SYNTHESIS OF PSEUDOSPARSOMYCINS

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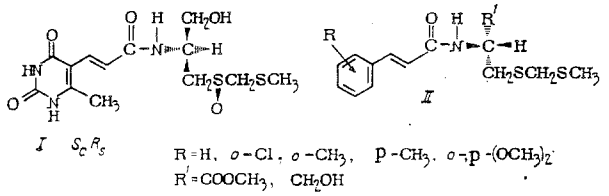
In a study of relationships between structure, activity, and toxicity, Dubois et al. [9] have recently reported the synthesis of some pseudoanalogs of the antitumor antibiotic sparsomycin (1) [11] of general formula (II).



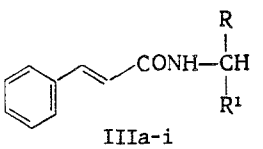
I S_cR_S

R=H, o-Cl, o-CH_3, p-CH_3, o-p-$(OCH_3)_2$
R'=$COOCH_3$, CH_2OH

It will be seen that in (II) the pyrimidine moiety of sparsomycin has been replaced by an aromatic ring, and the aminoalcohol moiety by (S-desoxo)-S-methylthiomethyl-L-cysteine methyl ester or by the residue of the corresponding L-cysteinol, i.e., the chiral carbon in (II) has the opposite configuration to that in the naturally occurring sparsomycin.

Despite these substantial changes in the sparsomycin molecule, compounds (II) show antitumor activity [9].

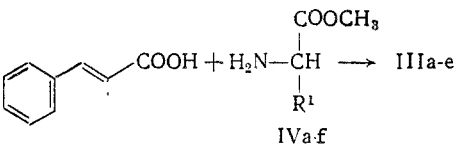
For this reason, and pursuing our studies [4] on the chemistry of sparsomycin with a view to obtaining derivatives of low toxicity, it was of interest to synthesize novel analogs of sparsomycin, namely cinnamides, in which the acid residue is kept unchanged, and the amide grouping is varied in accordance with the general formula (III).



IIIa-i

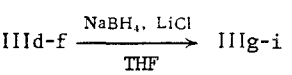
R = $COOCH_3$ (IIIa-e), CH_2OH (IIIg-i); R^1 = $CH(CH_3)_2$ (*D*, *L*) (IIIa), $(CH_2)_3CH_3$ (*D*, *L*) (IIIb), $CH_2CH_2SCH_3$ (*L*) (IIIc) $CH_2CH(CH_3)_2$ (*D*, *L*) (IIId, g), $CH_2CH(CH_3)_2$ (*D*) (IIIe,h), $CH_2C_6H_5$ (*D*, *L*) (IIIf, i)

Compounds (IIIa-f) were obtained by amidation of cinnammic acid with the aminoacid esters (IVa-f) by the mixed anhydride method, using isobutyl chloroformate [10], as follows:



IVa-f

Reduction of the amides (IIId-f) was accomplished under mild conditions ($NaBH_4$, LiCl, THF) to give the hydroxymethyl compounds (IIIg-i).



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The stuctures of (IIIa-i) followed from the method of synthesis, and were confirmed by the IR spectra and elemental analyses (Table 1).

EXPERIMENTAL

PMR spectra were obtained on a Varian T-60 (USA) in $CDCl_3$ solution, standard HMDS. Chromatography was carried out on Silufol UV-254 plates in the system ether–petroleum ether, 1:1, the spots being visualized with an UI-1 ultrachemoscope.

The aminoacid methyl esters (IVa-f) were obtained as described in [2].

Methyl Esters of N-Cinnamoylaminoacids (IIIa-f). To a solution of 1.48 g (0.01 mole) of cinnamic acid and 1.01 g (0.01 mole) of triethylamine in 30 ml of acetonitrile was added dropwise at −10°C 1.36 g (0.01 mole) of isobutyl chloroformate. The mixture was stirred for 10 min, and a mixture of the aminoacid methyl ester hydrochloride (0.01 mole), 1.01 g (0.01 mole) of triethylamine, and 30 ml of acetonitrile added at the same temperature. The mixture was kept overnight at room temperature, the acetonitrile distilled off, and the residue dissolved in CCl_4, washed successively with 10% sodium bicarbonate solution and 0.1 N HCl, dried over sodium sulfate, and passed through a funnel containing 10 g of silica gel (L-5/40, Czechoslovakian SSR). The CCl_4 was distilled off, and the residue recrystallized from hexane (Table 1). PMR spectrum, σ, ppm: N-cinnamoyl-D,L-valine methyl ester (IIIa), 0.90 d [6H, $CH(CH_3)_2$]; 2.20 m (1H, CH); 3.67 s (3H, $COOCH_3$); 4.67 m (1H, $CHCOOCH_3$); 6.63 d and 7.63 d (2H, AB spectrum, J = 16 Hz, CH=CH); 7.00 d (1H, NH); 7.24 m (5H, C_6H_5): N-cinnamoyl-D,L-norleucine methyl ester (IIIb), 0.50-1.93 m (9H, $CH_2CH_2CH_2CH_3$); 3.60 s (3H, $COOCH_3$); 4.60 m (1H, CH); 6.47 and 7.53 d (2H, AB spectrum, J = 16 Hz, CH=CH); 6.90 d (1H, NH); 7.16 m (5H, C_6H_5): N-cinnamoyl-L-methionine methyl ester (IIIc), 1.93 s (3H, SCH_3); 2.03-2.70 m (4H, CH_2CH_2S); 3.63 s (3H, $COOCH_3$); 4.80 m (1H, CH); 6.50 d and 7.57 d (2H, AB spectrum, J = 16 Hz, CH=CH); 7.00-7.36 br. m (6H, C_6H_5, NH): N-cinnamoyl-D,L-leucine methyl ester (IIId), 0.90 d [6H, $CH(CH_3)_2$]; 1.33-1.90 br. m [3H, $CH_2CH(CH_3)_2$]; 3.67 s (3H, $COOCH_3$); 4.80 m (1H, CH); 6.53 d and 7.63 d (2H, AB spectrum, J = 16 Hz, CH=CH); 7.07 d (1H, NH); 7.17-7.43 br. m (5H, C_6H_5): N-cinnamoyl-D-leucine methyl ester (IIIe), 0.83 d [6H, $CH(CH_3)_2$]; 1.37-2.00 br. m [3H, $CH_2CH(CH_3)_2$]; 3.60 s (3H, $COOCH_3$); 4.75 m (1H, CH); 6.54 d and 7.54 d (2H, AB spectrum, J = 16 Hz, CH=CH); 7.17 br. s (6H, C_6H_5, NH): N-cinnamoyl-D,L-phenylalanine methyl ester (IIIf), 3.03 d (2H, CH_2–C_6H_5); 3.60 s (3H, $COOCH_3$); 4.93 m (1H, CH); 6.37 d and 7.53 d (2H, AB spectrum, J = 16 Hz, CH=CH); 6.73 d (1H, NH); 6.97-7.33 m (5H, C_6H_5).

Amides (IIIg-i). To a mixture of 0.76 g (0.02 mole) of $NaBH_4$ and 0.85 g (0.02 mole) of LiCl in 50 ml of dry THF was added dropwise with stirring at 0°C a solution of 0.01 mole of the appropriate carbomethoxy-compound (IIIa-f) in 50 ml of dry THF. Stirring was continued at room temperature for 15 h, then the THF was distilled off, and the residue treated with water, extracted with CCl_4, dried over sodium sulfate, and passed through a funnel with 10.0 g of silica gel (L-5/40, Czechoslovakian SSR). After removal of the CCl_4, the product (IIIg-i) was recrystallized from hexane (Table 1). PMR spectra, σ, ppm: N-cinnamoyl-D,L-leucinol (IIIg), 0.80 d [6H, $CH(CH_3)_2$]; 1.17-1.73 m [3H, $CH_2CH(CH_3)_2$]; 3.33-4.33 br. m (4H, CH, CH_2OH, OH); 6.50 d and 7.57 d (2H, AB spectrum, J = 16 Hz, CH=CH); 6.87 d (1H, NH): N-cinnamoyl-D-leucinol (IIIh), 0.77 d [6H, $CH(CH_3)_2$]; 1.10-1.67 m [3H, $CH_2CH(CH_3)_2$]; 3.43 d (2H, CH_2O); 4.00 br. s (2H, CH, OH); 6.40 d and 7.53 d (2H, AB spectrum, J = 16 Hz, CH=CH); 6.93-7.40 m (6H, C_6H_5, NH): N-cinnamoyl-D,L-phenylalaninol (IIIi), 2.83 d (2H, CH_2–C_6H_5); 3.52 d (2H, CH_2OH); 4.22 br. peak (2H, CH, OH); 6.52 d and 7.45 d (2H, AB spectrum, J = 16 Hz, CH=CH); 7.00-7.28 m (6H, C_6H_5, NH).

EXPERIMENTAL (BIOLOGY)

The antitumor, antibacterial, mutagenic, and antimutagenic activities of the compounds were assessed. In all, 630 mice and 120 rats were used.

The toxicities of (IIIa-i) were determined in mongrel white mice weighing 18-20 g following a single intraperitoneal dose, and antitumor activity by intraperitoneal administration to rats and mice with transplanted tumors (sarcomas 45, 180, and 37) by standard methods [1, 3, 8].

The test results (Table 2) showed that the cinnamic acid derivatives, irrespective of the configuration of the aminoacid, were of relatively low toxicity. Most of the N-cinnamoyl-aminoacid methyl esters (IIIa-f) were of low activity against the test tumors. A relatively

TABLE 1. Properties of Compounds (IIIa-i)

Compound	Yield, %	mp, °C	R_f	Empirical formula
IIIa	85,1	133—134	0,64	$C_{15}H_{19}NO_3$
IIIb	65,0	78—79	0,58	$C_{16}H_{21}NO_3$
IIIc	58,1	76—77	0,41	$C_{15}H_{19}NO_3S$
IIId	65,3	122—123	0,57	$C_{16}H_{21}NO_3$
IIIe	57,5	100—101	0,57	$C_{16}H_{21}NO_3$
IIIf	68,5	126—127	0,53	$C_{19}H_{19}NO_3$
IIIg	64,7	115—116	0,28	$C_{15}H_{21}NO_2$
IIIh	62,5	90—91	0,28	$C_{15}H_{21}NO_2$
IIIi	85,3	135—136	0,30	$C_{18}H_{19}NO_2$

Note. The elemental analyses were in accordance with calculated values. (IIIc): sulfur, found 11.30%, calculated 10.93%. $[\alpha]_{346}^{20} = -31.8 \pm 0.07$, c 1.0, methanol; (IIIe): $[\alpha]_{346}^{24} = +16.96 \pm 0.07$; c 1.0, methanol. (IIIh): $[\alpha]_{346}^{20} = +3.18 \pm 0.07$; c 1.0, methanol.

TABLE 2. Toxicity and Antitumor Activity of (IIIa-i)

Compound	MID	LD_{50}	LD_{100}	Therapeutic dose, mg/kg	
	mg/kg			in mice	in rats
IIIa	1000	1059	1100	100	55
IIIb	2000	2075	2200	220	110
IIIc	2000	2046	2100	210	105
IIId	750	829	900	90	45
IIIe	2450	2495	2550	255	125
IIIf	1100	1128	1200	120	60
IIIg	625	692	750	75	35
IIIh	1200	1258	1300	130	75
IIIi	2100	2193	2300	230	115

active compound was N-cinnamoyl-L-methionine methyl ester (IIIc), which inhibited the growth of sarcomas 45, 180, and 37 by 53, 40, and 36%, respectively.

Examination of the hydroxymethylated N-cinnamoylaminoacids (IIIg-i) showed that reduction of the ester function to the alcohol resulted in a statistically significant increase in antitumor activity, seen clearly in the case of compounds (IIId-f) (from 24 to 47% and from 54 to 64% with sarcoma 45; from 0 to 65% with sarcoma 180, and from 28 to 47% for sarcoma 37).

Generalized staphylococcal infection in mice [5] was induced by intraperitoneal introduction of an 18-h culture of the Smith staphylococcus in a dose of 800 million microbial cells, which caused the deaths of the control, untreated animals within 24 h of infection. The test compounds were given in a single dose internally, simultaneously with the infection, in a dose of 1000 mg/kg, diluted with carboxymethylcellulose. When the compounds were given in doses of 2000 and 3000 mg/kg to healthy animals, no visible toxic effects were noted.

The phenylalanine derivatives were found to possess antistaphylococcal activity. For example, N-cinnamoyl-D,L-phenylalanine methyl ester (IIIf) increased the overall lifespan of the animals by 34% ($P < 0.001$), and N-cinnamoyl-D,L-phenylalaninol (IIIi) by 43%. Similar activity was shown by N-cinnamoyl-L-methionine methyl ester (IIIc) (the lifespan of the animals was increased by 42%). The other compounds (leucine and norleucine derivatives) were inactive. The other (III) were of low activity.

The mutagenic and antimutagenic properties of (IIIa-i) were examined with auxotrophic strains of Escherichia coli P-678 thr^- and Actinomyces rimosus 222 lys^- by the dose—effect method [6, 7]. Mutagenic activity was shown by (IIId) only, this inducing revertants with respect to the threonine locus of Escherichia coli three times more than the controls, and antimutagenic activity by (IIIh) and (IIIg) (a reduction in the numbers of spontaneous mutations by 21-33% over the controls).

These N-cinnamoyl derivatives of hydrophobic aminoacids are therefore compounds of relatively low toxicity, which do not possess mutagenic activity. Some of them (IIIc, f, h) possess weak antitumor and antistaphylococcal (IIIi) properties, indicating the desirability of further searches for more active pseudosparsomycin derivatives.

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SYNTHESIS, ANTITUMOR, AND ANTIMICROBIAL ACTIVITY OF N-SUBSTITUTED NITROFURYLVINYL(BUTADIENYL)-4-AMINO(HYDRAZINO)QUINOLINES

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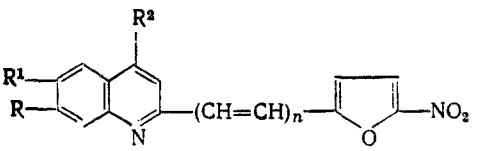
In continuation of searches [2, 4] for physiologically active nitrofurans, some novel N-substituted nitrofurylvinyl(and butadienyl)-4-amino(and hydrazino)quinolines have been obtained.



I—XIX

R = H (I—VII, XV—XVII), Cl (VIII—XIV, XVIII, XIX); R^1 = H (I, VI, VIII—XV, XVIII, XIX), OMe (II—V, VII, XVI, XVII); R^2 = $NHCH_2CH_2OH$ (I—III, IX, X), $NHCH_2CH_2CH_2OH$ (IV, V, XI, XII), $NHN(CH_2CH_2Cl)_2$ (VI, VII, XIV), $NHCH(CH_3)(CH_2)_3NEt_2$ (VIII), NHC_6H_4Cl-3 (XIII), Cl (XV—XIX); n = 1 (I, II, IV, VI—IX, XI, XIII—XVI, XVIII), 2 (III, V, X, XII, XVII, XIX); I—V, VIII—XII·$2H_3PO_4$

The nitrofurylvinylquinolines reported in the literature, with amino-, acetylamino-, chloro-, hydroxy-, ethoxy-, carboxy-, ethoxy-, carboxy- (sic — translator), or carbamoyl groups in the 3-, 4-, or 6-positions, were obtained only by the condensation of 2-methylquinoline or its derivatives with 5-nitrofurfural in acetic anhydride, acetic acid, or mixtures thereof [6, 7]. Attempts to obtain (I)-(XIV) by condensation resulted in the formation of small amounts only of the products of condensation of 5-nitrofurfural with the 2-methylquinoline component having a hydroxyalkylamino-group in the 4-position (I, II, IV, IX, XI).

The starting compounds used for the synthesis of (I-XIV) were the 4-hydroxy derivatives of nitrofurylvinyl(and butadientyl)quinolines, which have for the first time been reacted with thionyl chloride at 65-70°C to give preparative yields of the 4-chloro-compounds (XV-XIX), obtained by us previously by condensation [1, 5].

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