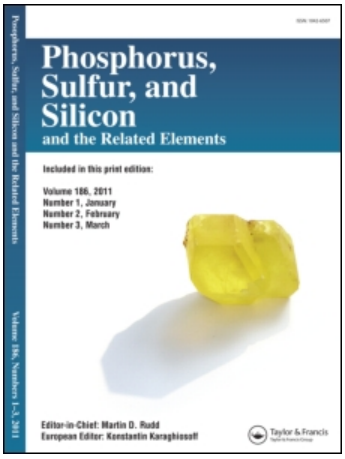


**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

# SYNTHESIS OF SULFUR ANALOGUES OF CYCLIC PHOSPHOLIPID CONJUGATED WITH $N^1$-(2-FURANIDYL)-$N^3$-(2-HYDROXYETHYL)-5-FLUOROURACIL

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**To cite this Article** Zhang, Chengxiang , Chen, Ruyu , Tang, Chuchi and Zhang, Zhongbiao(1998) 'SYNTHESIS OF SULFUR ANALOGUES OF CYCLIC PHOSPHOLIPID CONJUGATED WITH $N^1$-(2-FURANIDYL)-$N^3$-(2-HYDROXYETHYL)-5-FLUOROURACIL', Phosphorus, Sulfur, and Silicon and the Related Elements, 132: 1, 155 — 161
**To link to this Article: DOI:** 10.1080/10426509808036983
**URL:** http://dx.doi.org/10.1080/10426509808036983

*Phosphorus, Sulfur and Silicon*, Vol. 132, pp. 155-161
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# SYNTHESIS OF SULFUR ANALOGUES OF CYCLIC PHOSPHOLIPID CONJUGATED WITH $N^1$-(2-FURANIDYL)-$N^3$-(2-HYDROXYETHYL)-5-FLUOROURACIL

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*(Received 1 July, 1997; In final form 1 October, 1997)*



Two types of cyclic polythiophospholipid conjugated with $N^1$-(2-fu ran idyl)-$N^3$-(2-hydroxyethyl)-5-fluorou racil were synthesized. The hexaethyl phosphorous triamide, activated by a catalytic amount of iodine, was used as the phosphorylating reagent in a one-pot reaction resulting in a number of novel phospholipid-drug conjugates.

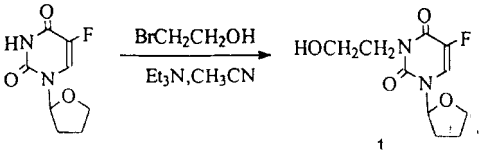
*Keywords:* Cyclic Polythiophospholipids; 5-Fluorouracil Derivatives; Conjugates; Hexaethylphosphorous Triamide

## INTRODUCTION

Phospholipid-nucleoside conjugates have demonstrated potent antitumor activity *in vitro* and *in vivo*.[1,2,3] In a previous paper, we have described the synthesis and antitumor activities of cyclic phospholipid-nucleoside conjugates.[4,5] As an extension of our work, this paper describes the synthesis of sulfur analogues of cyclic phospholipid conjugates of 5-fluorouracil derivatives. We became interested in sulfur-containing cyclic phospholipids since these compounds tend to be more lipophilic than their oxygen counterparts. Thus they may be more easily inserted into membranes and thus disrupt the membrane function.[6,7]At the same time the conjugates may generate two cytotoxic groups inside a neoplastic cell of a different target site: membrane and the synthesis of DNA.[6] $N^1$-(2-furanidyl)-fluorouracil (Tegafur) is a potent inhibitor of mammalian cell in clinical use, however, its side effects, such as hot sensation and pollakiuria syndrome, encour-

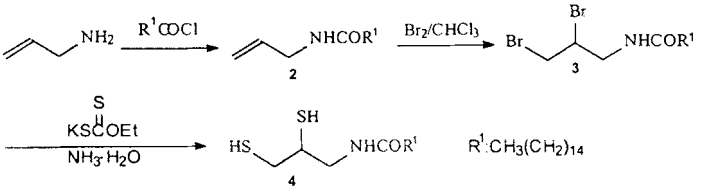
* Corresponding Author.

age people to develop a better drug.[8] So the aim is to synthesize the polythiosubstituted phospholipid conjugates of 5-fluorouracil derivatives.

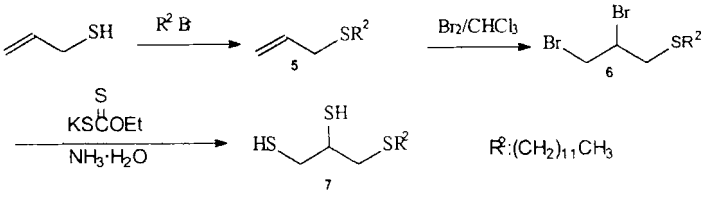


**Tegafur** 1

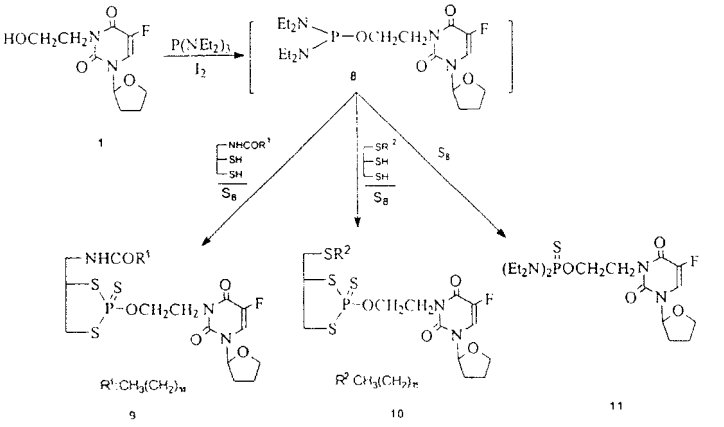
SCHEME 1



SHCEME 2



SCHEME 3



SCHEME 4

## RESULTS AND DISCUSSION

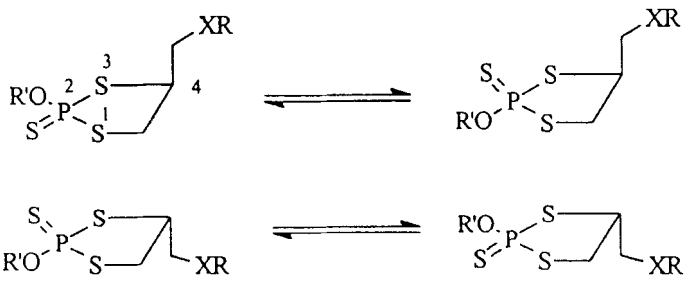
Tegafur(**1**) is one of the 5-fluorouracil antitumor agents. In order to improve its antitumor activity and reduce its side-effects, we attempted to synthesize its conjugates of cyclic polythiophospholipids. According to **Scheme 1**, the alkylation of tegafur with β-bromoethanol was carried out as described in a previous paper.[4]

**Scheme 2** describes the synthesis of N-(2, 3-dimercaptopropyl) palmitoylamide(**4**). Allyl amine reacted with palmitoyl chloride in the presence of pyridine to give compound **2** which reacted with bromine in chloroform to give compound **3** in nearly quantitative yield. The bromo groups in compound **3** were converted to mercaptan in compound **4** by means of potassiumethylxanthate as sulfurizing reagent.

**Scheme 3** describes the synthesis of 2, 3-dimercaptopropyl dodecyl sufide(**7**). 3-Bromopropene was reacted with 1-dodecanethiol to yield compound **5**. Compound **5** was converted to compound **7** by the same procedure.

Compounds **9** and **10** were obtained by a one-pot(two-step) reaction from β-hydroxyethyl tegafur(**1**) by means of hexaethyl phosphorous triamide, activated by iodine, as a phosphorylating reagent under mild conditions (**Scheme 4**). Thus the activated phosphorous triamide was reacted with compound **1** in stoichiometric amounts at 65°C to give the bis(N, N-diethylamido)-phosphite (**8**) in nearly quantitative yield. This was proven by transformation of **8** to the corresponding thiophosphate derivative **11**. The consecutive treatment of the intermediate **8** with an equivalent amounts of the dimercapto compounds and sulfur at 65°C for 4h and 30min respectively afford the compound **9** and **10**, which were isolated by column chromatography separately.

In the $^{31}$PNMR spectra of the target compounds **9** and **10**, doublets are presented in the spectra of the cyclic thiophosphates. this phenomena could be explained as below. The synthesized compounds may be disscussed as 4-substituted 1, 3, 2-dithiaphospholane derivatives, the cyclic derivatives contain two additional chiral centers(CH and P), thus the target compounds may have two pairs of diastereoisomers[(R, R)-(S, S)] and [(R, S)-(S, R)] (Fig. 1). The different intensity of the signals could be explained by the thermodynamically defined predominance of some of the assumed conformers. A steric induction resulting from the chiral exocyclic fragment may be considered another reason for the $^{31}$PNMR spectral anisochronicity detected. Our results are in agreement with those reported in the literature for analogous systems.[9,10] Further study on the physical properties and biological activities of the cyclic thiophosphates are under way.



9 : X=NH, R=$CH_3(CH_2)_{14}CO$; R'= fluorouracil derivative

10: X=S, R=$CH_3(CH_2)_{11}$ ; R'= fluorouracil derivative

FIGURE 1



## EXPERIMENTAL

IR spectra were recorded on a NICOLET 5DX instrument. NMR spectra were taken on a BRUKER AC-P200 spetrometer, TMS being used as an internal standard for $^1$HNMR and 85% $H_3PO_4$ as an external standard for $^{31}$PNMR spectroscopy. Elemental analyses were carried out with a YANACO CHN CORDER MT-3 elementary analyser. Melting points are uncorrected. Benzene and pyridine were distilled from sodium and potassium hydroxide, respectively, before being used. Petroleum ether refers to a fraction of b.p. 60–90 °C. Column chromatography was carried out with silica gel H(10–40 μm). Hexaethylphosphorous triamide was prepared according to the literature[11] and freshly distilled.

### N-Allyl palmitoylamide(2)

A solution of 2.4mL(8mmol)of palmitoyl chloride and 1.3mL (18mmol) of allylamine in 50mL of diethyl ether was stirred for 24h at room temperature. The solution was washed with water, 5% hydrochloric acid and water, then dried over $Na_2SO_4$. The solvent was evaporated, and the residue was recrystallized from diethyl ether to yield a white solid(2.0g, 84%).m.p. 82~84°C ; $C_{19}H_{37}NO$. Calcd: C, 77.29; H, 12.54; N, 4.75, Found: C, 77.32, H 12.48, N, 4.78. $^1$HNMR($CDCl_3$) δ 0.86( 3H, t, $CH_3$), 1.28( 24H, brs, $(CH_2)_{12}$), 1.59(2H, m, $CH_2CH_2CO$), 2.18(2H, t, $CH_2CO$), 3.40~4.10(5H, m, $CH_2CHCH_2$).

**N-(2, 3-Dibromopropyl) palmitoylamide (3)**

To a solution of 1.5g(smmol) of N-allyl palmitoylamide(2) in 20mL of chloroform, a solution of 0.26mL(5mmol) of bromine in 5mL chloroform was added dropwise at 0°C. The mixture was allowed to come to room temperature and stirred further for 20min at 50°C. The solvent was evaporated and the residue was rycrystallized from diethyl ether to yield a white solid (1.9g, 94%),. m.p. 84~86°C; $C_{19}H_{37}Br_2NO$. Calcd: C, 50.11; H, 8.13; N,3.08, Found: C, 50.21; H,8.13, N, 2.99. $^1$HNMR($CDCl_3$) δ 0.84( 3H, t, $CH_3$), 1.22(24H, brs, $(CH_2)_{12}$), 1.61(2H, m, $CH_2CH_2CO$), 2.20(2H, t, $CH_2CO$), 3.30~3.98(4H, m, $CH_2CHCH_2$), 4.60(1H, quint, CH), 5.60~5.80(1H, d, NH).

**N-(2, 3-dimercaptopropyl) palmitoylamide(4)**

A solution of 4.0g (10 mmol) of N-(2, 3-dibromo propyl) palmitoyl amide(3) and 1.6g (10 mmol) potassium ethylxanthate in 50mL of ethanol (95%) was stirred for 4 days at room temperature, 5mL of aqueous ammonia (28%) was added and the mixture was stirred for 5h at 50°C. The solvent was evaporated and the residue was recrystallized from ethanol to yield a pale yellow solid (3.2g, 88%). m.p. 90~92°C ; $C_{19}H_{39}NOS_2$. Calcd: C,63.15; H,10.80; N,3.88, Found: C,63.10; H,10.50, N,4.02. $^1$HNMR(CDCl3) δ 0.85(3H, t, $CH_3$), 1.22(24H, brs, $(CH_2)_{12}$), 1.61(2H, 2H, $CH_2CH_2CO$), 2.20(2H, t, $CH_2CO$), 3.50~4.20(4H, m, $CH_2CHCH_2$), 4.60(1H, quint, CH), 5.95(1H, brs, NH).

**2, 3-Dibromopropyl dodecyl sulfide (6)**

A solution of 3.3g (10 mmol) of dodecanethiol and 0.56 (10 mmol) of potassium hydroxyl in 30mL of ethanol (95%) was stirred for 30min at room temperature. A solution of 0.74g (10 mmol) of allyl mercaptan in 20mL of ethanol (95%) was added and the mixture was stirred for 48h at room temperature. The solvent was evaporated and the residue was dissolved in 40mL of chloroform, a solution of 0.52g (10 mmol) of bromine in 10mL of chloroform was added dropwise at 0°C. The mixture was allowed to come to room temperature and stirred further for 20min at 50°C. The solvent was evaporated and the residue was chromatographed by silica gel column using petroleum ether as eluent. A colorless oily product (3.6g, 90%) was obtained. Rf value: 0.80(petroleum ether); $C_{15}H_{30}Br_2S$. Calcd: C,44.78; H,7.46, Found: C,44.72; H, 7.30. $^1$HNMR($CDCl_3$) δ 0.85( 3H, t, $CH_3$), 1.22(18H, brs, $(CH_2)_9$), 1.60(2H, m, $CH_2CH_2S$), 2.54(2H, t, $CH_2S$), 3.18–4.00(4H, m, $CH_2CHCH_2$), 4.22(1H, quint, CH).

**2, 3-dimercaptopropyl dodecyl sulfide(7)**

A solution of 4.0g (10 mmol) of 2, 3-dibromopropyl dodecyl sulfide and 1.6g (10 mmol) potassium ethylxanthate in 50mL of ethanol (95%) was stirred for 4 days at room temperature, 5mL of aqueous ammonia (28%) was added and the mixture was stirred for 5h at 50°C. The solvent was evaporated and the residue was chromatographed by silica gel column using petroleum ether as eluent. A colorless oily product (2.2g, 74%) was obtained. Rf value: 0.50 (petroleum ether); $C_{15}H_{32}S_3$. Calcd: C,58.44; H,10.39, Found: C,58.20; H, 10.30. $^1$HNMR($CDCl_3$) δ 0.85 (3H, t, $CH_3$), 1.22(18H, brs, $(CH_2)_9$), 1.60(2H, m, $CH_2CH_2S$), 2.54(2H, t, $CH_2S$), 2.80~3.40(5H, m, $CH_2CHCH_2$).

**2-[1-($N^1$-(2-furanidyl)-5-fluorouracil-$N^3$-)ethyl-2-O-]-2-thio-4 palmitoylamino methyl-1, 3, 2-dithiaphospholane (9)**

A mixture of iodine (0.026 g, 0.1 mmol) and tris(N, N-diethyl)amide of phosphorus acid (0.519 g, 2.1 mmol) in benzene (50 mL) was heated at 65 °C in a stream of nitrogen for about 15 min. After the precipitate had dissolved, $N^1$-(2-furanidyl)-$N^3$-(2-hydroxyethyl)-5-fluorouracil (**1**) (0.490 g, 2.0 mmol) was added and the reaction system was heated at 65 °C for 3 hr. N-(2, 3-dimercaptopropyl) palmitoylamide(**4**) (0.640 g, 2.0 mmol) was then added, and the reaction mixture was heated at 65 °C for another 3 h. Sulfur (0.067 g, 2.1 mmol) was added and the reaction system was kept under the same conditions for 30 min. The solvent was evaporated *in vacuo*,and the residue was chromatographed by use of a silica gel column with petroleum ether-ethyl acetate (1:1, V/V) as the eluent. A colorless oily product (0.67 g, 50%) was obtained. $R_f$ value: 0.60 (petroleum ether/ethyl acetate, V/V, 1:1). $C_{29}H_{49}FN_3O_5PS_3$. Calcd: C, 52.33; H, 7.37; N, 6.32. Found: C, 52.52; H, 7.52; N, 6.59. IR (liq): 2914, 1718, 1689, 1378, 1264, 1234, 1067, 1018, 962, 878, 697cm$^{-1}$; $^1$HNMR ($CDCl_3$): δ 0.83 (3H, t, $CH_3$), 1.20 (24H, brs, $(CH_2)_{12}$), 1.51 (2H, m, $OCCH_2CH_2$), 1.79~2.46 (4H, m, 3′,4′-$CH_2$), 2.33 (2H, t, $CH_2CO$), 3.05~3.28 (4H, m, $CH_2CHCH_2$), 3.98(1H, m, 5′-$H_a$), 4.02~4.33 (6H, m, 5′-$H_b$, $CH_2CHCH_2$, $OCH_2CH_2N$), 5.92(1H, brs, 2′-H), 7.35(1H, d, $J_{HF}$=5.4Hz, 6-H), 9.60(1H, brs, NH); $^{31}$PNMR ($CDCl_3$, δ): 84.61, 84.37ppm(each d).

**2-[1-($N^1$-(2-furanidyl)-5-fluorouracil-$N^3$-)ethyl-2-O-]-2-thio-4-dodecyl mercapto methyl-1, 3, 2-dithiaphospholane (10)**

Using $N^1$-(2-furanidyl)-$N^3$-(2-hydroxyethyl)-5-fluorouracil (**2**) (0.490g, 2.0 mmol) and 2, 3-dimercaptopropyl dodecyl sulfide (0.620 g, 2.0 mmol), com-

pound **10** was synthesized and then purified in the same way as described for compound **9**. A pale yellow oily product (0.71g, 58%) was obtained. Rf value: 0.65(petroleum ether/ethyl acetate, 1 :1, V/V). $C_{25}H_{42}FN_2O_4PS_4$. Calcd.: C, 49.02; H, 6.86; N, 4.57. Found: C, 48.95; H, 6.74; N, 4.48. IR(liq.): 1718, 1689, 1660, 1460, 1378, 1264, 1062, 1018, 967, 878, 718, 697 $cm^{-1}$ ; $^1$HNMR ($CDCl_3$): δ 0.85 (3H, t, J=6.0Hz, $CH_3$), 1.22 (18H, brs, $(CH_2)_9$), 1.58 (2H, m, $SCH_2CH_2$), 1.79~2.46 (4H, m, 3′,4′-$CH_2$), 2.55 (2H, t, $CH_2S$), 2.80~3.20 (4H, m, CH2CHCH2), 3.95~4.20 (7H, m, 5′-$CH_2$, $OCH_2CH_2N$, CH2CHCH2), 5.96 (1H, brs, 2′-H), 7.35 (1H, d, $J_{HF}$=5.4Hz, 6-H); $^{31}$PNMR ($CDCl_3$, δ): 83.58, 83.68ppm(each d).

### 1-O-( $N^1$-( 2-furanidyl )-5-fluorouracil-$N^3$- )ethyl-bis(N, N-diethyl-amido)-thiophosphate (11)

A mixture of iodine (0.026 g, 0.1 mmol) and tris(N, N-diethyl)amide of phosphorus acid (0.519 g, 2.1 mmol) in benzene (50 mL) was heated at 65 °C in a stream of nitrogen for about 15 min. After the precipitate had dissolved, $N^1$-(2-furanidyl)-$N^3$-(2-hydroxyethyl)-5-fluorouracil (**1**) (0.490 g, 2.0 mmol) was added and the reaction system was heated at 65 °C for 3 hr. Then sulfur (0.067 g, 2.1 mmol) was added and the reaction system was kept under the same conditions for 30 min. The solvent was evaporated *in vacuo,* and the residue was chromatographed by use of a silica gel column with ethyl acetate as the eluent. A colorless oily product (0.72g, 83%) was obtained. $R_f$ value: 0.35 (ethyl acetate). $C_{18}H_{32}FN_4O_0PS$. Calcd: C, 48.00: H, 7.11; N, 12.44. Found: C, 47.82; H, 7.05; N, 12.59. $^1$HNMR ($CDCl_3$): δ 1.02(12H, t, $4CH_3$), 1.79~2.46(4H, m, 3′,4′-$CH_2$), 3.11(8H, q, $4CH_2$), 3.84(2H, t, $NCH_2$), 3.99(1H, m, 5′-$H_a$), 4.19(2H, t, $OCH_2$), 4.20(1H, m, 5′-$H_b$), 5.96(1H, brs, 2′-H), 7.40(1H, d, $J_{HF}$=5.4Hz, 6-H). $^{31}$PNMR ($CDCl_3$, δ): 77.6.

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