SYNTHESIS AND ANTIVIRAL ACTIVITY OF N^9-[β-D-ARABINOFURANOSYL]-GUANINE

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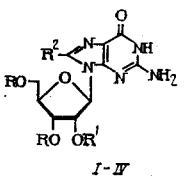
Purine nucleosides with the arabino-configuration exhibit high biological activity, and hence there is considerable interest in finding methods of synthesizing them. Compounds of this type are prepared by the glycosylation of pyurines with benzyl derivatives of D-arabinofuranose [6], and also by methods based on the stereoselective reduction of the carbonyl group of D-ribuloso-nucleosides [7], and in addition, by the substitution of the 2'-O-Ts-group of nucleosides [10] (including intramolecular substitution) [8]. The key stage in the method of synthesizing N^9-(β-D-arabinofuranosyl)-adenine (ARA-A), was developed by Divakar and Reese [5], and consists of the intramolecular substitution of the Ts-group of 8-carbamoyl-2'-O-p-toluenesulfnyl adenosine by the 8-carbamoyl group, followed by decarbamoylation.

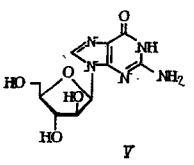
The synthesis consists of eight stages, five of which involve the introduction of the carbamoyl group. A single stage method for the carbamoylation of guanine and its derivatives using formamide with ammonium persulfate and ferrous sulfate is known [11]. This method, however, is unsuitable for the carbamoylation of adenine derivatives [4].

Using a single-stage carbamoylation of 2',3',5'-tri-O-acetylguanosine (I), we have synthesized N^9-(β-D-arabinofuranosyl)guanine (ARA-G) (V) in five stages, starting from guanosine.

Guanosine was acetylated with Ac_2O in pyridine, or Ac_2O, in the presence of BF_3Et_2O as described in [2]. The treatment of the acetate I with formamide in a solution of ammonium persulfate and ferrous sulfate gave 8-carbamoyl-2',3',5'-tri-O-acetylguanosine (II), which on deacetylation in MeOH yielded 8-carbamoylguanosine (III) [11]. The regiospecific tosylation of the nucleoside III [10] was achieved by heating it with an equivalent amount of dibutyl tin oxide in MeOH, followed by treatment of the stannylidene derivative with excess TsCl and Et_3N.



I-IV



V

I: $R = R^1 = Ac$, $R^2 = H$; II: $R = R^1 = Ac$, $R^2 = CONH_2$;
III: $R = R^1 = H$, $R^2 = CONH_2$; IV: $R = H$, $R^1 = Ts$, $R^2 = CONH_2$.

An almost quantitative yield of V was obtained by refluxing the tosylated IV in a mixture of pyridine and water (9:1).

Compound V exhibited antiviral activity against vaccinia virus and herpes simplex.

EXPERIMENTAL (CHEMISTRY)

UV spectra were recorded on a "Specord UV-VIS" spectrometer (Carl Zeiss, GDR), rotary-dispersion spectra on a JASCO-20 spectropolarimeter (JASCO, Japan). Compound III was obtained by the method given in [11].

8-Carbamoyl-2'-O-p-toluenesulfonyladenosine (IV). A mixture of compound III (0.8 g or 2.5 mmoles) and dibutyltin oxide (0.62 g of 2.5 mmoles) in 30 ml of MeOH was refluxed

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TABLE 1. Antiviral Activity of Compound V

Virus	Zone diam. in primary screening, mm		Plaque reduction test			Study using growing medium			
	toxicity	suppression of plaque-formation	concn., μg/ml	decrease in viral titer, log PFU/ml	CTI	concn., μg/ml	suppression of CPE, %	decrease in viral titer, log PFU/ml	CTI
VV	8	20	25	⩾1,88		25	0	0	
			12	⩾1,88		12	0	0	
			6	⩾1,88	4	6	0	0	0
			3	0,24		3	0	0	
HSV	6	18	25	1,16		25	25	1,82	
			12	1,19		12	25	0,43	
			6	0,3	2	6	25	0,54	1
			3	0,2		3	25	0,06	

Note. CTI is the chemotherapeutic index; CPE the cytopathic effect.

for 2 h, the solution cooled, and TsCl (7.0 g or 37.5 mmoles) and Et_3N (3.8 g or 37.5 mmoles) added to it. After 12 h the solution was evaporated to dryness, the residue triturated with 25 ml of water and 25 ml of hexane. The crystals which separated from the aqueous layer were washed with water and with ether, and dried to give 1.1 g (92%) of compound IV, mp 202-205°C (with decomposition). UV spectrum (EtOH) λ_{max}, nm (E): 224 (21,400), 270 (8300), 280 (9550), 300 (9750), 300 (9750); λ_{min}, nm: 207 (15,800), 247 (2700), 290 (9650). Rotary-dispersion spectrum (EtOH), λ: 210 (−10,000), 221 (0), 233 (−6200),247 (0), 262 (6200), 275 (0), 297 (−12400), 330 (0). Found, %: C 44.83; H 4.12; N 17.34; S 6.45. $C_{18}H_{20}N_6O_8$. Calculated, %: C 45.00; H 4.16; N 17.50; S 6.67.

N-(β-D-Arabinofuranosyl)guanine (V). A solution of 0.48 g of compound IV in 9 ml of pyridine and 1 ml of water was refluxed for 5 h, then evaporated to dryness and the residue recrystallized from aqueous MeOH to give 0.29 g of compound V, mp 219-223°C (literature value 223-225°C [3]).

EXPERIMENTAL (BIOLOGY)

The antiviral properties of compound V were studied using tests on tissue cultures as a monolayer under an agar overlay or in growing medium [1]; reduction of plaque formation was noted for the following viruses: classic avian plague, Newcastle disease, vesicular stomatitis, Venezuelan equine encephalitis, ECHO 6, vaccinia virus (VV), and herpes simplex type 1 (HSV).

For all but ECHO 6 virus, studies were carried out on monolayer cultures of primary trypsinated chick embryo fibroblasts. For ECHO 6 virus, studies were done on human embryo skin-muscle cells.

As can be seen from Table 1, compound V possesses antiviral activity.

The effectiveness was determined by standard methods for HS, and by the plaque reduction method for VV. The antiviral activity of compound V against both these viruses was small, shown both in the decrease in titers and in the low value of the chemotherapeutic index.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF 2-METHYL-5-METHOXYBENZOFURAN

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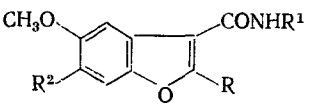
Continuing the search for biologically active benzofurans, we have synthesized amides, anilides, and other derivatives of 5-methoxybenzofuran-3-carboxylic acid.

From 2-methyl-5-methoxy- [1], 2-phenylthiomethyl-5-methoxy-6-bromo- [2], and 2-phenylthiomethyl-5-methoxybenzofuran-3-carboxylic acid (II), obtained by the methylation of the corresponding hydroxy derivative (I), were synthesized the acid chlorides, which without further purification were treated with ammonia, aniline, or γ-aminobutyric acid to give the amide of 2-methyl-5-methoxybenzofuran-3-carboxylic acid (IIIa), the amide and anilide of 2-phenylthiomethyl-5-methoxybenzofuran-3-carboxylic acid (IIIb and c), N-(2-methyl-5-methoxybenzofuroyl-3)- (IIId), and N-(2-phenylthiomethyl-5-methoxy-6-bromobenzofuroyl-3)-γ-aminobutyric acid (IIIe). Compound IIIc was oxidized with sodium iodide to the anilide of 2-phenylsulfinylmethyl-5-methoxybenzofuran-3-carboxylic acid (IIIf). Reaction with $SOCl_2$ led to the replacement of the phenylsulfinyl group of IIIf by chlorine to give the anilide of 2-chloromethyl-5-methoxybenzofuran-3-carboxylic acid (IIIg).



IIIa-g

a: R=Me, R^1=R^2=H; b: R=CH_2SPh, R^1=R^2=H; c: R=CH_2SPh, R^1=Ph, R^2=H;
d: R=Me, R^1=$(CH_2)_3COOH$, R^2=H; e: R=CH_2SPh, R^1=$(CH_2)_3COOH$, R_2=Br;
f: R=CH_2SOPh, R^1=Ph, R^2=H; g: R=CH_2Cl, R^1=Ph, R^2=H.

In addition, some reactions of 3-acyl-5-methoxybenzofuran derivatives were studied. It was found that on bromination of 2-methyl-3-acetyl-5-methoxybenzofuran [3] with an equimolar quantity of dibromodioxane, only 2-methyl-3-bromoacetyl-5-methoxybenzofuran (IV) was obtained; bromination of compound IV with dioxanedibromide gave 2-methyl-3-dibromoacetyl-5-methoxy-6-bromobenzofuran (V). Treatment of compound V with morpholine and hydrochloric acid gave (2-methyl-5-methoxy-6-bromobenzofuroyl-3)glyoxal (VI). The NMR spectrum of compound VI contained two singlets with δ 6.8 and 7.6 ppm, indicating the presence of a bromine atom at position 6 in both compound VI and the parent compound V.

Treatment of compound IV with morpholine and hydrogen chloride in ether gave the hydrochloride of 3-morpholinoacetyl, derivative (VII). Reaction of compound IV with sodium sulfide gave bis(2-methyl-5-methoxy-3-benzofuroylmethyl)sulfide (VIII).

It is interesting to note that bromination of 2-methyl-3-acetyl-5-methoxybenzofuran with N-bromosuccinimide gave 2-bromomethyl-3-acetyl-5-methoxybenzofuran (IX), not the bromoacetyl derivative of IV which was obtained on bromination with dioxanedibromide. Reaction of compound IX with morpholine gave 2-morpholinomethyl-3-acetyl-5-methoxybenzofuran (X), and treatment of IX with thiourea gave the thiourea salt (XI). With sodium sulfide, compound IX gave bis(2-methylene-3-acetyl-5-methoxybenzofuranyl)sulfide (XII).

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