the interaction of the thymine and phosphoraziridine moieties. Therefore, the corresponding carbamate derivatives will be synthesized and investigated.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. NMR spectra were obtained on Varian A-60 and T-60 spectrometers in deuterated chloroform solution, using tetramethylsilane as internal standard. Infrared spectra were taken in a Beckman IR-8 spectrometer. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA, or by Galbraith Laboratories, Inc., Knoxville, TN.

5′-(Dichlorophosphinyl)-3′-acetylthymidine (5). To a solution of $POCl_3$ (4.904 g, 32 mmol) in $(MeO)_3PO$ (10 mL), cooled in an ice bath, was added 3′-acetylthymidine (4;[10] 4.548 g, 16 mmol). The reaction mixture was stirred in a cold room (4–7 °C) for 16 h. The excess $POCl_3$ and the HCl formed were removed under high vacuum (0.5–1 mmHg) at room temperature for 4 h. The resulting solution was immediately used for the next reaction step.

5′-[Bis(1-aziridinyl)phosphinyl]-3′-acetylthymidine (6). To a three-neck round-bottom flask (100 mL, equipped with thermometer, drying tube, and pressure equalized additional funnel) was introduced a solution of aziridine (1.724 g , 50 mmol) and triethylamine (4.048 g, 40 mmol) in 40 mL of 1,2-dimethoxyethane (DME). The container was cooled to 0–5 °C on an ice bath. The solution of **5** (16 mmol) in 10 mL of $(MeO)_3PO$ (see above) was added dropwise. The reaction temperature was maintained below 9 °C. After the addition was completed, the reaction mixture was stirred in a cold room (4–7 °C) for 42 h. The precipitated solids were collected by filtration and washed with DME (20 mL) and then with ether (20 mL). The precipitate was extracted with DME (300 mL), and the extracted solution was concentrated to 10 mL at room temperature under reduced pressure. The residue was chilled overnight in the refrigerator to obtain 2.05 g (overall yield, 31%) of **6** as white crystals: mp 183–185 °C; NMR ($CDCl_3$) δ 7.54 (br, 1 H), 6.30 (q, J = 6 Hz, 1 H), 5.31 (m, 1 H), 4.38 (m, 2 H), 4.15 (m, 1 H), 2.25, 2.07 (d, J = 15 Hz, 13 H, methylene protons of aziridine rings, 2′-CH_2 of thymidine and CH_3 of acetyl), 1.93 (d, J = 1, Hz, CH_3); IR (KBr) 1730 (ester), 1675 (amide), 830 cm^{-1} (P-N); $[\alpha]^{25}_D$ +4.45° (c 1.12, $CHCl_3$). The analytical sample was recrystallized from DME. Anal. ($C_{16}H_{23}N_4O_7P$) C, H, N, P.

5′-[Bis(2,2-dimethyl-1-aziridinyl)phosphinyl]-3′-acetylthymidine (7). This compound was synthesized by the same method as described for the preparation of **6**. From 4.54 g (16 mmol) of compound **4** was obtained 3.4 g (7.2 mmol, 45%) of **7**: mp 171–173 °C; NMR ($CHCl_3$) δ 7.61 (br, 1 H), 6.43 (q, J = 6 Hz, 1 H), 5.35 (m, 1 H), 4.30 (m, 3 H), 2.21 (d, J = 14 Hz, 6 H; methylene protons of aziridines and 2′-CH_2 of thymidine), 2.12 (s, 3 H; acetyl), 1.95 (br, 3 H), 1.46 (s, 12 H; methyl protons of aziridine rings; IR (KBr) 1732 (ester), 1680 (amide), 1390, 1380 [$C(CH_3)_2$], 1270 (P=O), 955 (PN) cm^{-1}; $[\alpha]^{25}_D$ +7.14° (c 0.98, $CHCl_3$). The analytical sample was recrystallized from DME. Anal. ($C_{20}H_{31}N_4O_7P$) C, H, N, P.

5′-[Bis(1-aziridinyl)phosphinyl]thymidine (8). To 15 mL of absolute MeOH saturated with ammonia (10 mL) in an ice bath was added compound **6** (800 mg, 1.9 mmol). The solution was warmed up to room temperature, stirred for 4 h, and then evaporated to dryness. The residue was dissolved in $CHCl_3$ (10 mL), and dry ether (10 mL) was added until precipitation was observed. The solution was chilled in the refrigerator overnight; the precipitate was collected and dried under vacuum to give 0.50 g of **8** (1.3 mmol, 67%) as a foamy solid: mp 61–64 °C; NMR ($CDCl_3$) δ 7.47 (s, 1 H), 6.35 (t, J = 6 Hz, 1 H), 4.0–4.7 (two broad bands, 4 H), 2.32 (d, J = 15 Hz, 8 H, CH_2), 1.90 (s, 3 H, CH_3); IR (KBr) 1675 (CONH), 1266 (P=O), 930 (PN) cm^{-1}. The product was highly hygroscopic and difficult to analyze; therefore, its identification was based on the NMR spectra. The latter showed well-resolved peaks (see above) which integrated satisfactorily in the case of the freshly prepared sample; however, the spectra became blurred after a few days storage (even at refrigeration temperature), indicating polymerization.

5′-[Bis(2,2-dimethyl-1-aziridinyl)phosphinyl]thymidine (9). Compound **7** was deacetylated in the same manner as described for the preparation of **8**. From 800 mg (1.7 mmol) of compound **7** was obtained 0.433 g (yield 57%) of the deblocked compound **9**: mp 50–53 °C; NMR ($CDCl_3$) δ 7.46 (s, 1 H), 6.36 (t, 1 H), 4–4.6 (br m, 4 H, 3′-CH, 4′-CH, 5′-CH_2), 2.17 (d, J = 14 Hz, 6 H, CH_2), 1.92 (s, 3 H, CH_3), 1.42 (s, 12 H, CH_3); IR (KBr) 1680 (CONH) 1389, 1387 [$C(CH_3)_2$], 1270 (P=O), 960 (PN) cm^{-1}. The compound was highly hygroscopic and difficult to handle. Anal. ($C_{18}H_{29}N_4O_6P\cdot H_2O$) C, H, N.

Assays of Cholinesterase Inhibitory Activity. The in vitro inactivation of horse serum cholinesterase, with procaine hydrochloride as substrate, was measured by a slight modification of the method of Lalka and Bardos.[7] The enzyme solution, 20 mL, 5.0 units/mL in 0.066 M NaH_2PO_4 buffer, pH 7.4, was made 1.4×10^{-4} M with respect to the inhibitor, at time zero, by adding 1.0 mL of a 2.94×10^{-3} M solution of the inhibitor in the same buffer. The resulting solution containing the enzyme and the inhibitor were placed in a 37 °C shaker bath, and 1.5-mL aliquots were withdrawn at various times and cooled to 24 °C in tap water. The substrate solution, 1.5 mL of 5.6×10^{-5} M procaine hydrochloride in the same buffer, was added to each tube as well as to a control containing no inhibitor, and the initial rate of the decrease of absorbance at 300 nm was measured as described previously.[7]

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(Phenylthio)phenylamine Derivatives as Potential Antiinflammatory Compounds

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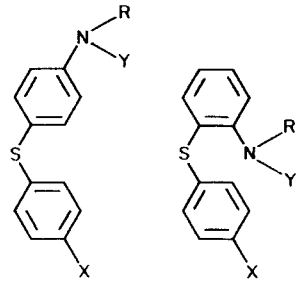
A series of (phenylthio)phenylamines and related compounds was prepared as potential antiinflammatory agents. Among them, *N*-[(diethylamino)acetyl]-4-[(4-chlorophenyl)thio]phenylamine and *N*-[(diethylamino)acetyl]-2-[(4-chlorophenyl)thio]phenylamine showed good antiinflammatory activity in the carrageenin assay on rats.

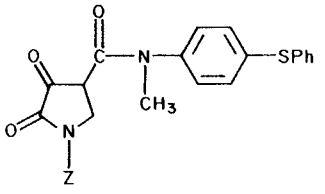
In a previous work, we reported the synthesis of 2-aminonicotinic acids, N-substituted by different diphenyl sulfide groups. Among these products, an analogue of compound III (Table I), with X = Cl, Y = H, and R =

0022-2623/81/1824-0889$01.25/0

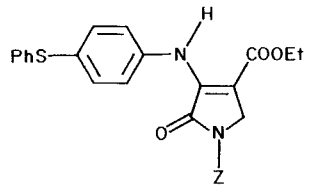
Table I. (Phenylthio)phenylamines and Derivatives



IV (40-42)



V (43-45)



VI (46, 47)

										antiinflammatory act. vs. carrageenin				
no.	X	R	Y	parent amine	method[a]	mp, °C	recrystn solvent	yield,[b] %	formula[c]	dose, mg/kg	% redn, 1 h	% redn, 2 h	% redn,[d] 3 h	ca. LD_{50}[e] in mice, mg/kg
1	H	H	H			96-96.5[f]	EtOH	90						
2	Cl	H	H			58-60[g]	95% EtOH	90						
3	H	Me	H			39.5-40.5[g]	*i*-PrOH	60						
4	Cl	Me	H			65	*i*-PrOH	60	$C_{13}H_{12}NSCl$					
5	Cl	Me	CHO			72	c-C_6H_{12}	73[j]	*i*					
6	H	Me	$COCH_2Cl$	3	A	121-122	*i*-PrOH	64[j]	$C_{15}H_{14}NOSCl$					
7	H	H	$COCH_2Cl$	1	A	121-121.5[h]	*i*-PrOH	89[j]	*h*					
8	Cl	H	$COCH_2Cl$	2	A	145	PrOH	84[j]	*i*					
9	Cl	Me	$COCH_2Cl$	4	A	93	95% EtOH	65[j]	$C_{15}H_{13}NOSCl_2$					
10	H	Me	$COCH_2NMe_2$	3	B	178.5	PrOH	78	$C_{17}H_{20}N_2OS \cdot C_2H_2O_4$	5 ip	18	14	22	50 iv
11	H	Me	$COCH_2NEt_2$	3	B	104-106	Et_2O[k]	65	$C_{19}H_{24}N_2OS \cdot C_2H_2O_4 \cdot 0.25H_2O$	5 ip	53	50	52*	30 iv[t]
12	H	Me	$COCH_2N(CH_2)_4$[l]	3	B	159-160	PrOH	78	$C_{19}H_{22}N_2OS \cdot C_2H_2O_4$	5 ip	18	18	23	35 iv
13	H	Me	$COCH_2N(CH_2)_5$[m]	3	B	170.5	PrOH	73	$C_{20}H_{24}N_2OS \cdot C_2H_2O_4$	5 ip	40	29	34*	45 iv
14	H	Me	$COCH_2NC_4H_8O$[n]	3	B	179.5	PrOH	68	$C_{19}H_{22}N_2O_2S \cdot C_2H_2O_4$	10 ip[r]	55	45	43*	75 iv
15	H	Me	$COCH_2NC_4H_8NMe$[o]	3	B	208	MeOH	70	$C_{20}H_{25}N_3OS \cdot 2C_2H_2O_4$	10 ip[s]	45	30	38*	75 iv
16	H	H	$COCH_2NMe_2$	1	B	164.5	PrOH	81	$C_{16}H_{18}N_2OS \cdot C_2H_2O_4$					
17	H	H	$COCH_2NEt_2$	1	B	163.5-165	*i*-PrOH	50	$C_{18}H_{22}N_2OS \cdot C_2H_2O_4$	25 ip	30	47	22	45 iv[u]
18	H	H	$COCH_2N(CH_2)_4$[l]	1	B	106	*i*-PrOH	86	$C_{18}H_{20}N_2OS$					
19	H	H	$COCH_2NC_4H_8NMe$[o]	1	B	208	90% EtOH	43	$C_{19}H_{23}N_3OS \cdot 2C_2H_2O_4$					
20	Cl	H	$COCH_2NMe_2$	2	B	92.5	70% EtOH	68	$C_{16}H_{17}N_2OSCl$					
21	Cl	H	$COCH_2NEt_2$	2	B	166.5-167	80% EtOH	49	$C_{18}H_{21}N_2OSCl \cdot C_2H_2O_4$	25 ip	56	74	72*	45 iv[v]
22	Cl	H	$COCH_2N(CH_2)_4$[l]	2	B	193	PrOH	38	$C_{18}H_{19}N_2OSCl \cdot C_2H_2O_4$[y]					
23	Cl	H	$COCH_2N(CH_2)_5$[m]	2	B	76.5-77.5	*i*-PrOH	43	$C_{19}H_{21}N_2OSCl$					
24	Cl	H	$COCH_2NC_4H_8O$[n]	2	B	195.5	95% EtOH	48	$C_{18}H_{19}N_2O_2SCl \cdot C_2H_2O_4$					
25	Cl	H	$COCH_2NC_4H_8NMe$[o]	2	B	214	*i*-PrOH	38	$C_{19}H_{22}N_3OSCl \cdot 2C_2H_2O_4$					
26	Cl	Me	$COCH_2NMe_2$	4	B	185	*i*-PrOH	53	$C_{17}H_{19}N_2OSCl \cdot C_2H_2O_4$					
27	Cl	Me	$COCH_2NEt_2$	4	B	oil	*p*	30	*p*	10 ip	13	15	0	45 iv[w]
28	Cl	Me	$COCH_2NC_4H_8NMe$[o]	4	B	224.5	80% EtOH	79	$C_{20}H_{24}N_3OSCl \cdot 2C_2H_2O_4$					
29	H	Me	4-ClC_6H_4CO	3	C	101-101.5	PrOH	58	$C_{20}H_{16}NOSCl$	500 po	65	60	48*	>1000 po
30	H	Me	2-$AcOC_6H_4CO$	3	D	102.5	95% EtOH	47	$C_{22}H_{19}NO_3S$	500 po	59	55	32*	>1000 po

31	H	Me	c-$C_3H_5CO^z$	3	C	46–48	petr ether	53	$C_{17}H_{17}NOS$	500 po	57	48	37*	>1000 po
32	H	H	4-ClC_6H_4CO	1	C	193–193.5	*i*-PrOH	71	$C_{19}H_{14}NOSCl$					
33	H	H	2-$AcOC_6H_4CO$	1	D	110.5–111.5	c-C_6H_{12}/EtOH	46	$C_{21}H_{17}NO_3S$					
34	H	H	c-$C_3H_5CO^z$	1	C	151	80% EtOH	75	$C_{16}H_{15}NOS$					
35	Cl	H	4-ClC_6H_4CO	2	C	226–227	EtOH	42	$C_{19}H_{13}NOSCl_2$					
36	Cl	H	2-$AcOC_6H_4CO$	2	D	134–135	toluene	30	$C_{21}H_{16}NO_3SCl$					
37	Cl	H	c-$C_3H_5CO^z$	2	C	181–182	MeCOEt	40	$C_{16}H_{14}NOSCl$					
38	Cl	Me	4-ClC_6H_4CO	4	C	92	95% EtOH	40	$C_{20}H_{15}NOSCl_2$					
39	Cl	Me	2-$AcOC_6H_4CO$	4	D	96.5–97	*i*-PrOH	28	$C_{22}H_{18}NO_3SCl$					
40	Cl	H	H			32[q]	70% EtOH	80						
41	Cl	H	$COCH_2Cl$	40	A	127–128	PrOH	76						
42	Cl	H	$COCH_2NEt_2$	40	B	149.5–150.5	95% EtOH	50	$C_{18}H_{21}N_2OSCl \cdot C_2H_2O_4$	30 ip	65	63	68*	55 iv[x]
43	H	Me	Z = Me	3	E	179–180	xylene	38	$C_{19}H_{18}N_2O_3S$	200 po	36	0	0	>1000 po
44	H	Me	Z = *i*-Pr	3	E	162–163	xylene	48	$C_{21}H_{22}N_2O_3S$	200 po	30	26	18	>1000 po
45	H	Me	Z = Ph	3	E	186.5–187	xylene	29	$C_{24}H_{20}N_2O_3S$	200 po	36	5	0	>1000 po
46	H	H	Z = Me	1	F	105–106	EtOH	72	$C_{20}H_{20}N_2O_3S$					
47	H	H	Z = *i*-Pr	1	F	101–103	EtOH	61	$C_{22}H_{24}N_2O_3S$	200 po	22	30	30	>1000 po
indomethacin										10 ip	61	65	67*	

[a] The letter refers to general procedure given in the Experimental Section. [b] The yield of analytically pure compounds is given, unless otherwise noted, and, in most cases, no attempt was made to optimize the yields. [c] The compounds were analyzed, unless otherwise noted, for C, H, N, S and, where present, Cl and O; results are within ±0.04% of theoretical values. [d] An asterisk indicates that the result is significant on Student's *t* test at $p < 0.01$. [e] LD_{50}, approximative values, ten animals per dose. [f] Previously described, refs 6 and 11. [g] Previously described, ref 6. [h] Lit.[11] mp 115 °C. [i] Compound was not analyzed but used without further purification. [j] Crude yield. [k] The compound crystallized by trituration with Et_2O. [l] $N(CH_2)_4$ = pyrrolidino. [m] $N(CH_2)_5$ = piperidino. [n] NC_4H_8O = morpholino. [o] $NC_4H_8NCH_3$ = 4-methylpiperazino. [p] See Experimental Section. [q] Lit.[2] bp (0.05 mm) 135–140 °C. [r] 5 mg ip, 24, 31, and 33% reduction. [s] 5 mg ip, 24, 27, and 32% reduction. [t] LD_{50} ip = 140 mg ± 40. [u] LD_{50} ip = 275 mg ± 25. [v] LD_{50} ip = 275 mg ± 25. [w] LD_{50} ip = 175 mg ± 45. [x] LD_{50} ip = 350 mg ± 50. [y] Analyzed only for CHNO. [z] c-C_3H_5 = cyclopropyl.

Scheme I

Scheme II

2-nicotinic acid,[2] had, in the rat paw carrageenin test, significant antiinflammatory activity relative to the standard indomethacin and was less toxic (LD_{50} to mice 10 times ED_{50} to rats). In recent years, a number of nonacidic antiinflammatory agents with an amino or an amido group have been reported, like fluoroalkanesulfonanilides[3a] or some aminopyrimidines.[3b] In addition, in a few cases the reported compounds had an ether structure, like I,[4] or a thioether structure, like cinanserin II.[5] In the present work, we describe the synthesis and the antiinflammatory activity of amides with diphenyl sulfide groups III–V (Table I). Table I lists the compounds prepared, together with the physical data and biological activity.

Chemistry. The starting materials required for the synthesis were 4-(phenylthio)phenylamine (**1**),[6] 4-[(4-chlorophenyl)thio]phenylamine (**2**),[6] 2-[(4-chlorophenyl)-thio]phenylamine (**40**),[2] *N*-methyl-4-(phenylthio)phenylamine (**3**),[6] and *N*-methyl-4[(4-chlorophenyl)thio]-phenylamine (**4**). Compound **4** was prepared from **2** and trimethyl orthoformate, via the formyl derivative **5**[6] (Scheme I).

Syntheses of compounds **43–47** were performed by using 4-carbethoxy-2,3-dioxopyrrolidines which were prepared by a literature procedure.[7,8] Reaction of 4-carbethoxy-

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(2) A. Marcincal-Lefebvre, J. C. Gesquiere, G. Bethegnies, B. Dupuis, A. Vincent, and C. Lemer, *Ann. Pharm. Fr.*, **38**, 243 (1980).
(3) (a) J. K. Harrington, J. E. Robertson, D. C. Kvam, R. R. Hamilton, K T. McGurran, R. J. Trancik, K. F. Swingle, G. G. I. Moore, and J. F. Gerster, *J. Med. Chem.*, **13**, 137 (1970). (b) S. A. Lang, Jr., and E. Cohen, *J. Med. Chem.*, **18**, 623 (1975).
(4) W. S. Marshall, British Patent (to Eli Lilly and Co.) 1 377 480 (1974).
(5) R. C. Millonig, B. J. Amrein, J. Kirschbaum, and S. M. Hess, *J. Med. Chem.*, **17**, 772 (1974).
(6) D. Bar, A. Marcincal-Lefebvre, and J. C. Gesquiere, *Ann. Pharm. Fr.*, **38**, 161 (1980).

2,3-dioxopyrrolidines (Scheme II) with *N*-methyl-4-(phenylthio)phenylamine (**3**) gave us amides **43** (Z = Me), **44** (Z = *i*-Pr), and **45** (Z = Ph). In our hands, using the primary amine 4-(phenylthio)phenylamine (**1**) did not give us amides but rather enamines **46** and **47**. Other compounds were prepared by standard methods of organic chemistry. Further details are available in Table I.

Pharmacology. Compounds were tested for LD_{50} and for their antiinflammatory activity using the carrageenin-induced paw edema method[9,10] (see Experimental Section and results in Table I).

We first tested aminoacetyl compounds **10–15** (III, R = Me), the activity of which could not be attributed to the presence of an acidic hydrogen. Modification of the amino group changed the activity: the best results were obtained with a morpholino group (**14**), and especially with a diethylamino group (**11**) (55% edema inhibition at a dose of 5 mg/kg ip; i.e., one-thirtieth of LD_{50} ip). Then, other compounds with diethylamino groups were tested, to give us the following results: the loss of the methyl group of **11** to give **17**, which possesses an amidic hydrogen, caused a slight decrease in activity and, paradoxically, introduction of a chlorine atom on the structure **11** gave us the nearly inactive product **27**, whereas chlorination of the nonmethylated compound **17** gave us **21** that, like its ortho isomer **42**, exhibited a good dose–response (one-fifteenth of LD_{50} ip) with an activity comparable with the standard indomethacin. Compounds **21** and **42**, which exhibited the best activity when injected intraperitoneally, were tested when administered by gavage, but they did not exhibit any activity (at 50, 100, and 200 mg/kg po). Among insoluble compounds **29–31**, **43–45**, and **47**, only **29** exhibited a significant activity. Other compounds were not tested. For active compounds, experimental results were controlled by a Student's *t* test.

Experimental Section

All melting points were determined using a Tottoli melting point apparatus and are uncorrected. The structures of all compounds (as free bases) were consistent with their IR and NMR spectra. Purity of all products was established by demonstrating a single spot on TLC. Reactions were monitored by TLC, using Merck 60 F 254 silica gel plastic sheets. Preparations of compounds **1–3**[6] and **40**[2] have been reported.

***N*-Formyl-*N*-methyl-4-[(4-chlorophenyl)thio]phenylamine (5).** A mixture of 20 g (0.08 mol) of 4-[(4-chlorophenyl)thio]-phenylamine (**2**), 12.8 g (0.12 mol) of trimethyl orthoformate, and 0.26 mL of concentrated sulfuric acid was heated by an oil bath to 120 °C and then the MeOH produced was distillated. Trimethyl orthoformate (5 mL) was added twice, while heating was continued, until there was no primary amine in the mixture (TLC). The still head was then replaced by a refluxing column, 5 mL of trimethyl orthoformate was added, and the temperature was raised to 170 °C. After heating for 3 h, the excess of ortho ester was distillated under reduced pressure, to give crude **5** which will be used to prepare compound **4**. An analytical sample can be prepared by recrystallization from cyclohexane.

***N*-Methyl-4-[(4-chlorophenyl)thio]phenylamine (4).** The crude **5** was added to 5 mL of concentrated HCl and 20 mL of H_2O and heated to reflux during 4 h. The cooled reaction mixture was treated with 15% NaOH until basic and extracted with Et_2O. The ether solution was washed, dried (Na_2SO_4), and added to a solution of an excess of oxalic acid in Et_2O. The precipitated oxalic salt was recrystallized from 95% EtOH. Compound **4** was obtained as a free base from its oxalic salt and 15% NaOH.

***N*-(Chloroacetyl)-4-[(4-chlorophenyl)thio]phenylamine (8). Procedure A.** To a solution of 9.4 g (0.04 mol) of **2**, in 30 mL of AcOH, was added dropwise 4 mL (0.05 mol) of chloroacetyl chloride in 4 mL of AcOH. After 60 min, the resulting precipitate was collected and washed thoroughly with water to give 10.5 g of **8** (84%), mp 142 °C, which was used without further purification in subsequent reactions. An analytical sample was prepared by recrystallization from PrOH, mp 145 °C.

Other substituted chloroacetyl derivatives (**6**, **7**, **9**, and **41**) were obtained in the same way from the appropriate amines and chloroacetyl chloride.

***N*-[(Diethylamino)acetyl]-4-[(4-chlorophenyl)thio]-phenylamine (21). Procedure B.** A mixture of 1.9 g (0.006 mol) of **8** and 10 mL of diethylamine was stirred with refluxing for 2 h and then at room temperature overnight. After evaporation under reduced pressure, the residual oil was added to 50 mL of Et_2O. The resulting solution was washed three times with H_2O, dried (Na_2SO_4), and added dropwise to a stirred solution of an excess of oxalic acid in Et_2O. The white, flocculent crystals were filtered, washed with Et_2O, and recrystallized from EtOH–H_2O to give 0.9 g of **21** (oxalic salt) (49%).

Compounds **18**, **20**, and **23**, after evaporating the reaction mixture, were obtained as crystallized free base products; purification was then continued by recrystallizing them as free bases.

Compound **27** gave us an oily free base and a pastly oxalic salt. It was purified by performing the sequence free base/oxalic salt/free base three times to give us a product, the purity of which was established by TLC and IR and NMR spectra.

***N*-(4-Chlorobenzoyl)-4-(phenylthio)phenylamine (32). Procedure C.** To a stirred solution of 2 g (0.01 mol) of **1** in 15 mL of AcOH was added dropwise a solution of 1.75 g (0.01 mol) of 4-chlorobenzoyl chloride in 15 mL of AcOH. After 15 min the precipitated product was collected by filtration, washed three times with AcOH, and recrystallized from *i*-PrOH to give 2.4 g of **32** (71%), mp 193–193.5 °C.

This procedure was followed to prepare compounds **29**, **35**, and **38** from the appropriate amines and 4-chlorobenzoyl chloride, while compounds **31**, **34**, and **37** were obtained using cyclopropylcarbonyl chloride.

***N*-[2-(Acetyloxy)benzoyl]-4-(phenylthio)phenylamine (33). Procedure D.** A solution of 3.5 g (0.018 mol) of acetylsalicyloyl chloride in 25 mL of Et_2O was added dropwise to a stirred solution of 3 g (0.015 mol) of **1** and 1.2 mL (0.015 mol) of pyridine in 40 mL of Et_2O. After 2 h, the solid product was collected by filtration and recrystallized, once in EtOH, once in EtOH–cyclohexane, and twice in *i*-PrOH to give 2.5 g of **33** (46%), mp 111 °C.

Compounds **30**, **36**, and **39** were prepared in the same way, using acetylsalicyloyl chloride and appropriate amines.

***N*-Methyl-*N*-[(4-phenylthio)phenyl]-2,3-dioxo-1-methylpyrrolidine-4-carboxamide (43). Procedure E.** To a boiling mixture of 2 g (0.011 mol) of 4-carbethoxy-2,3-dioxo-1-methylpyrrolidine in 10 mL of xylene was added dropwise a solution of 2.36 g (0.011 mol) of **3** in 10 mL of boiling xylene, and refluxing was continued for 1 h. As the solution was heating, the solvent was slowly removed by means of a still head and xylene was added occasionally, in order to maintain a volume greater than 15 mL. The mixture was then poured into 10 mL of petroleum ether and cooled. A precipitate formed which was filtered, dried, and recrystallized from xylene to give 1.5 g (40%) of **43**, mp 179–180 °C.

Compounds **44** and **45** were similarly obtained from **3** and appropriate 1-substituted 4-carbethoxy-2,3-dioxopyrrolidines. Treating the same amount of the primary amine **1** gave us enamines **46** and **47** in poor yields.

4-Carbethoxy-1-methyl-2-oxo-3-[[4-(phenylthio)phenyl]-amino]-3-pyrroline (46). Procedure F. A stirred solution of 2 g (0.011 mol) of 4-carbethoxy-2,3-dioxo-1-methylpyrrolidine and 2.2 g (0.011 mol) of **1** in 50 mL of EtOH was refluxed for 48 h. The resulting mixture was then concentrated under reduced pressure to 25 mL. After the mixture cooled, the solid material was collected by filtration, dried, and recrystallized from EtOH to give 2.9 g of **46** (72%), mp 105–106 °C.

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Secondary arylalkylamines, like 3, did not react in our hands to give formation of enamines.

Pharmacological Methods. Antiinflammatory activity was measured by the method of Winter. Fifteen male Wistar rats weighing 170–220 g were used for each group. Compounds having amino groups in their structures were injected intraperitoneally as their soluble oxalic salts. Insoluble compounds were administered by gavage. Thirty minutes later, carrageenin (0.05 mL, 1%) in physiological saline was injected subcutaneously under the plantar skin of the hind paw. The volume of the injected paw was measured just before (T_0) and 1, 2, and 3 h after the injection of carrageenin for calculation of percent inhibition (Table I).

Nucleosides. 114. 5′-*O*-Glucuronides of 5-Fluorouridine and 5-Fluorocytidine. Masked Precursors of Anticancer Nucleosides[1]

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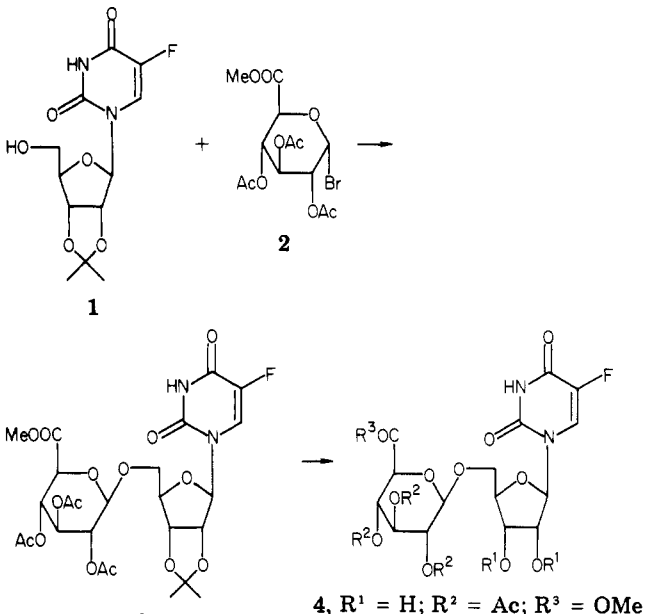
5′-*O*-Glucuronides of anticancer nucleosides, 5-fluorouridine and 5-fluorocytidine, were synthesized by three different methods. The best preparative procedure was the one starting from benzyl 5-*O*-(methyl 2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosyluronate)-2,3-*O*-isopropylidene-β-D-ribofuranoside (15) that was obtained almost quantitatively by condensation of benzyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (8) with methyl (2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate (2). After de-O-isopropylidenation of 15, the crystalline product, benzyl 5-*O*-(methyl 2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosyluronate)-β-D-ribofuranoside (16), was de-O-benzylated catalytically to 5-*O*-(methyl 2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosyluronate)-D-ribofuranose (17). Compound 17 was acetylated to crystalline 5-*O*-(methyl 2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosyluronate)-1,2,3-tri-*O*-acetyl-β-D-ribofuranose (18) and condensed with trimethylsilylated 5-fluorouracil of 5-fluorocytosine in the presence of $SnCl_4$ to afford the corresponding protected nucleosides 5 and 19 in good yields. Saponification of these compounds gave 5′-*O*-β-D-glucuronides of 5-fluorouridine and 5-fluorocytidine (20 and 21) isolated as their crystalline Na salts. These glucuronides were substrates of both bacterial and bovine β-glucuronidase. They were, as expected, much less toxic against several leukemic cell lines in tissue culture.

Elevated β-glucuronidase activity in malignant human tumors was first reported by Fishman et al.[2] Subsequently, many reports up to 1966 were reviewed by Levvy and Conchie[3] showing that the activity of this enzyme in human cancer tissues is extraordinarily high, relative to normal tissues. Sweeney et al.[4] later showed that mycophenolic acid, a compound which inhibits mecca lymphosarcoma and CA-755 mammary carcinoma, is converted into the glucuronide as the only metabolite. They also showed[4] that, in general, the tumors most responsive to mycophenolic acid are those in which β-glucuronidase activity is highest, while it is the lowest in nonresponsive tumors. Conners et al.[5] demonstrated that the *N,N*-bis-(2-chloroethyl)aniline is oxidized in vivo to the corresponding 4-hydroxy derivative, which is then converted into its glucuronide. This aromatic nitrogen mustard is uniquely effective against the mouse ADJ/PCS plasma cell tumor which exhibits particularly high levels of β-glucuronidase activity.[6]

5-Fluorouracil (FU) is a potent agent presently used in the treatment of certain solid tumors.[7] The corresponding ribonucleoside (FUR)[8] and deoxyribonucleoside (FUDR)[9] are also active. These compounds are converted in vivo into FUDR-5′-P, which then interferes with thymidylate

Scheme I



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