Potential Anticancer and Antiviral Agents. Substituted 3-[1′(2′,3′,4′-tri-*O*-benzoyl-β-D-ribopyranosyl)]-2-benzoxazolinones (1)

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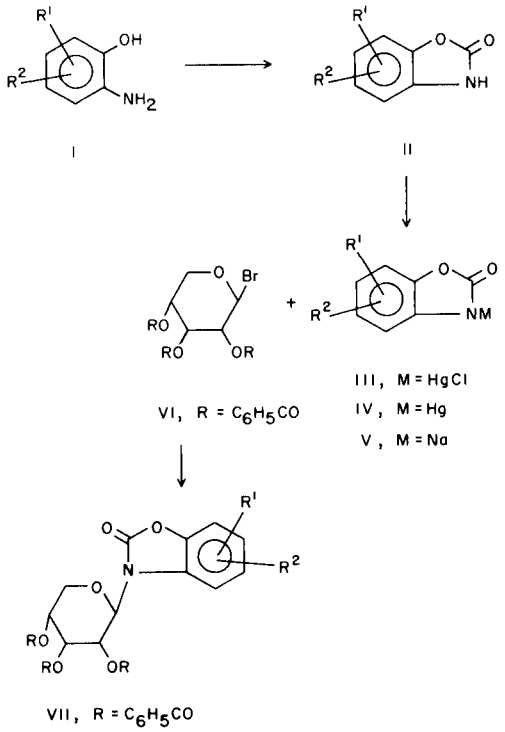
In the search for effective anticancer agents numerous modifications of known compounds possessing antitumor activity have been reported (3). Various purine and pyrimidine nucleosides have been found to posses anticancer or antiviral activity. Benzimidazole ribosides inhibit both DNA and RNA but are less active as antiviral and anticancer agents (4). Benzoxazolinone ribosides, because of their isosteric relationship to benzimidazoles and purines, were prepared for investigation for anticancer and antiviral activity.

Many nucleosides have been prepared by methods similar to that originally described by Fischer and others (5,6). The silver salts initially used have been replaced by chloromercuri salts because of the ease of the isolation of the nucleosides (7).

Substituted 2-benzoxazolinones (II) were prepared by (a) fusion of 2-aminophenols (I) with urea (8,9) and (b) the treatment of 2-aminophenols with phosgene in solution (8,10). The chloromercuri salts (III) were prepared by treating II with alcoholic mercuric chloride solution (7). Silver salts (IV) were prepared by treating II with ammoniacal silver nitrate solution (11); the sodium salts (V) were prepared by refluxing a sodium ethoxide solution containing II.



The substituted 3-[1′(2′,3′,4′-tri-*O*-benzoyl-β-D-ribopyranosyl)]-2-benzoxazolinones (VII) were prepared in approximately 30% yields by refluxing the salts of substituted 2-benzoxazolinones with tri-*O*-benzoyl-β-D-ribopyranosyl bromide (VI) (12) in xylene solution for 6-48 hours. The addition of celite (diatomaceous earth) to the reaction mixture increased the yields to over 70%. The β-configuration is assigned to the ribosides on the basis of Tipson's *trans* rule (13). The attachment of the glycosidic group to the nitrogen is predicated on the basis of similar reactions of V with alkyl halides (14). Since nucleosides containing the benzoyl groups are known to be longer acting and less toxic than the free nucleosides (15), no concerted effort was made to remove the benzoyl blocking groups of the ribosides (VII). Several attempts, however, at the hydrolysis of the ester groups of VII with sodium hydroxide or sodium ethoxide caused cleavage of the glycosidic linkage giving 2-benzoxazolinone. Preliminary studies with methanolic ammonia solutions (16) also were unsuccessful.

The infrared spectral studies of the substituted benzoxazolinone ribosides (VII) showed characteristic absorption bands at 3330 cm^{-1}, 1775 cm^{-1}, 1725 cm^{-1}, 1280-1250 cm^{-1}, 1110-1060 cm^{-1}, and 715 cm^{-1}. A doublet usually was observed in the carbonyl region. The broad bands in the regions of 1280-1250 cm^{-1} and 1110-1060 cm^{-1} were usually divided into three or four small indistinct peaks. A broad band was observed at 715 cm^{-1}.

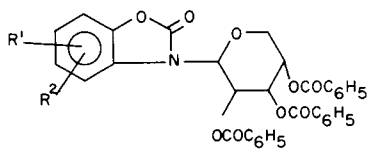
The ribosides currently are being screened for anticancer and antiviral activity.

EXPERIMENTAL

The intermediates, tri-*O*-benzoyl-β-D-ribopyranosyl bromide (12), 2-benzoxazolinone (8), 6-nitro-2-benzoxazolinone (18), 5,6-dinitro-2-benzoxazolinone (18), 5-nitro-2-benzoxazolinone (19), 5-chloro-2-benzoxazolinone (19), 5-iodo-2-benzoxazolinone (20), 5-fluoro-2-benzoxazolinone (8), 5-trifluoromethyl-2-benzoxazoli-

TABLE I

2-Benzoxazolinone Ribosides



No.	R_1	R_2	Method	Yield %	M.P. °C	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	H	H	F	24	227-228 (a)	$C_{33}H_{25}NO_9$	68.36	4.35	2.42	68.59	4.52	2.86
2	5-NO_2	6-NO_2	J	53	208-208.5 (a)	$C_{33}H_{23}N_3O_{13}$	59.20	3.46	6.27	59.13	3.62	6.11
3	5-Cl	H	H, L	40, 46	260-260.5 (b)	$C_{33}H_{24}ClNO_9$	64.54	3.94	2.28	64.47	4.12	2.38
4	5-I	H	J	23	253-254 (a)	$C_{33}H_{24}INO_9$	56.18	3.43	1.99	56.05	3.51	2.06
5	6-NO_2	H	K	32	267-268 (a)	$C_{33}H_{24}N_2O_{11}$	63.46	3.87	4.49	63.39	3.94	4.76
6	5-NO_2	H	K	28	256-257 (a)	$C_{33}H_{24}N_2O_{11}$	63.46	3.87	4.49	63.10	4.32	4.83
7	6-Cl	H	J, L	35, 40	269-269.5 (a)	$C_{33}H_{24}ClNO_9$	64.54	3.94	2.28	64.29	4.06	2.15
8	5-Cl	6-Cl	G	72	256.5-258.5 (d)	$C_{33}H_{23}Cl_2NO_9$	61.12	3.55	2.16	61.04	3.73	2.37
9	7-Cl	5-NO_2	H, I	29, 72	230-231 (c)	$C_{33}H_{23}ClN_2O_{11}$	60.14	3.52	4.25	59.80	3.80	4.28
10	5-Cl	6-Br	H, I	30, 76	259-260 (a)	$C_{33}H_{23}BrClNO_9$	57.21	3.35	2.02	57.75	3.43	1.95
11	5-F	H	G	77	237-238 (a)	$C_{33}H_{24}FNO_9$	66.33	4.06	2.34	66.47	4.21	2.39
12	5-CF_3	H	G	75	246.5-248.5 (d)	$C_{34}H_{24}F_3NO_9$	63.06	3.73	2.16	63.04	3.91	2.36

(a) Recrystallized from glacial acetic acid. (b) Recrystallized from chloroform. (c) Recrystallized from a mixture of ethanol and chloroform. (d) Recrystallized from benzene.

none (20), 5,6-dichloro-2-benzoxazolinone (21), 5-chloro-6-bromo-2-benzoxazolinone (21), were prepared according to procedures described in the literature.

7-Chloro-5-nitro-2-benzoxazolinone.

Method A.

The general procedure described by Bywater and associates (8) was followed using 18.8 g. (0.1 mole) of 2-amino-6-chloro-4-nitrophenol and 8.0 g. (0.133 mole) of urea. The mixture was fused in a preheated oil bath at 150° for 1 hour. The residue was recrystallized from ethanol-water to give 3.9 g. (20%) of product, m.p. 230-232°.

Anal. Calcd. for $C_7H_3ClN_2O_4$: C, 39.25; H, 1.40; N, 13.08. Found: C, 39.36; H, 1.57; N, 13.01.

Method B.

The general procedure described by Zinner and coworkers (19) was followed. A well stirred solution of 18.8 g. (0.1 mole) of 2-amino-6-chloro-4-nitrophenol in 50 ml. of 4 *N* sodium hydroxide solution at 0-5° was treated dropwise with a solution of 20.0 g. (0.2 mole) of phosgene in 50 ml. of toluene. The temperature was kept at 0-5° for 1 hour. The precipitate was removed by filtration, washed with water and then recrystallized from ethanol-water to give 21.1 g. (98%) of product, m.p. 232-232.5°.

3-Chloromercuri-2-benzoxazolinones (III).

Method C.

The procedure outlined by Davoll and Lowy (7) for the preparation of chloromercuripurines was followed. The substituted 2-benzoxazolinone was dissolved in hot water containing one equivalent of sodium hydroxide and mixed with one molecular proportion of mercuric chloride dissolved in a minimum amount of hot ethanol. The precipitated solid was removed by filtration and dried *in vacuo* at room temperature to give 80-90% yields of the chloromercuric salt.

3-Sodium-2-benzoxazolinone (IV).

Method D.

A solution of 0.12 mole of sodium in 100 ml. of ethanol was treated with 0.1 mole of substituted 2-benzoxazolinone. The resulting mixture was refluxed for 10 minutes and thereafter was concentrated under reduced pressure. The product (80-90%) was washed with ether and dried.

3-Silver-2-benzoxazolinone (V).

Method E.

The method of Yamaoka and associates (11) for the preparation of the silver salt of 6,8-dichloropurine was followed. Substituted 2-benzoxazolinone was dissolved in ethanol and treated with 50 ml. of 37% ammonium hydroxide containing 0.1 mole of silver nitrate. The product (80-90%) was isolated by filtration and dried.

Substituted 3-[1′(2′,3′,4′-tri-*O*-benzoyl-β-D-ribopyranosyl)]-2-benzoxazolinone (VII).

Method F.

The procedure utilized by Baker and coworkers (22) for the preparation of 6-chloro-9-α-L-rhamnopyranosylpurine was followed. A stirred mixture of 2.0 g. of substituted 3-chloromercuri-2-benzoxazolinone and 2.0 g. tri-*O*-benzoyl-β- -ribopyranosyl bromide in 200 ml. of xylene was refluxed for 24 hours. The mixture was filtered hot; the filter cake was washed with two portions of 100 ml. of chloroform. Distillation of the filtrate under reduced pressure left a solid. A warm chloroform solution (200 ml.) of the solid was washed with 30% potassium iodide and water respectively and then dried over anhydrous magnesium sulfate. The chloroform was distilled under reduced pressure and the product recrystallized from a suitable solvent.

Method G.

The procedure outlined for Method F was followed by adding 2.0 g. celite to the refluxing mixture.

Method H.

A modified procedure of Davoll and associates (7) was followed. A stirred mixture of 1.0 g. of substituted 3-chloromercuri-2-benzoxazolinone, 1.0 g. tri-*O*-benzoyl-β-D-ribopyranosyl bromide, and 100 ml. of xylene was refluxed for 8 hours and filtered hot. The filtrate was treated with 450 ml. of petroleum ether (30-60°) and then cooled in an ice bath. The solid or oil obtained was then treated as in procedure F.

Method I.

The procedure outlined in Method H was followed, however, 2.0 g. of celite was added to the refluxing mixture.

Method J.

The procedure outlined in Method H was followed. The solid obtained after the addition of petroleum ether (30-60°) was directly recrystallized without further treatment.

Method K.

The procedure outlined in Method J was followed using substituted 3-sodium-2-benzoxazolinones.

Method L.

The procedure outlined in Method J was followed using substituted 3-silver-2-benzoxazolinones.

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