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Antineoplastic Agents. The Preparation of 5-Fluorouracil-1-acetic Acid Derivatives

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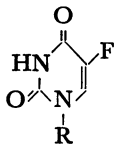
Synopsis. The condensations of 5-fluorouracil with α-halogenoacetic acid derivatives in the presence of alkali gave the 5-fluorouracil-1-acetic acid derivatives.

5-Fluorouracil (I)[1] and 1-(2-tetrahydrofuryl)-5-fluorouracil (II)[2] as antineoplastic agents have received much attention because of their antitumor activities. In a previous paper,[3] the preparations of various 1-acyl, 1-alkanesulfonyl-, and 1-arenesulfonyl-5-fluorouracils from I were reported. In an attempt to improve the antitumor activities, the introduction of the acetic acid group into the 1-position of I has been attempted. The preparations of 5-fluorouracil-1-acetic acid derivatives will be reported here.

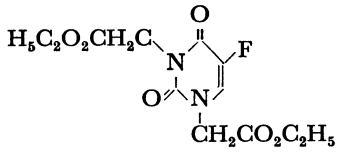
The condensation of I with α-chloroacetic acid in the presence of potassium hydroxide in water afforded 5-fluorouracil-1-acetic acid (III) in a 66% yield; this acid formed ammonium salt (IV) upon subsequent treatment with ammonium hydroxide. The reaction of I with ethyl α-bromoacetate in the presence of anhydrous potassium carbonate in dimethylformamide gave both ethyl 5-fluorouracil-1-acetate (V) in a 57% yield and diethyl 5-fluorouracil-1,3-diacetate (VI) in a 22% yield.



I: R=H

II: R= 

III: R=CH_2CO_2H
IV: R=$CH_2CO_2NH_4$
V: R=$CH_2CO_2C_2H_5$
VII: R=$CH_2CO_2CH_3$



VI

The acid hydrolysis of V gave the corresponding carboxylic acid, III, in a quantitative yield; this acid was subsequently converted into V by esterification with ethanol in the presence of such catalysts as sulfuric acid and *p*-toluenesulfonic acid. Compound III was treated with methanol to afford the methyl ester (VII) in a good yield; this ester was then hydrolyzed with hydrochloric acid to give III. Compound VII was also obtained from I by the reaction of I with methyl α-bromoacetate.

1-Substitution on I has been established by a comparison of the absorption spectra (Table 1) of the products with those of authentic 5-fluorouracil derivatives.[4-6] The structures of the products have been further supported by their NMR spectra.

The above products are now being used for animal testing; the results will be reported elsewhere.

Table 1. Ultraviolet spectral data

Comp.	Solvent	λ nm max (log ε)	λ nm min (log ε)
III	0.1M HCl	269 (3.98)	234 (3.35)
	0.1M NaOH	271 (3.84)	247 (3.58)
V	0.1M HCl	268 (4.00)	233 (3.35)
	0.1M NaOH	272 (3.75)	248 (3.50)
VI	0.1M HCl	269 (3.96)	235 (3.30)
	0.1M NaOH	272 (3.92)	236 (3.43)
VII	0.1M HCl	268 (3.98)	233 (3.30)
	0.1M NaOH	272 (3.87)	247 (3.62)

Experimental

All the melting points are uncorrected. The ultraviolet spectra were taken with a Hitachi Model 124 spectrophotometer. The NMR spectra were recorded in DMSO-d_6 (internal TMS standard) with a Varian Model 60T spectrophotometer.

5-Fluorouracil-1-acetic Acid (III). From I: Into a solution of I (1.3 g, 10 mmol) and potassium hydroxide (1.12 g, 20 mmol) in water (7.5 ml), a solution of α-chloroacetic acid (950 mg, 10 mmol) in water (4 ml) was stirred at room temperature. The pH of the reaction mixture was adjusted to, and kept at, 10 by the drop-by-drop addition of a potassium hydroxide aqueous solution. The mixture was then refluxed for 2 h, cooled, and acidified to pH 2 by the addition of concentrated hydrochloric acid. The crystals which separated were collected and washed with a little cold water to give III (1.24 g) in a 66% yield. The products were dissolved in saturated aqueous potassium bicarbonate and reprecipitated with concentrated hydrochloric acid to give colorless needles; mp 276—277 °C.

Found: C, 38.38; H, 2.72; N, 14.64%. Calcd for $C_6H_5FN_2O_4$: C, 38.31; H, 2.68; N, 14.89%.

NMR (DMSO-d_6): δ 4.40 (2H singlet, 1-CH_2-), 8.09 (1H doublet, J=7 Hz, H_6), 11.18 (1H broad singlet, 3-NH).

From V: A solution of V (430 mg, 2 mmol) in 12N hydrochloric acid (6 ml) was gently refluxed for 2.5 h and then diluted with water (6 ml). The crystals thereby separated were collected and washed with cold water to give III (240 mg). After the removal of the solvent, an additional 120 mg portion of III was obtained from the mother liquor. The total yield of III was 96%.

From VII: Compound VII was treated as in the case described above to give III (95%).

Ammonium 5-Fluorouracil-1-acetate (IV). To a suspension of III (940 mg, 5 mmol) in water (5 ml), concentrated ammonia water (0.6 ml) was added. The mixture was warmed on a water bath for 5 min. After the removal of the solvent under reduced pressure, the residue was recrystallized from diluted ethanol to give IV (0.5 g, 49%); mp 225—227 °C.

Found: C, 35.28; H, 4.12; N, 20.17%. Calcd for $C_6H_8FN_3O_4$: C, 35.13; H, 3.93; N, 20.48%.

The Reaction of 5-Fluorouracil (I) with Ethyl α-Bromoacetate. Into a suspension of powdered I (5.2 g, 40 mmol) and

anhydrous potassium carbonate (3.04 g, 44 mmol) in dimethylformamide (60 ml), ethyl α-bromoacetate (7.34 g, 44 mmol) was added. The reaction mixture was vigorously stirred at 100 °C for 10 h, cooled to room temperature, and then filtered off. The filtrate was evaporated to dryness under reduced pressure, and the residue was then extracted with absolute ethanol. The extract was concentrated by evaporation. After dilution with water, the crystals which separated were collected. Recrystallization from ethanol afforded needles (4.9 g) of ethyl 5-fluorouracil-1-acetate (V) in a 57% yield; mp 164—165 °C.

Found: C, 44.37; H, 4.39; N, 12.70%. Calcd for $C_8H_9FN_2O_4$: C, 44.45; H, 4.20; N, 12.96%.

From the mother liquor, the crystals were obtained after evaporation under reduced pressure. Recrystallization from diluted ethanol formed diethyl 5-fluorouracil-1,3-diacetate (VI), (2.60 g) as needles in a 22% yield; mp 84—85 °C.

Found: C, 47.66; H, 4.98; N, 9.58%. Calcd for $C_{12}H_{15}FN_2O_6$: C, 47.68; H, 5.00; N, 9.27%.

NMR (DMSO-d_6): δ 1.22 (6H triplet, J=7 Hz, $-OCH_2\underline{CH_3}$), 4.18 (4H, quartet, J=7 Hz, $-O\underline{CH_2}CH_3$), 4.60 (4H singlet, 1-CH_2–), 8.30 (1H, doublet, J=7 Hz, H_6).

Ethyl 5-Fluorouracil-1-acetate (V). A solution of III (940 mg, 5 mmol) in absolute ethanol (30 ml) and concentrated sulfuric acid (0.2 ml) was refluxed for 8 h and then concentrated to one-third its original volume. After the addition of ice water, sodium bicarbonate was added to the reaction mixture. The crystals thereby separated were collected and washed with cold water to give V (750 mg, 69%). The mother liquor was then extracted with chloroform. The chloroform extract was washed with water and dried over anhydrous magnesium sulfate; an additional 50 mg portion of V was thus obtained; mp 164—165 °C. The total yield of V was 74%.

A solution of III (940 mg) and *p*-toluenesulfonic acid (0.5 g) in absolute ethanol (30 ml) was treated as in the above experiment to give V (425 mg, 40%).

Diethyl 5-Fluorouracil-1,3-diacetate (VI). Into a suspension of powdered I (2.6 g, 20 mmol) and anhydrous potassium carbonate (1.52 g, 11 mmol) in absolute ethanol (60 ml), ethyl α-bromoacetate (3.67 g, 22 mmol) was added. The mixture was refluxed with stirring for 10 h and then filtered off. The filtrate was concentrated under reduced pressure to give both I (350 mg, 14%) and V (300 mg, 7%). From the mother liquor, crystals (1.72 g, 29%, mp 84—85 °C) of VI were obtained after further concentration under reduced pressure.

Methyl 5-Fluorouracil-1-acetate (VII). *From I*: Into a suspension of powdered I (1.3 g, 10 mmol) and anhydrous potassium carbonate (1.52 g, 11 mmol) in dimethylformamide (30 ml), a solution of methyl α-bromoacetate (1.68 g, 11 mmol) in dimethylformamide (5 ml) was stirred. The reaction mixture was then further stirred at 100 °C for 10 h and treated as in the above experiment to give VII (960 mg, 48%). Recrystallization from methanol afforded needle; mp 185—186 °C.

Found: C, 41.63; H, 3.53; N, 13.65%. Calcd for $C_7H_7FN_2O_4$: C, 41.59; H, 3.49; N, 13.86%.

From III: A solution of III (1.88 g, 10 mmol) in absolute methanol (60 ml) and concentrated sulfuric acid (0.6 ml) was refluxed for 8 h, after which the reaction mixture was treated as in the procedure used in the preparation of the ethyl ester, V, to give VII (1.05 g, 52%).

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