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THE SYNTHESIS OF THE POTENT ANTI-HERPES VIRUS AGENT, E-5(2-BROMOVINYL)-2'-DEOXYURIDINE AND RELATED COMPOUNDS

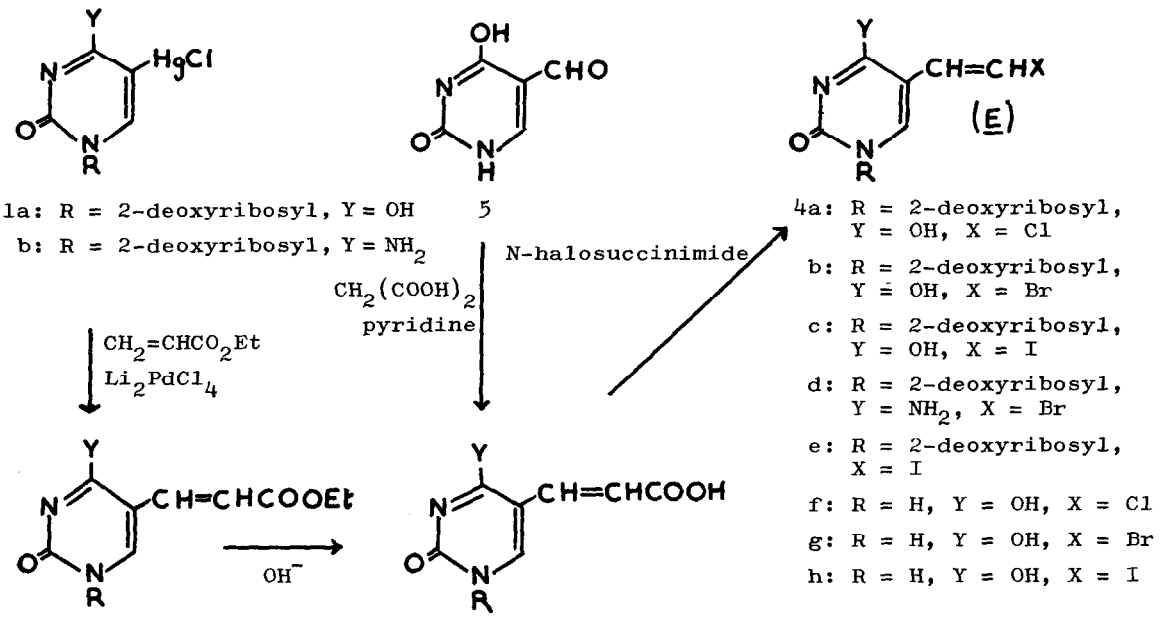
A. S. Jones*, G. Verhelst and R. T. Walker

The Chemistry Department, Birmingham University, Birmingham B15 2TT, U.K.

The synthesis of E-5(2-bromovinyl)-2'-deoxyuridine in good yield from deoxyuridine via an intermediate organopalladium derivative is described. The corresponding chloro and iodo compounds have also been made as have the corresponding bromo and iodo 2'-deoxycytidines.

We have for some time been concerned with the synthesis of some 5-substituted uracil derivatives,[1,2] initially as potential radiation sensitizing agents,[1,2,3] but more recently, in the form of their deoxynucleosides, as anti-herpetic agents.[4] To date, the most potent and selective agent against herpes simplex virus type 1 is E-5-(2-bromovinyl)-2'-deoxyuridine[4] (4b), the synthesis of which from 5-acetyluracil via 5-vinyluracil has previously been briefly described.[2] However as commercially even 5-acetyluracil is not readily available and the many further steps to the drug all proceed in rather poor yield (overall <10% from 5-acetyluracil) and finally requires the separation of α and β deoxynucleoside anomers, we here report a much more convenient synthesis which can readily be adapted to the synthesis of related compounds. The method is a modification of that used by Bergstrom and coworkers[5,6] and uses 2'-deoxyuridine or 2'-deoxycytidine as the starting material. Whereas the reaction of organopalladium intermediates derived in situ from C-5-mercurated uracil derivatives with simple mono-substituted (e.g. aryl and alkyl) olefins proceeds smoothly in methanol, ethylene and its 1-halo derivatives give rise to several products, many of which are methoxy derivatives.[6] Thus the reaction of C-5-mercurated nucleosides with Li_2PdCl_4 and ethylene does not give any substantial quantity of the 5-vinylnucleoside[6] and the corresponding reaction with vinyl-bromide gives no 5-bromovinyl derivative at all but gives small quantities of the 5-vinylnucleoside and many methoxylated products.[7]

However, condensation of a C-5-mercurated nucleoside (1a, b) with Li_2PdCl_4 and ethylacrylate[6] gave the corresponding E-5-(2-carbethoxyvinyl)nucleosides (2a, b) in good yields from 2'-deoxyuridine and 2'-deoxycytidine. These could be readily hydrolysed to the E-5-(2-carboxyvinyl)nucleosides (3a, b) under basic conditions (0.5 M NaOH, room temperature, 2h).



1a: R = 2-deoxyribosyl, Y = OH
b: R = 2-deoxyribosyl, Y = NH_2

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4a: R = 2-deoxyribosyl, Y = OH, X = Cl
b: R = 2-deoxyribosyl, Y = OH, X = Br
c: R = 2-deoxyribosyl, Y = OH, X = I
d: R = 2-deoxyribosyl, Y = NH_2, X = Br
e: R = 2-deoxyribosyl, X = I
f: R = H, Y = OH, X = Cl
g: R = H, Y = OH, X = Br
h: R = H, Y = OH, X = I

2a: R = 2-deoxyribosyl, Y = OH
b: R = 2-deoxyribosyl, Y = NH_2

3a: R = 2-deoxyribosyl, Y = OH
b: R = 2-deoxyribosyl, Y = NH_2
c: R = H, Y = OH

The final step involves the reaction of 3a, b with N-halosuccinimide to produce the E-5-(2-halovinyl)nucleosides (4a-e). For example E-5-(2-carboxyvinyl)-2'-deoxyuridine (3a) (298 mg, 1mmol) was dissolved in water (15 ml) by heating with potassium acetate (200 mg, 2mmol). While still hot (60°), a total of 178 mg (1mmol) N-bromosuccinimide was added in small portions to the clear reaction mixture. This was accompanied by an immediate evolution of gas and the mixture was stirred at room temperature for 2h. After cooling, the product (4b) crystallized out and further material could be obtained after the remaining solution had been taken to dryness and the residue fractionated on a silica column *n* $CHCl_3$: MeOH, 90:10. The product (69% yield) was identical in all respects with the compound previously prepared.[2] The chlorovinyl derivative (4a) is prepared in the same way except that the reaction is heated at 100° for 3h. The iodovinyl derivative (4c) cannot be prepared under aqueous conditions due to the instability of N-iodosuccinimide but otherwise identical conditions are used in dry dimethylformamide and the reaction stirred at room temperature for 24h. The bromo- and iodo-vinyl 2'-deoxycytidines (4d, e) are prepared similarly from 2'-deoxycytidine. Attempts to prepare E-5-(2-chlorovinyl)-2'-deoxycytidine have failed. Little reaction took place so that much starting material could be recovered and substantial quantities of an unidentified nucleoside were present.

Table

Compound	Yield (%) (Last stage)	UV data (Ethanol) λ_{max} (nm)	ε	λ_{min} (nm)	ε	NMR data (δ, $[CD_3]_2SO$) H-6 (s)	H-1' (t)	Vinylic H's (d, J = 13 Hz)
4a	39	250 293	15,990 11,620	276	7,690	8.02	6.11	7.14 6.54
4b	69	252 296	13,825 11,665	272	6,770	8.07	6.12	7.25 6.81
4c	43	251 298	13,820 11,730	275	8,080	8.05	6.11	7.14*
4d	48	254 312	16,010 6,610	290	5,040	8.10	6.10	7.05 6.70
4e	28	256 315	15,160 6,220	293	4,700	8.06	6.08	7.26 6.64
4f	71	248 291	14,720 9,610	268	5,800	7.60+	—	7.14 6.56
4g	81	251 290	17,500 9,930	275	8,280	7.70+	—	7.30 6.80
4h	61	250 294	15,200 9,900	278	9,250	7.72+	—	7.24*

* [(d), J = 6 Hz] +Two almost coincident vinylic doublets

At the base level, it is more convenient, and cheaper to prepare E-5-carboxyvinyluracil from 5-formyluracil which can be prepared in high yield from the readily available 5-hydroxymethyluracil.[8] 5-Formyluracil(5) (3.65g, 22.6 mmol) was suspended in dry pyridine (10 ml) and malonic acid (2.35g, 22.6mmol) and piperidine (0.5 ml) added. The mixture was heated on a steam bath until evolution of CO_2 had ceased (2h) and the product worked up in the usual way to give 3.3g (80%) yield of 3c. This could then be converted to the E-5-(2-halovinyl)

uracils (4 f-h) as described for the corresponding deoxynucleosides. No attempt has been made to synthesise the cytisine derivatives in this way as 5-formylcytosine is not readily available. The yield and spectral data of the compounds synthesised are given in the Table.

No evidence for the presence of the Z-isomers has been found during any of these preparations.

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9. Elemental analyses gave satisfactory values.

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