Synthesis of 5-Ethynylorotic Acid (1a)

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Condensation of 2,4-dimethoxy-5-iodo-6-carbomethoxypyrimidine (**10**) with copper (I) 3-tetrahydropyranyloxyprop-1-ynide (**4**) afforded 2,4-dimethoxy-5-(3′-tetrahydropyranyloxyprop-1′-yn)-6-carbomethoxypyrimidine (**11**), which was hydrolyzed to produce 2,4-dimethoxy-5-(3′-hydroxyprop-1′-yn)-6-carbomethoxypyrimidine (**12**). Oxidation of **12** with dimethyl sulfoxide-oxalyl chloride reagent gave the acetylenic aldehyde (**13**), which on treatment with sodium methoxide in dry tetrahydrofuran yielded 2,4-dimethoxy-5-ethynyl-6-carbomethoxypyrimidine (**14**). The trimethylsilyl derivative (**15**) was deprotected by sequential treatment with iodotrimethylsilane and aqueous sodium hydroxide, leading to the formation of 5-ethynylorotic acid (**1**).

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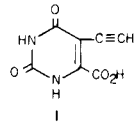
In continuation of our interest in derivatives of uracil as anticancer agents (2-4), we have recently devoted our attention to derivatives of orotic acid (uracil-6-carboxylic acid), a key intermediate in the *de novo* synthesis of pyrimidine ribo-nucleotides and deoxyribonucleotides (5-8). We desired to synthesize a compound that might serve as a metabolic antagonist of this substance. In view of the pronounced inhibitory effects of 5-fluoroorotic acid and 5-azaorotic acid on the biosynthesis of pyrimidines in nucleic acids (9,10), plus the fact that the various drugs incorporating the acetylenic moiety can function as specific enzyme inhibitors (11-13), we devised 5-ethynylorotic acid as a possible inhibitor of dihydroorotate dehydrogennase. In this paper, we report the chemical synthesis of 5-ethynylorotic acid (**1**).



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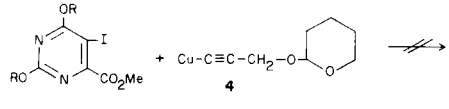
Kwatra and co-workers have reported (14) the use of copper(I) 3-tetrahydropyranyloxyprop-1-ynide (**4**) (15) to synthesize aryl acetylenic compounds. We first tried unsuccessfully to condense methyl 5-iodoorotate (**2**) with this reagent. The coupling reaction between the di-*O*-silylated methyl 5-iodoorotate (**3**) and the copper(I) acetylenide (**4**) also did not work, which we attribute to the steric hindrance of the C-4 trimethylsilyloxy group on the C-5 position of the pyrimidine ring.



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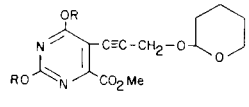
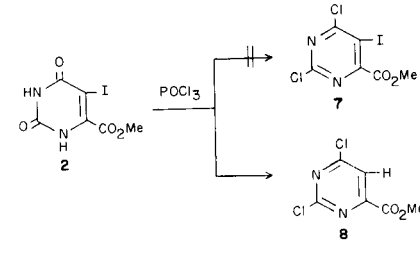
2, R = H
3, R = $SiMe_3$



5, R = H
6, R = $SiMe_3$

We then chose 2,4-dimethoxy-5-iodo-6-carbomethoxypyimidine (**10**) as the starting material for the synthesis of the target compound, **1**. Preparation of **10** was initially attempted by intereaction of methyl 5-iodoorotate (**2**) with phosphorus oxychloride in the presence of dimethylaniline with the intent of reacting the resulting dichloride, **7**, with sodium methoxide (Scheme 1). This reaction produced a dichloride, but its nmr and mass spectral analyses showed that it had lost the iodine at C-5. In the nmr spectrum (deuteriochloroform-TMS) of the dichloride the singlet resonance at δ 7.95 was diagnostic of the presence of H-5. Further identification of this compound was done by comparing its mp 54-56° with the mp (55-56°) as reported by Daves, *et al.* (16). Thus, this dichloride was identified as 2,4-dichloro-6-carbomethoxypyrimidine (**8**). Compound **8** on treatment with sodium methoxide in boiling methanol produced 2,4-dimethoxy-6-carbomethoxy-pyrimidine (**9**) which had a mp 108-109° identical to that reported in the

Scheme I



literature (17). Gershon (17) had previously described the preparation of compound **9** by treatment of orotic acid with phosphorus oxychloride followed by reaction with sodium methoxide. Because of the low cost of orotic acid, we adopted Gershon's procedure for the preparation of compound **9**.

Iodination of compound **9** with *N*-iodosuccinimide (Scheme II) in refluxing glacial acetic acid and acetic anhydride (5:1) yielded 2,4-dimethoxy-5-iodo-6-carbomethoxypyrimidine (**10**) in 30% yield. However, when the

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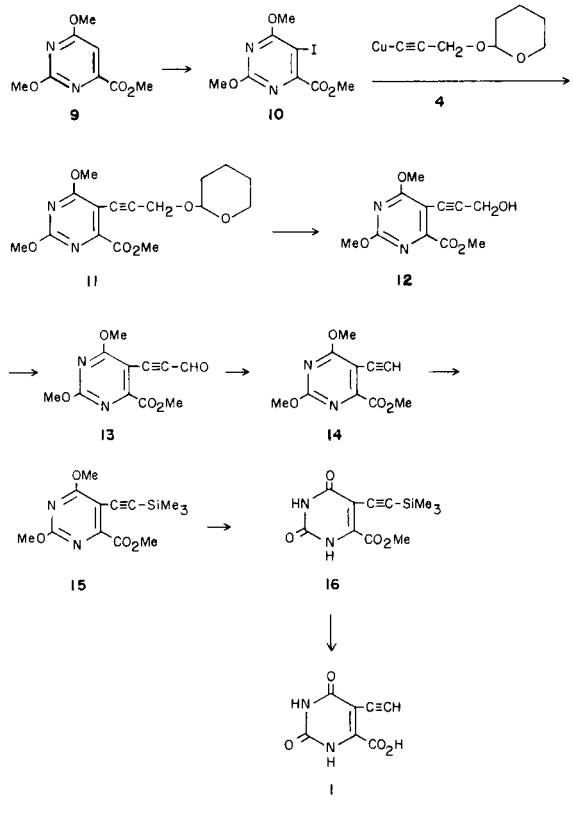
iodination was performed in a mixture of trifluoroacetic acid and trifluoroacetic anhydride, the yield increased to 95-97%. The substitution at C-5 of compound **9** was readily confirmed by the disappearance of the singlet due to H-5 at δ 7.05 in the nmr spectrum of compound **10**. Compound **10** also displayed a molecular ion at m/e 324 consistent with its structural formula, which was further confirmed by its elemental analysis.

Condensation of compound **10** with copper(I) acetylenide (**4**) in dry pyridine, under argon at reflux temperature resulted in 80-85% yield of 2,4-dimethoxy-5-(3′-tetrahydropyranyloxyprop-1′-yn)-6-carbomethoxypyrimidine (**11**), which was characterized by its elemental analysis and spectroscopic data. Although infrared spectrum showed a very weak C≡C triple bond absorption at 2100 cm^{-1}, the nmr spectrum, in addition to showing the resonances due to methoxy groups, displayed resonances of the protons of the side chain attached to the C≡C triple bond. In particular, the low field distinct singlet at δ 4.5 integrating for two hydrogens was readily assigned to the methylene hydrogens between C≡C triple bond and the oxygen atom (C≡C-CH_2-O-). The broad resonance at δ 4.9, integrating for one hydrogen, was attributed to -O-CH-O- of the tetrahydropyranyloxy ring.

Scheme II

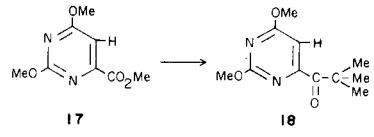


Acidic hydrolysis of **11** with *p*-toluenesulfonic acid in refluxing methanol for ½ hour gave the corresponding acetylenic-alcohol (**12**) in almost quantitative yeild. The disappearance of the broad resonance at δ 4.9 and the multiplet resonance at δ 1.65 in compound **12** was indicative of the removal of the tetrahydropyranyloxy group.

The transformation of compound **12** into the acetylenic-aldehyde (**13**) was accomplished in 70-84% yield by reaction with a reagent prepared by the treatment of oxalyl chloride with dimethyl sulfoxide in dichloromethane at -78°, followed by reaction with triethylamine (18). The mass spectrum of **13** showed a correct molecular ion and the nmr spectrum displayed a singlet at δ 9.5, integrating for one hydrogen, which is diagnostic of the presence of an aldehydic proton.

Treatment of compound **13** with dry sodium methoxide in dry tetrahydrofuran, under argon, afforded 2,4-dimethoxy-5-ethynyl-6-carbomethoxypyrimidine (**14**), in 70% yield. The presence of the ethynyl proton was readily recognized in the nmr spectra of compound **14**, which exhibited a singlet at δ 3.55. The infrared spectrum of compound **14** showed a weak, but sharp, absorption at 2095 cm^{-1}, characteristic of a C≡C triple bond. Except for the acetylenic-aldehyde, **13**, the infrared spectra of all these compounds displayed rather a weak absorption due to the C≡C triple bond.

A trialkylsilyl group (19-21) was shown to provide a satisfactory means of protection of terminal acetylenic moiety. Thus, silylation of compound **14** was conducted by reacting its tetrahydrofuran solution at -78° with *t*-butyllithium, under argon, followed by addition of chlorotrimethylsilane, to afford 2,4-dimethoxy-5-(trimethylsilylacetylene)-6-carbomethoxypyrimidine (**15**) in low yield (25%). Unfortunately, the use of other bases, such as lithium diisopropylamide (22) and lithium bis(trimethylsilyl) amide (23) did not improve the yield. In each case a mixture of several products was obtained. The desired product, compound **15**, had an R*f* slightly higher than the starting material, while all other products moved to the solvent front. Because of the very similar R*f* values of the faster moving products, their resolution could not be effected. However, we believe that one of the faster moving products, probably the major product, was the one formed by the concomitant nucleophilic attack of the base on the ester group. For example, when 2,4-dimethoxy-6-carbomethoxypyrimidine (**17**) was reacted with *t*-butyllithium under the same reaction conditions, followed by the addition of chlorotrimethylsilane, the sole product obtained was the tertiary butyl ketone (**18**) which was identified by its nmr and mass spectra.



Selective de-*O*-methylation of compound **15** was accomplished according to the procedure of Jung, *et al.* (24). A carbon tetrachloride solution of **15** in a sealed nmr tube was reacted with iodotrimethylsilane at 52° for four days. The progress of the reaction was monitored by nmr spectroscopy. Disappearance of the singlets due to methoxy groups at δ 4.05 in the nmr spectrum and the appearance of a methyl iodide singlet around δ 2.0 was indicative of the completion of the reaction. The addition of water or methanol to the residue left after removing the solvent gave the deblocked methyl ester, **16**, in 52% yield.

Treatment of a methanol solution of compound **16** with aqueous sodium hydroxide for 2 hours at room temperature after neutralization with 0.1*N* hydrochloric acid to *p*H 5.5, gave the desired 5-ethynylorotic acid (**1**) in 40% yield, which was characterized by its spectroscopic data and elemental analysis.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Mass spectra were recorded by Dr. H. Boettger of the Jet Propulsion Laboratory, Pasadena, CA on an MS-9 instrument at 70 eV and a source temperature of 150-200°. Nuclear magnetic resonance spectra were determined on a Varian EM-390 90 MHz spectrometer in the solvents indicated, using tetramethylsilane as an internal indictor. Unless otherwise mentioned, ir spectra were recorded as potassium bromide plates on a Beckman IR-10. The uv spectra were performed on a Beckman Model-25 spectrophotometer. Copper(I) 3-tetrahydro-pyranyloxyprop-1-ynide (**4**) was prepared according to the method of Owsley and Castro (25). The elemental analyses of all new compounds were performed by Spang Microanalytical Laboratory, Ann Arbor, MI. Unless otherwise mentioned, tlc was performed on Eastman chromagram sheets (6060 silica gel with fluorescent indicator) in solvents as indicated. Tlc's of reaction mixtures in pyridine or acetic acid solution were taken after completely removing the solvent by co-evaporation with toluene.

2,4-Dimethoxy-5-iodo-6-carbomethoxypyrimidine (**10**).

A mixture of compound **9** (17.38 g, 87.8 mmoles) was refluxed for 20 minutes with trifluoroacetic acid (150 ml) and trifluoroacetic anhydride (30 ml). *N*-Iodosuccinimide (39.5 g, 175 mmoles) was added and the reaction mixture was refluxed for 8 hours when tlc (chloroform-ethyl acetate, 15:1) showed that the starting material had disappeared, giving rise to a faster moving product. After allowing the reaction mixture to cool to room temparature, the solvent was removed *in vacuo*. The residue left was dissolved in chloroform (600 ml), and successively washed with water (50 ml), saturated sodium bicarbonate (2 x 40 ml), saturated sodium thiosulfate (2 x 40 ml) and water (2 x 40 ml). The chloroform solution was dried over magnesium sulfate and concentrated to dryness to give 27.53 g (97%) of compound **10**, mp 110-112°. For most purposes compound **10** was used without any further purification. An analytical sample prepared by crystallizing **10** from hot methanol showed mp 112-113°; nmr (deuteriochloroform): δ 3.95 (s, 3H, $COOCH_3$), 4.0 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3); ms: m/e 324 (M^+), 309 ($M-CH_3$); ir: ν max 1715 cm^{-1} ($COOCH_3$); uv (methanol): λ max 283 nm (ε 4,080), 231 nm (ε 7,800).

Anal. Calcd. for $C_8H_9IN_2O_4$: C, 29.62; H, 2.78; N, 8.64. Found: C, 29.74; H, 2.79; N, 8.65.

2,4-Dimethoxy-5-(3'-tetrahydropyranyloxyprop-1'-yn)-6-carbomethoxypyrimidine (**11**).

A suspension of **10** (3.24 g, 10 mmoles) and copper(I) 3-tetrahydropyranyloxyprop-1-ynide (**4**) (2.42 g, 12 mmoles) in dry pyridine (50 ml) under argon was refluxed for 2 hours. Tlc (chloroform-ethyl acetate, 15:1) showed that the starting material had disappeared and that a slower moving product was formed. The reaction mixture was cooled to room temperature, and most of the pyridine was evaporated under vacuum. The resulting dark residue was poured into ice-water (100 ml) and extracted with chloroform (3 x 150 ml). The combined chloroform solution was washed with cold 1*N* hydrochloric acid (2 x 50 ml), water, saturated sodium bicarbonate and again with water. After drying (magnesium sulfate), the chloroform solution was concentrated to dryness to give a greenish mobile syrup. Elution on a column of silica gel (300 g) with chloroform-ethyl acetate (50:1) afforded **11** (2.85 g, 85%); mp 80-81°; nmr (deuteriochloroform): δ 1.65 (m, 6H, 3 x CH_2), 3.55 (t, 2H, OCH_2 of tetrahydropyran ring), 3.95 (s, 3H, $COOCH_3$), 4.05 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 4.5 (s, 2H, $C\equiv C\text{-}CH_2\text{-}O$), 4.9 (broad, 1H,-O-CHO-); ms: m/e 336 (M^+), 321 ($M-CH_3$), 278 ($M-COOCH_2$), 235 ($M-C_4H_9O_2$); ir: 2100 ($C\equiv C$), 1728 cm^{-1} ($COOCH_3$); uv (methanol); λ 304 nm (ε 5,100), 244 nm (ε 11,100).

Anal. Calcd. for $C_{16}H_{22}N_2O_6$: C, 57.14; H, 5.95; N, 8.33. Found: C, 57.20; H, 6.03; N, 8.35.

2,4-Dimethoxy-5-(3'-hydroxyprop-1'-yn)-6-carbomethoxypyrimidine (**12**).

A mixture of **11** (6.7 g, 19.9 mmoles) and *p*-toluenesulfonic acid monohydrate (0.377 g, 1.988 mmoles) in methanol (80 ml) was refluxed for 1 hour when tlc (chloroform-ethyl acetate, 8:1) showed completion of the reaction. The reaction mixture was cooled to room temperature and treated with anhydrous potassium carbonate (1.38 g, 10 mmoles). After stirring for 5 minutes, the reaction mixture was filtered and the filtrate was concentrated to dryness. The residue was dissolved in chloroform (300 ml) and washed with water (3 x 20 ml). After drying over anhydrous magnesium sulfate, the chloroform solution was concentrated to dryness to yield **12** in almost quantitative yield, and was used as such for most purposes. An analytical sample was prepared by crystallizing a small amount from dichloromethane-petroleum ether, mp 136-137°; nmr (deuteriochloroform): δ 3.95 (s, 3H, $COOCH_3$), 4.05 (s, 3H, OCH_3), 4.1 (s, 3H, OCH_3), 4.5 (s, 2H, $C\equiv C\text{-}CH_2\text{-}O$); ms: m/e 252 ($M^+$), 237 ($M-CH_3$), 194 ($M-COOCH_2$); ir: 3450 cm^{-1} (OH), 2100 cm^{-1} ($C\equiv C$), 1720 cm^{-1} ($COOCH_3$); uv (methanol): λ max 295 nm (ε 6,050), 245 nm (ε, 11,000).

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.76; N, 11.11. Found: C, 62.32; H, 4.77; N, 11.02.

2,4-Dimethoxy-5-(2'-formyl-1'-ethynyl)-6-carbomethoxypyrimidine (**13**).

To a cooled (-78°) solution of oxalyl chloride (4.77 ml, 54.68 mmoles) in dichloromethane (30 ml) under argon was added dropwise with stirring a dichloromethane solution of dimethyl sulfoxide (7.75 ml, 109.35 mmoles). Ten minutes after the addition was over, the resulting solution was slowly treated with a solution of **12** (10.6 g, 42.06 mmoles) in dichloromethane (170 ml) and dimethyl sulfoxide (10 ml). After stirring for ½ hour at -78°, triethylamine (36 ml) was added and the reaction mixture was slowly allowed to warm to room temperature. The reaction mixture was diluted with dichloromethane (300 ml) and washed consecutively with water (2 x 50 ml), saturated sodium chloride (2 x 80 ml) and water (2 x 30 ml). The dichloromethane solution was dried over anhydrous magnesium sulfate and concentrated in a rotary evaporator to a pinkish residue, which was eluted on a silica gel column with chloroform-ethyl acetate (40:1). Crystallization from dichloromethane-petroleum ether gave 7.5 g (71%) of **13**, m.p. 156-158; nmr (deuteriochloroform): δ 4.0 (s, 3H, $COOCH_3$), 4.09 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 9.5 (s, 1H, CHO); ms: m/e 250 (M^+), 235 ($M-CH_3$); ir: 2195 cm^{-1} ($C\equiv C$), 1728 cm^{-1} ($COOCH_3$), 1640 cm^{-1} ($C\equiv C\text{-}CHO$); uv (methanol): λ max 295 nm (ε 6,100), 245 nm (ε, 11,800).

Anal. Calcd. for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.00; N, 11.2. Found: C, 52.68; H, 3.98; N, 11.2.

2,4-Dimethoxy-5-ethynyl-6-carbomethoxypyrimidine (**14**).

To a solution of **13** (2.60 g., 10 mmoles) in dry tetrahydrofuran (100 ml) was added dry sodium methoxide (0.648 g, 12 mmoles) and stirred under argon at room temperature for 1 hour. Tlc (chloroform-ethyl acetate, 10:1) showed that all of the starting material had been consumed and that a faster moving product had appeared. The reaction mixture was concentrated to dryness. The residue was taken up in chloroform (250 ml)

and washed with saturated ammonium chloride (2 x 20 ml) and then with water 2 x 25 ml). The chloroform solution was dried over anhydrous magnesium sulfate and concentrated to dryness in a rotary evaporator. The resulting reddish-brown residue was chromatographed on a silica gel column with chloroform-ethyl acetate (50:1). Crystallization from carbon tetrachloride afforded 1.54 g (70%) of **14**, mp 135-137°; nmr (deuteriochloroform): δ 3.55 (s, 1H, C≡CH), 3.95 (s, 3H, $COOCH_3$), 4.05 (s, 3H, OCH_3), 4.1 (s, 3H, OCH_3), 4.1 (s, 3H, OCH_3); ms: m/e 222 (M^+); ir: 3225 (C≡C-H), 2095 (C≡C), 1720 cm^{-1} ($COOCH_3$); uv (methanol): λ max 290 nm (ε 5,900), 242 nm (ε 11,900).

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.50; N, 12.61. Found: C, 53.87; H, 4.41; N, 12.47.

2,4-Dimethoxy-5-(trimethylsilylethynyl)-6-carbomethoxypyrimidine (**15**).

To a cooled (-78°) solution of **14** (0.44 g, 2 mmoles) in dry tetrahydrofuran (50 ml) under argon, was added *t*-butyllithium (1.1 ml of 2*M* solution, 2.2 mmoles) and was stirred for 3-4 minutes. Trimethylsilyl chloride was added and the reaction mixture was allowed to warm to room temperature. Tlc (chloroform ethyl acetate, 15:1) showed completion of the reaction, with one spot moving slightly faster than the starting material and several other spots moving to the solvent front. After diluting with ether (200 ml), the reaction mixture was washed with water (3 x 20 ml). After drying over anhydrous magnesium sulfate, the ether solution was concentrated to dryness. The residue was eluted on a silica gel column with chloroform-ethyl acetate (50:1) to give **15** (0.147 g, 25%), mp 57-58°; nmr (deuteriochloroform): δ 0.22 [s, 9H, $Si-(CH_3)_3$], 3.9 (s, 3H, $COOCH_3$), 4.0 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3); ms: m/e 279 ($M-CH_3$), 249 ($M-CH_3-OCH_2$); ir (chloroform): 2150 cm^{-1} (C≡C), 1730 cm^{-1} ($COOCH_3$); uv (methanol): λ max 299 nm (ε 4,300), 250 nm (ε, 8,200).

Anal. Calcd. for $C_{13}H_{18}N_2O_4Si$: C, 53.06; H, 6.14. Found: C, 52.99; H, 6.11.

Following the above procedure and under identical conditions 2,4-dimethoxy-6-carbomethoxypyrimidine (**17** (0.198 g, 1 mmole) was reacted with *t*-butyllithium (0.55 ml of 2 M solution, 1.1 mmoles) and chlorotrimethylsilane (1.5 mmoles). After working up the reaction as described above for compound **15**, 196 mg (87.5%) of 2,4-dimethoxy-6-*t*-butylacylpyrimidine (**18**), was obtained, mp 59-60°; nmr (deuteriochloroform); δ 1.4 [s, 9H, $C(CH_3)_3$], 4.0 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 6.8 (s, 1H, H-5); ms: m/e 224 (M^+), 209 ($M-CH_3$); uv (methanol): λ max 268 nm (ε 3,200), 284 nm (ε 3,000).

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 68.92; H, 7.4; N, 12.5. Found: C, 58.88; H, 7.31; N, 12.48.

Methyl 5-(Trimethylsilylethynyl)orotate (**16**).

To a solution of **15** (0.078 g, 0.265 mmoles) in carbon tetrachloride (0.7 ml) in a nmr tube was added iodotrimethylsilane (0.136 ml, 0.955 mmole). The nmr tube was tightly sealed and heated at 52° for 4 days or until the nmr analysis indicated the disappearance of *O*-methoxy resonances. The reaction contents were then poured into a small round bottom flask, and the solvent was evaporated under a stream of argon. Any residual iodotrimethylsilane was removed on a vacuum pump. The resulting residue was treated with methanol (0.5 ml). The crystalline precipitate was filtered and washed with a small amount of methanol and ether to give **16** (0.037 g, 52%), mp 170-173 dec.; nmr (DMSO-d_6): δ 0.18 [s, 9H, $Si(CH_3)_3$], 3.8 (s, 3H, $COOCH_3$), 11.5 (broad, 2H, NH's); ms: m/e 251 ($M-CH_3$), 193 ($M-CH_3-COOCH_2$); ir: 2090 (C≡C), 1715 cm^{-1} ($COOCH_3$); uv (methanol): λ max 311 nm (ε 5,000), 232 nm (ε 9,000).

Anal. Calcd. for $C_{11}H_{14}N_2O_4Si$: C, 49.73; H, 5.26; N, 10.52. Found: C, 49.63; H, 5.02; N, 10.19.

5-Ethynylorotic Acid (**1**).

A solution of **16** (0.053 g, 0.2 mmole) in methanol (1 ml) was treated with aqueous sodium hydroxide (40 mg, 1 mmole) dissolved in 1 ml of water and the reaction mixture stirred at room temperature for 2 hours. Tlc on silica gel (chloroform-methanol, 8:1) showed that the starting material had disappeared. Tlc on cellulose (2-propanol-ammonium hydroxide-water, 7:1:3) showed a spot with $Rf = 0.38$. The reaction mixture was concentrated to dryness. The residue was dissolved in water and acidified to *p*H 5.5 by adding 0.1*N* hydrochloric acid. This solution was applied on the top of a DEAE-cullulose column (ammonium formate form) and eluted with water to remove inorganic salts. The product was then eluted with a gradient of ammonium formate (20 mmoles to 200 mmoles) to afford, after lyophilization, **1**, as its ammonium salt (0.016 g, 40%); nmr (deuterium oxide-SDSS): δ 3.75 (s, 1H, C≡CH); ms: m/e 180 (M^+); ir: 2110 (C≡C), 3228 cm^{-1} (C≡C-H); uv (water): λ max 288 nm (ε, 6,100), 224 nm (ε 13,200).

Anal. Calcd. for $C_7H_7N_3O_4$: C, 42.63; H, 3.55. Found: C, 42.28; H, 3.21.

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