acetylribopyranose).[5] The solution was stirred vigorously during the course of the addition of chlororibose and for an additional 10 h. When the reaction was monitored by TLC ($CHCl_3$–C_2H_5OH, 19:1), no hydrolysis of 1-chloro-2,3,4-tri-*O*-acetylribopyranose to a substance with the smaller R_f expected for 2,3,4-tri-*O*-acetylribopyranose was observed. The organic layer was separated, washed with 40 mL of water, dried, and concentrated to a gum which was purified by column chromatography on silica gel. Compound **2** was eluted with benzene and crystallized from ethanol (0.38 g, 10%). This product was shown to be identical with **2** prepared by the acetylation of **1** as shown by the identity of the melting point, mixture melting point, and IR, NMR, and mass spectra. The yield was not improved when triethylbenzylammonium chloride was used as the phase-transfer catalyst.

Preparation of *N*-(2′,3′,5′-Tri-*O*-acetylribofuranosyl)anthranilonitrile (3). A mixture of triethylbenzylammonium chloride (0.40 g, 0.0017 mol), NaOH (0.4 g, 0.01 mol), and anthranilonitrile (1.18 g, 0.01 mol) in 25 mL of water was stirred for 1 h, and then 15 mL of CCl_4 was added to it. The mixture was stirred vigorously for 2 h, and then 15 mL of a solution of 1-chloro-2,3,5-tri-*O*-acetyl-D-ribofuranose (freshly prepared from 3.18 g, 0.01 mol, of 1,2,3,5-tetra-*O*-acetylribofuranose[6] in CCl_4) was added to it. The mixture was stirred vigorously for 8 h at room temperature and for 20 h at 60 °C. When the reaction was monitored by TLC ($CHCl_3$–C_2H_5OH, 19:1), no hydrolysis of 1-chloro-2,3,5-tri-*O*-acetylribofuranose to a substance with the smaller R_f expected for 2,3,5-tri-*O*-acetylribofuranose was observed. The organic phase was separated, washed with 30 mL of water, dried, and concentrated to a yellow gum (2.9 g, 86%) which gave crystals of **3** from a 3:2 mixture of ether–petroleum ether: mp 79–80 °C; NMR ($CDCl_3$) δ 5.75 (d, 1, J = 2.5 Hz, H-1′), 2.21 (s, 3, CH_3), 2.07 (s, 3, CH_3), 2.05 (s, 3, CH_3); IR (Nujol) 3455 (m, N–H), 2215 (m, C≡N), 1745 (s, C=C) cm^{-1}; UV max (CH_3OH) 217 nm (ε 3.15×10^4), 247 (9.22×10^3), 318 (4.61×10^3); mass spectrum, *m/e* 376 (molecular ion).

Anal. Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.32; N, 7.44. Found: C, 57.28; H, 5.35; N, 7.27.

A 30–50% yield of **3** was obtained when tetrabutylammonium sulfate (0.01 mol) was used as the phase-transfer catalyst.

Reaction of *N*-(2′,3′,5′-Tri-*O*-acetyl-D-ribofuranosyl)anthranilonitrile with Methanolic Ammonia. Compound **3** (0.376 g, 0.001 mol) was added to 5 mL of cooled (0–5 °C) methanol saturated with ammonia. The mixture was stirred at 0–5 °C for 3 h and at room temperature for 3 h. The solvent was evaporated, and the residue crystallized from ethanol to give 0.266 g (89%) of **1**, mp 195–196 °C. The product was shown to be identical with a sample of **1** prepared by the direct condensation of ribose and anthranilonitrile by comparison of melting point, mixture melting point, and IR, NMR, and UV spectra.

Synthesis of the Tricarbamate 4. Compound **1** (1.25 g, 0.005 mol) and phenyl isocyanate (0.6 g, 0.005 mol) were dissolved in dry pyridine, and the mixture was stirred for 3 h. The reaction solution was added over a 30-min period to 100 mL of ice water, and the precipitated solid (1.53 g, 50%) was removed by filtration and washed thoroughly with water. The product was recrystallized from benzene: mp 209–210 °C; NMR (Me_2SO-d_6–D_2O) δ 5.70 (d, 1), 7.15 (m, 19, aromatic protons); IR (Nujol) 2230 (s, C≡N), 1688 (s, C=O) cm^{-1}; UV max (methanol) 219 nm (ϵ 4.8×10^4), 236 (4.4×10^4), 319 (7.0×10^3).

Anal. Calcd for $C_{33}H_{29}N_5O_7 \cdot H_2O$: C, 63.35; H, 4.99; N, 11.19. Found: C, 63.10; H, 4.63; N, 11.06.

Synthesis of 1-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribopyranosyl)-2-thio-3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline (5a). To a cooled (5–10 °C) solution of triacetate **2** (3.76 g, 0.01 mol) and phenyl isothiocyanate (1.36 g, 0.01 mol) in dimethyl sulfoxide was added NaH (0.48 g, 0.01 mol, a 50% dispersion in oil) over a period of 5 min. The reaction mixture was stirred at room temperature for 7 h and was added, over a 25-min period, with vigorous stirring to 200 mL of ice water. The yellow precipitate which formed was filtered, washed thoroughly with water, and dried to give 4.8 g (94%) of **5a.** Crystallization from a mixture of 7:3 ethanol–chloroform gave a yellow product: mp 234–234.5 °C; NMR ($CDCl_3$) δ 7.72 (d, 1, J = 10 Hz, H-1′), 5.71 (m, 1, H-2′), 2.18 (s, 3, CH_3), 2.02 (s, 3, CH_3), 1.82 (s, 3, CH_3); IR (Nujol) 3385 (w, NH), 1755 (s, C=O), 1635 (s, C=C) cm^{-1}; UV max (CH_3OH) 208 nm (ϵ 3.2×10^4), 219 (3.08×10^4), 242 (2.56×10^4), 287 (3.66×10^4); mass spectrum, m/e 511 (molecular ion).

Anal. Calcd for $C_{25}H_{25}N_3O_7S$: C, 58.69; H, 4.92; N, 8.21. Found: C, 58.61; H, 5.07; N, 8.14.

The UV spectrum of **5a** was virtually identical with that of 2-thio-3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline prepared by the condensation of anthranilonitrile and phenyl isothiocyanate:[16] UV max (CH_3OH) 207 nm (ϵ 4.22×10^4), 222 (2.23×10^4), 240 (1.90×10^4), 291 (2.74×10^4).

Acid Hydrolysis of 5a to 2-Thio-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (8a). A suspension of compound **5a** (1.25 g, 0.0025 mol) in 60 mL of 10% HCl was heated to reflux for 1 h. On cooling, light brown crystals formed which were filtered and washed with water to give 0.23 g (49%). Recrystallization from ethanol gave pure **8a,** mp 304–306 °C (lit.[16] mp 305–306 °C). The product had IR and mass spectra which were identical with those of an authentic sample.[16]

Synthesis of 1-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribopyranosyl)-2-thio-3-methyl-4-imino-1,2,3,4-tetrahydroquinazoline (5b). The procedure used was identical with that for the synthesis of **5a** with the exception that the reaction was allowed to proceed for 5 h at 10 °C and for 19 h at room temperature. The crude product was boiled with petroleum ether to remove some oil used to disperse the NaH to yield 3.3 g (73%) of an amorphous powder, mp 89–92 °C (contracts at 75 °C). Efforts to purify this product by chromatography or crystallization were unsuccessful: NMR ($CDCl_3$) δ 1.70 (s, 3, CH_3), 2.01 (s, 3, CH_3), 2.20 (s, 3, CH_3), 3.91 (s, 3, NCH_3); IR (Nujol) 3350 (m, NH), 1750 (s, C=O), 1670 (w), 1610 (w) cm^{-1}; UV max (CH_3OH) 208 nm (ϵ 1.16×10^4), 220 (1.18×10^4), 240 (1.28×10^4), 281 (1.9×10^4); mass spectrum, m/e 449 (molecular ion).

Acid hydrolysis of **5b,** performed under the same conditions used for the hydrolysis of **5a,** yielded 2-thio-3-methyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**8b**), mp 259–260 °C, which was shown to be identical with an authentic sample[22] by comparison of IR, NMR, and mass spectra.

2-Thio-3-methyl-4-imino-1,2,3,4-tetrahydroquinazoline (7b). A mixture of anthranilonitrile (1.18 g, 0.01 mol) and methyl isothiocyanate (0.73 g, 0.01 mol) was heated at 110 °C for 4 h in a sealed tube. After cooling, the yellow solid which separated was filtered and washed with 25 mL of ether. Crystallization of this solid from methanol gave the title compound: 1.54 g (80%); mp 289–291 °C; NMR (Me_2SO-d_6) δ 3.80 (s, 3, NCH_3), 7.34 (m, 4, aromatic + NH), 8.05 (m, 1, aromatic); IR (Nujol) 3195 (m, NH), 1625 (s, C=C), 1575 (m), 1525 (s) cm^{-1}; UV (methanol) 206 nm (ϵ 1.1×10^4), 221 (1.14×10^4), 238 (1.2×10^4), 290 (1.85×10^4); mass spectrum, m/e 191 (molecular ion).

Anal. Calcd for $C_9H_9N_3S$: C, 56.52; H, 4.74; N, 21.97. Found: C, 56.53; H, 4.76; N, 22.06.

Acid hydrolysis of **7b** using 10% hydrochloric acid yielded a light yellow solid (80%) which was found to be identical (melting point, mixture melting point, and IR) with **8b.**[22]

Reaction of 1-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribopyranosyl)-2-thio-3-methyl-4-imino-1,2,3,4-tetrahydroquinazoline with Methanolic Ammonia. Compound **5b** (4.49 g, 0.01 mol) was added to 20 mL of cooled (0–5 °C) methanol saturated with ammonia. The mixture was stirred at 0–5 °C for 3 h and then at room temperature for 12 h. A light yellow precipitate formed which was filtered and dried to give 1.05 g of **15.** The filtrate was concentrated to dryness and washed with ether, and the residue was boiled with 30 mL of absolute ethanol. The insoluble material was filtered and the filtrate cooled to give 0.27 g of product. The total yield of **15** was 1.32 g (40%). Recrystallization from methanol gave light yellow crystals: mp 200–201 °C; NMR (Me_2SO-d_6–D_2O) δ 3.76 (s, 3, NCH_3), 6.94 (d, 1, J = 10 Hz, H-1′); IR (Nujol) 3500 (w), 3350 (w), 3150 (w), 1620 (s) cm^{-1}; UV max (CH_3OH) 206 nm (ϵ 1.39×10^4), 222 (1.37×10^4), 241 (1.48×10^4), 281 (2.17×10^4); mass spectrum (chemical ionization, CH_4), m/e 323 (molecular ion).

Anal. Calcd for $C_{14}H_{17}N_3O_4S$: C, 52.00; H, 5.30; N, 12.99. Found: C, 51.68; H, 5.50; N, 12.82.

Acid hydrolysis of **15** gave a 48% yield of **8b,** mp 256–258 °C (lit.[25] mp 260–261 °C). The identity of **8b** was established by comparison of IR and mass spectra with an authentic sample of **8b.**[22]

Reaction of 1-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribopyranosyl)-2-thio-3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline with Ethanolic Ammonia. Compound **5a** (1.25 g, 0.00244 mol) was added to 25 mL of absolute ethanol saturated with NH_3 and cooled to 0–5 °C, and the mixture was stirred for 5 h. The solution was then allowed to warm to room temperature, and the mixture was stirred for 6 days. The insoluble product was filtered, washed with ethanol, and dried to give 0.308 g (40%) of **10,** mp 193–196 °C. Recrystallization from water gave a product of mp 216–217 °C: NMR (Me_2SO-d_6–D_2O) δ 7.46 (d, 1, J = 9.5 Hz, H-1′), 4.20 (m, 1, H-2′); IR (Nujol) 3450 (broad, N–H, O–H), 1655 (s), 1620 (s), 1600 (w) cm^{-1}; UV max (CH_3OH) 222 nm (ϵ 1.69×10^4), 234 (1.44×10^4), 289 (3.46×10^4); mass spectrum (chemical ionization, CH_4), m/e 309 (molecular ion).

Anal. Calcd for $C_{13}H_{15}N_3O_4S \cdot H_2O$: C, 47.69; H, 5.23; N, 12.83. Found: C, 47.95; H, 4.78; N, 13.08.

The ethanol filtrate was evaporated to dryness, the residue was disolved in methanol, and the solution was cooled at 0 °C for 3 days. A dark yellow precipitate formed which gave 0.26 g of a yellow powder after filtering and drying. This was shown by TLC to be a 9:1 mixture of **11** and **10,** respectively. Pure **11** was obtained by repeated crystallization from methanol: mp 142.5–143 °C; NMR (Me_2SO-d_6–D_2O) δ 6.47 (d, 1, J = 10 Hz, H-1′); IR (Nujol) 3465 (w, OH), 3350 (w, OH), 3175 (w, NH), 1675 (s), 1605 (s) cm^{-1}; UV max (CH_3OH) 229 nm (ϵ 1.98×10^4), 249 (2.16×10^4), 327 (5.86×10^4), and inflections at 215 nm (1.57×10^4) and 277 (1.59×10^4); mass spectrum (chemical ionization, CH_4), m/e 368 (molecular ion).

Anal. Calcd for $C_{19}H_{20}N_4O_4 \cdot H_2O$: C, 59.05; H, 5.73; N, 14.49. Found: C, 58.87; H, 5.79; N, 14.29.

Hydrolysis of **10** (0.1 g) with 50 mL of 10% HCl for 1 h at 100 °C gave 25 mg (40%) of **13.** Recrystallization from ethanol yielded a product which was identical (melting point, mixture melting point, and IR, and mass spectra) with an authentic sample of **13.**[16]

Acid hydrolysis of **11** by the same procedure gave 2-anilino-4-oxo-3,4-dihydroquinazoline (**14**), which was purified by crystallization from methanol, mp 260–261 °C (lit.[16,23] mp 260–261 °C). An authentic sample of **14** was prepared by the literature procedure, and the two samples were shown to be identical by comparison of IR, UV, and mass spectra.

Preparation of 1-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribopyranosyl)-2-thio-4-acetamido-1,2-dihydroquinazoline (12). Compound **10** (0.2 g, 0.0064 mol) was added to 10 mL of a 1:1 mixture of pyridine and acetic anhydride cooled to 0–5 °C, and the mixture was stirred at this temperature for 5 h and then at room temperature for 5 h. The reagents were removed under aspirator vacuum, the residue was taken up in 25 mL of water, and the mixture was stirred. The yellow precipitate which formed was filtered, washed with water, and dried to give 0.22 g (72%), mp 105–110 °C. The product was purified by recrystallization from ethanol. Some decomposition was observed as shown by the formation of a dark precipitate along with the crystals. The crystals were separated mechanically from the precipitate: mp

155.5–157 °C; NMR ($CDCl_3$) δ 1.83 (s, 3, CH_3), 2.06 (s, 3, CH_3), 2.25 (s, 3, CH_3), 2.36 (s, 3, CH_3); IR (Nujol) 3410 (m, NH), 1755 (s, C=O), 1725 (s, C=O), 1630 (s, C=O) cm^{-1}; UV max (CH_3OH) 212 nm (ε 1.48×10^4), 234 (9.31×10^3), 287 (3.29×10^4), and inflection at 312 nm (1.15×10^4); mass spectrum, *m/e* 477 (molecular ion).

Anal. Calcd for $C_{21}H_{23}N_3O_8S$: C, 52.82; H, 4.85; N, 8.8. Found: C, 52.56; H, 4.75; N, 8.2.

Hydrolysis of **12** with 10% HCl at 100 °C gave **13**.

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Registry No.—**1**, 68225-78-5; **2**, 68225-79-6; **3**, 68225-80-9; **4**, 68225-81-0; **5a**, 68225-82-1; **5b**, 68225-83-2; **7b**, 68225-84-3; **10**, 68225-85-4; **11**, 68225-86-5; **12**, 68225-87-6; **15**, 68225-88-7; ribose, 50-69-1; anthranilonitrile, 1885-29-6; 1-chloro-2,3,4-tri-*O*-acetylribopyranose, 57236-99-4; 1-chloro-2,3,5-tri-*O*-acetyl-D-ribofuranose, 40554-98-1; phenyl isocyanate, 103-71-9; methyl isothiocyanate, 556-61-6.

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Novel Synthesis of 2-Selenienylalanine

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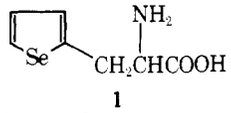
A novel synthesis of 2-selenienylalanine [2-amino-3-(selenophen-2′-yl)propanoic acid] was designed to permit the insertion of selenium late in the synthetic pathway so that a subsequent synthesis using selenium-75 would maximize the radiochemical yield while minimizing radiation exposure of the chemist. The coupling of *N*-acetylpropargylglycine ethyl ester with trimethylsilylacetylene in the presence of Hay's catalyst gave ethyl *N*-acetyl-2-amino-7-(trimethylsilyl)-4,6-heptadiynoate in 57% yield. This product was reacted with sodium hydrogen selenide which was prepared from selenium metal and sodium borohydride, and 2-selenienylalanine was generated in 33% yield.

As part of a current project investigating new radiopharmaceuticals for organ imaging, we desired to prepare 2-selenienylalanine [2-amino-3-(selenophen-2′-yl)propanoic acid], **1**, by a synthetic pathway which would allow insertion



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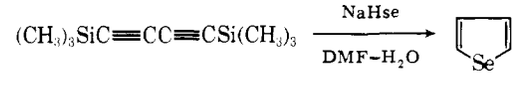
of radioactive selenium as late in the synthesis as possible. Thus, the radiochemical yield could be maximized while minimizing radiation exposure of the chemist. We expect that this compound will localize in the pancreas as do other aromatic amino acids.[2] The γ radiation of selenium-75 would then permit external visualization of the organ with a γ-scintillation camera, and a pathological lesion would be detected as a negative or "cold area" within the organ. This amino acid can be synthesized by the well-established method used to make thienylalanine,[3] beginning with selenophene, but the selenium must then be incorporated at the first step of a multistep synthesis.

Since the reaction of 1,4-bis(trimethylsilyl)butadiyne with sodium hydrogen selenide generated from selenium metal gives selenophene **2**,[4] it was felt that the analogous reaction



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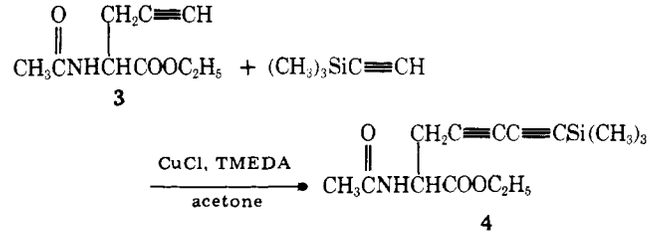
of a suitably substituted butadiyne should give a substituted selenophene. Accordingly, the diyne **4** was prepared, as shown in the following scheme, from the known *N*-acetylpropargylglycine ethyl ester, **3**.[5] The coupling of **3** with trimethylsilylacetylene in the presence of Hay's catalyst[6,7] gave **4** in 55%



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