added with stirring to 35 ml of concentrated H_2SO_4 in 10 min at −5°. Fuming HNO_3 (0.9 ml) was added with stirring during 45 min at −3 to −8°. After stirring for 0.5 h at −8°, the reaction mixture was poured into a stirred mixture of 350 ml of ice water and 200 ml of ethyl acetate. The aqueous phase was washed with ethyl acetate. The combined ethyl acetate solution was washed with Na_2CO_3 solution and with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was crystallized from SDA 30 (0.67 g, 15%): uv max (SDA 30) 353 nm (ε 12 700). Anal. ($C_6H_7N_2O_6$) C, H, N.

3-[[(3,4-Dimethoxy-5-nitro-2-furanyl)methylene]amino]-2-oxazolidinone (7). To a solution of 0.3 g of 5-nitro-3,4-dimethoxy-2-furancarboxaldehyde oxime in 15 ml of SDA 32 at 55° were added 5 ml of 24% H_2SO_4 and a solution of 0.3 g of 3-amino-2-oxazolidinone in 2 ml of water. The solution was heated to 75° during 0.5 h and cooled. The crude product (0.23 g) was recrystallized from SDA 30 containing a small amount of nitromethane: mp 198°; uv max (SDA 30) 370 nm (ε 18 900); ir 1350 (NO_2), 1590 (CH=N–), 1770 cm^{-1} (COO–); TLC on silica gel chromagram sheet (Eastman) in $CHCl_3$–CH_3NO_2–CH_3OH (7:2:1), R_f 0.92; in $CHCl_3$–CH_3NO_2 (8:2), R_f 0.44. Anal. ($C_{10}H_{11}N_3O_7$) C, H, N.

Ethyl Nitronic Ester of 3-[(5-*aci*-Nitro-4,5-dihydro-4-oxo-2-furanyl)methylene]amino]-2-oxazolidinone (6). The photosynthetically prepared aldehyde was coupled with 3-amino-2-oxazolidinone in acid and crystallized from sodium acetate buffer. A stirred slurry of 0.69 g (2.6 mmol) of finely powdered sodium salt in 40 ml of methylene chloride was cooled in an ice bath and a solution of 0.8 g (4.2 mmol) of triethyloxonium fluoborate in 10 ml of methylene chloride was added rapidly.[9] After stirring for 5 h, 25 ml of nitromethane and ca. 0.5 g of filter aid was added. The solid was washed with nitromethane; the combined filtrate and wash was extracted three times with water, dried over Na_2SO_4, and concentrated to low volume in vacuo. The solid was recrystallized from 35 ml of acetonitrile to yield 0.27 g (39%) of orange crystals; uv max (SDA 30) 385 nm (ε 20 800); ir 1400 (NO–OC_2H_5), 1630 (CH=N); NMR (Me_2SO-d_6) δ 7.54 (s, 1, CH=N), 7.02 (s, 0.5, 3 CH), 6.84 (s, 0.5, 3 CH), 4.4 (m, 4, $-CH_2CH_2-$), 3.9 (q, 2, $-CH_2O$), 1.29 (t, 3, CH_3–). Anal. ($C_{10}H_{11}N_3O_6$) C, H, N.

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Antidepressant and Anticonvulsant Activity of 1-(5-Phenyl-4-oxo-2-oxazolin-2-yl)-4-substituted Piperazines

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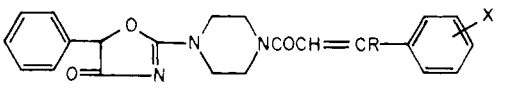
1-(5-Phenyl-4-oxo-2-oxazolin-2-yl)-4-substituted cinnamoylpiperazines and 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)-4-carbamoylpiperazine and derivatives were synthesized and evaluated for antidepressant activity in the mouse Dopa potentiation test. 1-(5-Phenyl-4-oxo-2-oxazolin-2-yl)-4-carbamoylpiperazine and derivatives were further evaluated for anticonvulsant activity in the audiogenic seizure test in mice.

As a continuing study in our laboratories for the modification of 2-amino-5-phenyl-2-oxazolin-4-one (pemoline) in search of potential CNS drugs,[1,2] it is of interest to replace the amino group by substituted piperazines. It was reported that some substituted cinnamoylpiperazines showed a strong sedative activity with a weak antihistamine activity.[3] Also, 1-heterocyclo-4-substituted carbamoylpiperazines were found to have anticonvulsant activity when tested against audiogenic seizure in rats.[4,5] Accordingly, several 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)-4-(substituted cinnamoyl)piperazines and 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)-4-carbamoylpiperazine and derivatives were synthesized.

Chemistry. 2-Acetamido-5-phenyl-2-oxazolin-4-one (1) was obtained by heating 2-amino-5-phenyl-2-oxazolin-4-one with acetic anhydride.[6] Reaction of 1 with 2 equiv of piperazine in dioxane at room temperature yielded 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (2) (Scheme I). This method is preferred to the procedure of heating 2-amino-5-phenyl-2-oxazolin-4-one with piperazine in xylene.[7] 1-(5-Phenyl-4-oxo-2-oxazolin-2-yl)-4-substituted cinnamoylpiperazines (**3a–e**) (Table I) were prepared by reaction of **2** with substituted cinnamoyl chlorides. 1-(5-Phenyl-4-oxo-2-oxazolin-2-yl)-4-carbamoylpiperazine

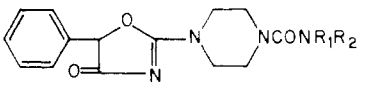
Table I. 1-(5-Phenyl-4-oxo-2-oxazolin-2-yl)-4-(substituted cinnamoyl)piperazines



Compd	X	R	Mp, °C	Yield, %[a]	Formula[b]
3a	4-F	H	241–243	64	$C_{22}H_{20}FN_3O_3$
3b	4-OCH_3	H	211–212	64	$C_{23}H_{23}N_3O_4$
3c	3,4,5-$(OCH_3)_3$	H	222–223	61	$C_{25}H_{27}N_3O_6$
3d	3-Br-4,5-$(OCH_3)_2$	H	227–229	69	$C_{24}H_{24}BrN_3O_5$
3e	3,4,5-$(OCH_3)_3$	CH_3	164–165	54	$C_{26}H_{29}N_3O_6$

[a] After recrystallization from EtOH. [b] All compounds were analyzed for C, H, and N.

Table II. 1-(5-Phenyl-4-oxo-2-oxazolin-2-yl)-4-carbamoylpiperazine and Derivatives



Compd	R_1	R_2	Mp, °C	Yield, %	Crystn solvent	Formula[a]
4a	H	H	244-246	71	MeOH	$C_{14}H_{16}N_4O_3$
4b	H	CH_3	138-140	54	C_6H_6	$C_{15}H_{18}N_4O_3$
4c	C_2H_5	C_2H_5	159-160	43	EtOAc	$C_{18}H_{24}N_4O_3$
4d	H	C_6H_5	176-177	65	EtOH	$C_{20}H_{20}N_4O_3$
4e	H	4-ClC_6H_4	192-193	54	EtOH	$C_{20}H_{19}ClN_4O_3$
4f	H	4-$OCH_3C_6H_4$	205-207	56	EtOH	$C_{21}H_{22}N_4O_4$

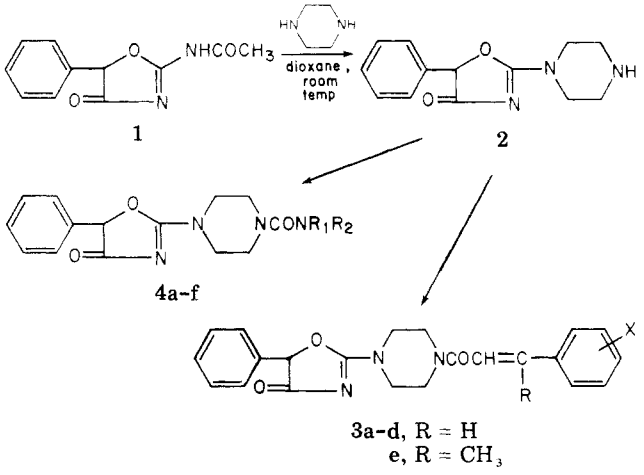
[a] All compounds were analyzed for C, H, and N.

Table III. Antidepressant Activity in the Mouse Dopa Potentiation Test

	Antidepr act. (oral route, 4 h), behavioral rating[a,b]		
Compd	25 mg	50 mg	100 mg
3a	2	3	
3b	1	2	
3c	2	3	
3d	2	3	
3e	2	2	
4a	1		2
4b	1		2
4c	1		1
4d	1		2
4e	1		2
4f	1		1
Pemoline	2	3	3

[a] Behavioral rating: 1 = slight potentiation; 2 = moderate; 3 = marked. [b] Four mice per dose.

Scheme I



(**4a**) and derivatives (**4b–f**) (Table II) were obtained by the usual procedures (see Experimental Section).

Pharmacology. These compounds were evaluated for antidepressant activity in the mouse Dopa potentiation test[8] (Table III). Compounds **3a–e** have good activity when compared with pemoline, on a molar basis; **3a** is two times, **3c** is 2.5 times, and **3d** is three times the potency of pemoline. However, compounds **4a–f** are less potent than pemoline in this test. In addition, compounds **4a–f** were evaluated for anticonvulsant activity in mice susceptible to audiogenic seizure[9] and were found to have moderate activity (Table IV). Unexpectedly, 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)-4-(*p*-methoxycinnamoyl)-piperazine (**3b**) was found to have antimalarial activity, which led to the synthesis of a large number of analogues.[10]

Table IV. Anticonvulsant Activity in the Mouse Audiogenic Seizure Test

Compd	Anticonv act. (oral route), % protection,[a,b] 100 mg/kg
4a	10
4b	50
4c	60
4d	50
4e	50
4f	20
Pemoline	90

[a] Percent of animals protected from tonic extensor component. [b] Ten mice per dose.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical value.

1-(5-Phenyl-4-oxo-2-oxazolin-2-yl)piperazine (2).[7] 2-Acetamido-5-phenyl-2-oxazolin-4-one[6] (4.36 g, 0.02 mol) was added to a stirred solution of 3.44 g (0.04 mol) of piperazine in 150 ml of dioxane. After stirring at room temperature for 5 h, the solution was filtered and the filtrate was evaporated in vacuo. The residue was triturated with ether, filtered, and recrystallized from C_6H_6: mp 144–145°; 3.8 g (77%). Anal. ($C_{13}H_{15}N_3O_2$) C, H, N.

1-(5-Phenyl-4-oxo-2-oxazolin-2-yl)-4-(3,4,5-trimethoxycinnamoyl)piperazine (3c). A mixture of 5.0 g (0.021 mol) of 3,4,5-trimethoxycinnamic acid, 5.15 g (0.023 mol) of phosphorus trichloride, and 25 ml of C_6H_6 was stirred and refluxed for 1 h. The hot mixture was filtered and the filtrate was evaporated in vacuo. The residue was dissolved in 15 ml of dimethylacetamide and added dropwise to a stirred solution of 3.92 g (0.016 mol) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (**2**) and 1.61 g (0.016 mol) of Et_3N in 60 ml of dimethylacetamide. After stirring at room temperature for 2 h, the mixture was filtered. The filtrate was diluted with H_2O and the product was collected and recrystallized from EtOH.

Compounds **3b**, **3d**, and **3e** were prepared as above; **3a** was obtained by treatment of the acid chloride (prepared from the acid with $SOCl_2$ in C_6H_6) with **2**.

1-Carbamoyl-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (4a). A solution of 1.09 g (0.0134 mol) of potassium cyanate in 5 ml of H_2O was added gradually to a stirred solution of 3.77 g (0.0134 mol) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine hydrochloride in 55 ml of H_2O. The mixture was stirred at room temperature for 1.5 h. The product was filtered, washed with H_2O, and recrystallized.

1-(Methylcarbamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (4b). A mixture of 7.35 g (0.03 mol) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine, 17 ml of methyl isocyanate, and 50 ml of dry pyridine was stirred and refluxed for 2.5 h. The excess methyl isocyanate and pyridine were removed by distillation under reduced pressure and the residue was recrystallized.

1-(Diethylcarbamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (4c). A solution of 4.07 g (0.03 mol) of diethylcarbamoyl chloride in 15 ml of C_6H_6 was added dropwise

to a stirred, near boiling solution of 7.35 g (0.03 mol) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine and 3.34 g (0.033 mol) of Et_3N in 250 ml of C_6H_6. The mixture was refluxed for 1 h and, after cooling, the solid was filtered and washed with H_2O. The C_6H_6 filtrate was evaporated in vacuo leaving a solid residue. The combined solids were purified by recrystallization.

1-(Phenylcarbamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (4d). A solution of 2.38 g (0.02 mol) of phenyl isocyanate in 5 ml of dioxane was added dropwise to a stirred, hot solution of 4.9 g (0.02 mol) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine in 150 ml of dioxane. The mixture was refluxed with stirring for 1 h and evaporated to dryness in vacuo and the residue was recrystallized. Compounds **4e** and **4f** were similarly prepared.

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Communications to the Editor

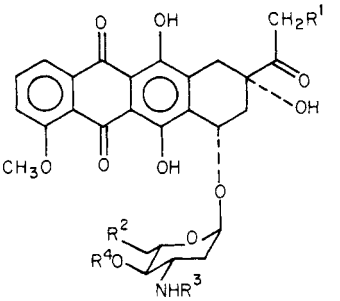
Stereocontrolled Glycosidation of Daunomycinone. Synthesis and Biological Evaluation of 6-Hydroxy-L-arabino Analogues of Antitumor Anthracyclines

Sir:

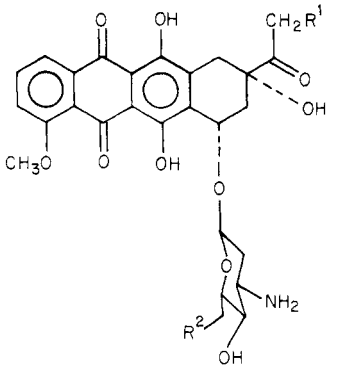
Daunorubicin and adriamycin are anthracycline glycosides which are clinically useful chemotherapeutic agents against cancer.[1] The synthesis of analogues in which the carbohydrate component is functionally and/or configurationally altered is of great biochemical and practical interest, particularly with the finding[2,3] that the semisynthetic analogues **1** and **2**, possessing an inverted configuration at C-4', display high activity against experimental tumors in mice. It is also of interest in this connection that the β anomers **6** and **7** have a much lower biological activity than the α anomers.[2,3] It is apparent, therefore, that the stereospecific synthesis of glycosides in this class of compounds is of paramount importance. To date, all glycosidations in this series have been carried out by the classical Koenigs–Knorr procedure and have led to anomeric mixtures that necessitated separation.[3]

We report herein on the stereocontrolled synthesis of 7-*O*-(3-amino-2,3-dideoxy-α-L-*arabino*-hexopyranosyl)-daunomycinone (**4**), via an acid-catalyzed glycosidation of a glycal intermediate, and the chemical conversion of **4** into the corresponding adriamycin analogue **5**.

The key intermediate for the stereocontrolled glycosidation of daunomycinone, 1,2,3-trideoxy-4,6-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-*arabino*-hex-1-enopyranose (**10**), was prepared from methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*ribo*-hexopyranoside, following procedures available in the literature for the D series,[4] via methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-L-*arabino*-hexopyranoside. The latter compound was converted to methyl 3-amino-2,3-dideoxy-α-L-*arabino*-hexopyranoside, mp 120° dec, $[\alpha]^{20}D$ −92° (*c* 0.4, H_2O),[5] upon treatment with methanolic hydrogen chloride. This compound was hydrolyzed (1 N HCl for 5 h at 95°) to the free amino sugar, mp 155–157° dec, $[\alpha]^{20}D$ −55° (*c* 0.5, H_2O), previously unknown in the L series, and the latter was converted to the trifluoroacetyl derivative **9**, mp 177°, $[\alpha]^{20}D$ −58° (*c* 0.5, dioxane), by treatment with trifluoroacetic anhydride in dichloromethane (25°, 20 h) and hydrolysis of the 1,6-di-*O*-trifluoroacetyl groups with methanol (25°, 20 h). *p*-Nitrobenzoylation of **9** with *p*-nitrobenzoyl chloride in pyridine followed by treatment with aqueous sodium bicarbonate afforded 1,2,3-trideoxy-4,6-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-*arabino*-hex-1-enopyranose (**10**), mp 214–215°, $[\alpha]^{20}D$ −117° (*c* 0.5, $CHCl_3$). The overall yield of **10** from methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-*arabino*-hexopyranoside was 70%.



1, $R^1 = R^2 = R^3 = R^4 = H$
2, $R^1 = OH$; $R^2 = R^3 = R^4 = H$
3, $R^1 = H$; $R^2 = pNBzO$; $R^3 = COCF_3$; $R^4 = pNBz$
4, $R^1 = R^3 = R^4 = H$; $R^2 = OH$
5, $R^1 = R^2 = OH$; $R^3 = R^4 = H$



6, $R^1 = R^2 = H$
7, $R^1 = OH$; $R^2 = H$
8, $R^1 = H$; $R^2 = OH$