clusion of a σ^+ term excludes II as an important species in the rate-determining step unless the transition state is "late" and essentially resembles IV.

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Synthesis and Structure–Activity Relationships of Fibrinolytic 1,ω-Diphenyl-1,ω-alkanediamines

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The promising results obtained in animal clot lysis experiments with the fibrinolytic bis(tetrahydroisoquinolines) VI prompted the preparation of a related series of 1,ω-diphenyl-1,ω-alkanediamines V. As measured in the standard rat screen (ip) the compounds were found to possess similar fibrinolytic activity. Structural variations discussed include N-substitution, aromatic substitution pattern, and chain length. The three-step synthesis generally involved Friedel–Crafts acylation of an aromatic compound I with a dibasic acid chloride II to yield a bis(ketone) III. The bis(oxime) or bis(methoxime) derivatives IV of the latter were then reduced to the corresponding V.

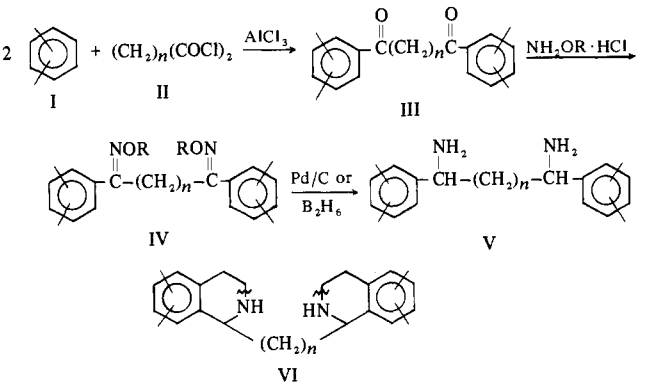
One of the goals of antithrombotic therapy is the development of effective, readily available, fibrinolytic-thrombolytic agents for both acute and prophylactic use. The encouraging results obtained in animal clot lysis experiments with the synthetic bis(tetrahydroisoquinolines) VI† have been described previously along with their structure-activity relationships.[1] Continued molecular modification in this area has uncovered a series of 1,ω-diphenyl-1,ω-alkanediamines V with similar fibrinolytic potential. Their relationship to the bis(tetrahydroisoquinolines) VI may be envisaged by formally cleaving the 2-3 bonds in the heterocyclic rings of the latter.

In general, the potencies of the two classes of compounds were comparable in the standard rat screen, although the most potent VI was approximately six times more active than the most potent V. A limited number of V have been reported previously;[2,3] however, our literature searches have revealed no detailed pharmacological investigations on this class of compounds.

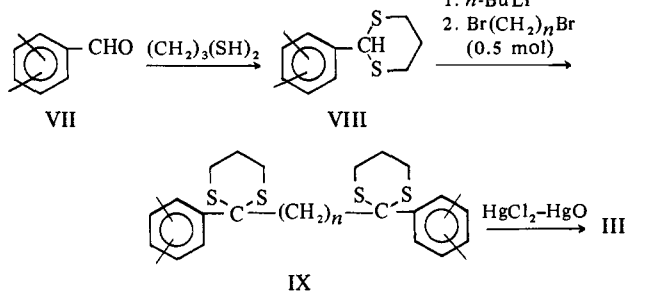
Chemistry. The general synthetic route (Scheme I) to bis(amines) V has been described previously;[2,3] and with suitable modifications depending on the nature of the aromatic substituents, this approach has been consistently employed.

The bis(ketones) III were generally available *via* Friedel-Crafts acylation of 2 mol of the aromatic compound I with 1 mol of a dibasic acid chloride II (Table I, methods A, B, and C). Tetrachloroethane was found to be an excellent solvent for most of these reactions, frequently giving better yields and purer products than literature procedures using either no solvent or other standard solvents (*cf.* Table I). Since acylation of aromatic compounds bearing two different activating substituents would yield a mixture of

Scheme I



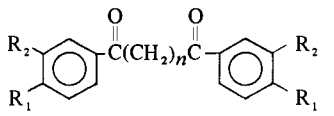
Scheme II



products, the ketones **11–13** were prepared by the Corey dithiane procedure.[4] As shown in Scheme II, the substituted aromatic aldehydes VII were converted to their dithiane derivatives VIII by reaction with 1,3-propanedithiol. Alkylation of 2 mol of VIII with 1 mol of the appropriate 1,ω-dibromoalkane in the presence of 2 mol of *n*-butyllithium yielded the bis(dithianes) IX which were in turn hydrolyzed to the desired bis(ketones) III.[5] The dithiane procedure was also used for the synthesis of **1**, since attempted Friedel-

†Roman numerals refer to Schemes I and II and arabic numerals refer to compounds in the tables.

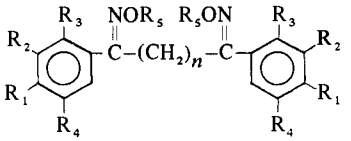
Table I[a]



No.	n	R_1	R_2	Method[b]	Yield, %[c]	Recrystn solvent	Mp, °C	Formula[d]
1	3	MeO	MeO	D	85	EtOH	120-121[e]	$C_{21}H_{24}O_6$
2	4	MeO	MeO	A	68	PhH	149-150	*f*
3	5	MeO	MeO	A	68	MeOH	91-93[g]	$C_{23}H_{28}O_6$
4	6	MeO	MeO	A	63	MEK	141-143[h]	$C_{24}H_{30}O_6$
5	7	MeO	MeO	A	66	EtOAc	98-100[i]	$C_{25}H_{32}O_6$
6	4	MeO	H	A	55	EtOAc	144-146	*j*
7	4	$O\text{-}CH_2\text{-}O$		C	11	$PhCH_3$	179-180[k]	$C_{20}H_{18}O_6$
8	4	EtO	EtO	A	39	EtOH	132-134	$C_{26}H_{34}O_6$
9	4	*n*-PrO	*n*-PrO	A	48	PhH	144-146	$C_{30}H_{42}O_6$
10	4	*n*-BuO	*n*-BuO	A	61	PhH	123-125	$C_{34}H_{50}O_6$
11	4	EtO	MeO	D	85	95% EtOH	130-131	$C_{24}H_{30}O_6$
12	4	$PhCH_2O$	MeO	D	70	PhH	163-164	$C_{34}H_{34}O_6$
13	4	MeO	Me	D	81	$MeOCH_2CH_2OH$	160-161	$C_{22}H_{26}O_4$
14	4	Me	Me	B	86	$MeOCH_2CH_2OH$	126-127	$C_{22}H_{26}O_2$
15	4	$-(CH_2)_4-$		B	65	EtOH	91-92	*l*
16	*m*	MeO	MeO	A	38	EtOH	91-94	$C_{23}H_{28}O_6$
17	*n*	MeO	MeO	A	56	$MeOCH_2CH_2OH$	184-188	$C_{26}H_{26}O_6$[o]

[a]For the synthesis of intermediates which are not described, see ref 9, S. Skraup and S. Guggenheimer, *Ber.*, 58B, 2488 (1925), and U. Ulfvarson, *Acta Chem. Scand.*, 12, 1342 (1958). [b]See Experimental Section. [c]One recrystallization. [d]Unless indicated, satisfactory analyses were obtained for C and H. [e]M. Pailer and W. Reifschneider, *Monatsh. Chem.*, 84, 585 (1953), mp 121°. [f]O. Gisvold, D. Buelow, and E. H. Carlson, *J. Amer. Pharm. Ass.*, 35, 188 (1946), mp 149-150°. [g]D. Chakravarti and M. Saha, *Sci. Cult.*, 35, 333 (1969); *Chem. Abstr.*, 72, 100224f (1970), mp 95°. [h]Footnote *g*, mp 143°. [i]Footnote *g*, mp 102°. [j]R. C. Fuson, S. B. Kuykendall, and G. W. Wilhelm, *J. Amer. Chem. Soc.*, 53, 4187 (1931), mp 141.5-142.5°. [k]C. M. Samour and J. P. Mason, *J. Amer. Chem. Soc.*, 76, 441 (1954), mp 179.4-180.4°. [l]B. Bannister and B. B. Elsner, *J. Chem. Soc.*, 1055 (1951), mp 91-92°. [m]$(CH_2)_n$ = $CH_2CH_2CH(CH_3)CH_2$. [n]$(CH_2)_n$ = *p*-xylylene. [o]C: calcd, 71.87; found, 71.38.

Table II[a]



No.	n	R_1	R_2	R_3	R_4	R_5	Method[b]	Yield, %[c]	Recrystn solvent	Mp, °C	Formula[d]
18	3	MeO	MeO	H	H	Me	A	93	EtOH	112-114	$C_{23}H_{30}N_2O_6$
19	4	MeO	MeO	H	H	H	A	88	95% EtOH	151-153	$C_{22}H_{28}N_2O_6$
20	5	MeO	MeO	H	H	H	B	71	EtOH	115-117	$C_{23}H_{30}N_2O_6$
21	6	MeO	MeO	H	H	H	A	85	EtOH	140-143	$C_{24}H_{32}N_2O_6$
22	7	MeO	MeO	H	H	H	B	62	EtOH	108-110	$C_{25}H_{34}N_2O_6$
23	4	Cl	H	H	H	H	A	85	$EtOCH_2CH_2OH$	227-229	$C_{18}H_{18}Cl_2N_2O_2$
24	4	$O\text{-}CH_2\text{-}O$		H	H	Me	A	87	EtOH	117-121	$C_{22}H_{24}N_2O_6$
25	4	EtO	EtO	H	H	H	A	75	EtOH	135-139	$C_{26}H_{36}N_2O_6$
26	4	*n*-PrO	*n*-PrO	H	H	H	A	76	90% EtOH	142-143	$C_{30}H_{44}N_2O_6$
27	4	*n*-BuO	*n*-BuO	H	H	H	A	69	95% EtOH	123-124	$C_{34}H_{52}N_2O_6$
28	4	EtO	MeO	H	H	H	A	94	$MeOCH_2CH_2OH$	187-189	$C_{24}H_{32}N_2O_6$
29	4	$PhCH_2O$	MeO	H	H	Me	A	81	EtOH-PhH	125-126	$C_{36}H_{40}N_2O_6$
30	4	MeO	Me	H	H	H	A	80	$MeOCH_2CH_2OH$	178-179	$C_{22}H_{28}N_2O_4$
31	4	Me	Me	H	H	H	A	88	$MeOCH_2CH_2OH$	176-178	$C_{22}H_{28}N_2O_2$
32	4	$-(CH_2)_4-$		H	H	H	A	94	$MeOCH_2CH_2OH$	187-190	$C_{26}H_{32}N_2O_2$
33	4	H	H	MeO	MeO	Me	A	75	MeOH	85-90	$C_{24}H_{32}N_2O_6$
34	*e*	MeO	MeO	H	H	H	B	55	EtOH	127-130	$C_{23}H_{30}N_2O_6$
35	*f*	MeO	MeO	H	H	H	A	50	*i*-PrOH	198-200	$C_{26}H_{28}N_2O_6$

[a]For the synthesis of intermediates which are not described, see ref 2 and footnote *j*, Table I. [b]See Experimental Section. [c]One recrystallization. [d]Satisfactory analyses were obtained for C, H, and N. [e]$(CH_2)_n$ = $CH_2CH_2CH(CH_3)CH_2$. [f]$(CH_2)_n$ = *p*-xylylene.

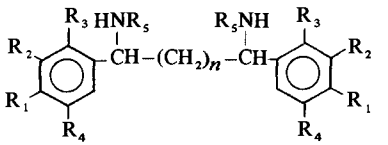
Crafts acylation of veratrole with glutaryl chloride under various conditions gave poor results.

Conversion of the bis(ketones) III to the bis(oximes) IV (R = H) or bis(methoximes) IV (R = Me) was effected in the usual manner. In several cases crystalline oximes (**20**, **22**, **34**) could be obtained readily only when the reaction was carried out with aqueous ethanol-sodium acetate in place of the standard ethanol-pyridine system (Table II).

Reduction of the bis(oximes) IV (R = H) to the bis(amines) V was accomplished smoothly with 10% Pd/C in glacial acetic acid at room temperature and moderate pressure. Where it was anticipated that the aromatic substituents would be labile to hydrogenation conditions, the bis(amines) V (*e.g.*, **43** and **49**) were prepared by diborane reduction of the bis(methoximes) IV (R = Me) or bis(oxime acetates) IV (R = Ac).[6,7] The diborane procedure also served for the preparation of the bis(amine) **53** since catalytic reduction of the corresponding bis(oxime) was extremely sluggish.

Two secondary amines, **56** and **57**, were synthesized from the corresponding primary amines, **38** and **41**, respectively, by standard methods and submitted to fibrinolytic evaluation.

Table III[a]



No.	n	R_1	R_2	R_3	R_4	R_5	Method[b]	Yield, %[c]	Recrystn solvent	Mp, °C[d]	Formula[e]	ED_{50}, mg/kg[f]
36	3	MeO	MeO	H	H	H	B	45	95% EtOH–EtOAc	275–276 dec	$C_{21}H_{32}Cl_2N_2O_4$	1.5
37	4	MeO	MeO	H	H	H	A	46	MeOH–Et_2O	286–288 dec	$C_{22}H_{34}Cl_2N_2O_4$	0.4
38	5	MeO	MeO	H	H	H	A	52	95% EtOH–EtOAc	254–255 dec	$C_{23}H_{36}Cl_2N_2O_4$	0.4
39	6	MeO	MeO	H	H	H	A	30	MeOH–EtOAc	284–287 dec	$C_{24}H_{38}Cl_2N_2O_4$	15
40	7	MeO	MeO	H	H	H	A	54	MeOH–EtOH	284–286 dec	$C_{25}H_{40}Cl_2N_2O_4$	2
41	4	H	H	H	H	H	A	33	95% EtOH	>360[g]	$C_{18}H_{26}Cl_2N_2$	19
42	4	MeO	H	H	H	H	A	39	Aqueous EtOH–EtOAc	270–272 dec	$C_{20}H_{30}Cl_2N_2O_2$	<12
43	4	Cl	H	H	H	H	C	45	95% EtOH–Et_2O	301–303 dec	$C_{18}H_{24}Cl_4N_2$	6
44	4	$O\text{-}CH_2\text{-}O$		H	H	H	B	53	95% EtOH–EtOAc	259–260 dec	$C_{20}H_{26}Cl_2N_2O_4$	>50
45	4	EtO	EtO	H	H	H	A	25	EtOH	253–255 dec	$C_{26}H_{42}Cl_2N_2O_4$	0.3
46	4	*n*-PrO	*n*-PrO	H	H	H	A	18	95% EtOH	243–245 dec	$C_{30}H_{50}Cl_2N_2O_4$	5
47	4	*n*-BuO	*n*-BuO	H	H	H	A	27	Aqueous EtOH	208–209	$C_{34}H_{58}Cl_2N_2O_4\text{-}0.5H_2O$	5
48	4	EtO	MeO	H	H	H	A	29	Aqueous EtOH	247–249	$C_{24}H_{38}Cl_2N_2O_4$	0.4
49	4	$PhCH_2O$	MeO	H	H	H	B	50	EtOH–*i*-PrOH	170–172	$C_{40}H_{52}N_2O_{10}$	5
50	4	MeO	Me	H	H	H	A	45	95% EtOH	273–274 dec	$C_{22}H_{34}Cl_2N_2O_2$	10–25
51	4	Me	Me	H	H	H	A	39	EtOH	273–274 dec	$C_{22}H_{34}Cl_2N_2$	4
52	4	$\text{-}(CH_2)_4\text{-}$		H	H	H	A	20	95% EtOH	298–300 dec	$C_{26}H_{38}Cl_2N_2$	8
53	4	H	H	MeO	MeO	H	B	54	EtOH–EtOAc	228–230	$C_{22}H_{34}Cl_2N_2O_4$[h]	>25
54	*i*	MeO	MeO	H	H	H	A	39	*i*-PrOH–EtOAc	238–240 dec	$C_{23}H_{36}Cl_2N_2O_4\text{-}0.5H_2O$	<1
55	*j*	MeO	MeO	H	H	H	A	22	95% EtOH–Et_2O	267–269 dec	$C_{26}H_{34}Cl_2N_2O_4\text{-}H_2O$	1
56	5	MeO	MeO	H	H	Me	D	27	MeOH–EtOAc	254–256 dec	$C_{25}H_{40}Cl_2N_2O_4$	>50
57	4	H	H	H	H	Me	D	41	EtOH–Et_2O	274–276	$C_{20}H_{30}Cl_2N_2$	>50
Serotonin												1
EN-1661[k]												0.3

[a]All compounds are in the form of dihydrochloride salts, except **49** (dilactate salt). [b]See Experimental Section. [c]One recrystallization. [d]Analytical sample. [e]Satisfactory analyses were obtained for C, H, and N. [f]For mixture of isomers, except for serotonin and EN-1661. [g]Reference 3, mp 330°. [h]H: calcd, 7.43; found, 7.01. [i]$(CH_2)_n = CH_2CH_2CH(CH_3)CH_2$. [j]$(CH_2)_n$ = *p*-xylylene. [k]*meso*-1,1'-Tetramethylenebis(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline) dilactate. See ref 2.

Except for **54** which has an additional asymmetric center, each of the diphenylalkanediamines (Table III) has two centers of asymmetry which are identical and which give rise to meso, D, and L forms. In all cases the crude mixtures of isomeric dihydrochloride salts resulting from the reduction step were purified by recrystallization from suitable solvents (Table III). Recrystallization was often difficult and frequently entailed considerable loss of product due to the differing solubilities of the component isomers. This is reflected in the moderate yields (after one recrystallization) reported in Table III; however, crude yields varied between 50 and 90%. As expected, the melting points of the crude (not reported) and recrystallized dihydrochloride salts frequently showed wide separation.

Biological Evaluation. In no case was an attempt made to separate the pure meso and DL forms. For testing purposes the crude mixture of isomeric dihydrochloride salts was recrystallized once or twice. The ED_{50} values reported in Table III are therefore for compounds whose isomeric composition will vary between a 1:1 mixture of the meso and DL forms and 100% of the less soluble isomer. In our animal screen, previous work in the area of the related, fibrinolytic bis(tetrahydroisoquinolines) has shown, in two cases, that the potencies of the pure meso and pure DL forms do not differ significantly.[1]

The testing protocol was identical with that described in previous articles.[1,8] The ED_{50} (mg/kg) represents that dose which causes 50% of the rat clot to lyse in a standard period of time (4 hr). A minimum of three rats was used for each ip dose. Base line fibrinolytic activity was determined by injection of vehicle in place of the test compound. Serotonin was used as the standard for synthetic agents.[8]

Structure-Activity Relationships. Once it was established that a primary amino function was vastly more effective in imparting fibrinolytic activity than a secondary amino function (*cf.* **38** and **41** *vs.* **56** and **57**), structural variants were selected for synthesis and evaluation largely on the basis of prior experience with the bis(tetrahydroisoquinolines) VI.[1] Thus, emphasis was placed upon bis(amines) V with methylene group chains of moderate length and aromatic substitution patterns consisting of one or more alkoxy groups suitably situated meta and/or para to the aminoalkyl side chain. In several cases the biological data are incomplete (**42**, **50**, **54**) and these examples are not included in the discussion.

The series **36–40** illustrates the effect of varying the distance between the two benzylamine moieties while maintaining a constant aromatic substitution pattern. Activity reached a maximum at four or five methylene groups and declined as the chain was either lengthened or shortened. At present no suggestion can be advanced for the abrupt decrease in potency for **39**.

Since the methylene chains are flexible, under the demands of a biological substrate the amino functions could adopt a variety of conformations with respect to one another. However, even with the more rigid *p*-xylylene bridge in **55**, substantial fibrinolytic activity was retained.

Activity was affected by the number, type, and position of substituents on the aromatic rings. For a constant chain length of four methylene groups, the following order of decreasing activity was observed: 3,4-$(EtO)_2 \cong$ 3,4-$(MeO)_2 \cong$ 3-MeO, 4-EtO > 3,4-$(Me)_2$ > 3,4-(*n*-PrO)$_2 \cong$ 3,4-(*n*-BuO)$_2 \cong$ 3-MeO, 4-$PhCH_2O$ > 4-Cl > 3,4-$(CH_2)_4$ > unsubstituted > 2,6-$(MeO)_2 \cong$ 3,4-(CH_2O_2).

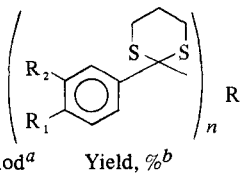
Experimental Section

Unless otherwise stated, the yields, melting points, recrystallization solvents, and elemental analyses for all compounds are given in Tables I–IV. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Ir spectra (Nujol mulls) were measured on a Perkin-Elmer Model 137 spectrometer. Absorption bands were as expected. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. EtOH refers to a commercial 2B grade of absolute EtOH.

Ketones (Table I). Method A. The following procedure is typical of the reaction conditions employed. A stirred solution of 151.8 g (1.1 mol) of veratrole in 750 ml of dry tetrachloroethane was maintained at −10 to 0° while 159.6 g (1.2 mol) of anhydrous $AlCl_3$ was added in portions. With stirring and cooling at 0–3°, 98.5 g (0.5 mol) of pimeloyl chloride was then added dropwise during 2 hr. After stirring in the same temperature range for an additional 4 hr, the mixture was poured slowly into a large beaker containing 1 kg of crushed ice, 125 ml of H_2O, and 125 ml of concentrated HCl. During this addition, a further 1 kg of crushed ice was added in portions to ensure that the temperature remained <0°. After stirring for an additional 15 min at <0°, the mixture was warmed to room temperature and, if necessary, sufficient $CHCl_3$ was added to give two clear layers. The aqueous layer was withdrawn and further extracted with 400 ml of $CHCl_3$ and the combined organic extracts were washed successively with H_2O (1 × 300 ml), 10% K_2CO_3 (4 × 300 ml), and H_2O (3 × 300 ml). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to dryness, and the solid residue was triturated with Et_2O to remove the excess veratrole and the last traces of tetrachloroethane. After filtering, washing, and drying the crude 3 was recrystallized.

For compounds 2, 6, and 8, instead of stirring for 4 hr at 0–3°,

Table IV



No.	*n*	R	R_1	R_2	Method[a]	Yield, %[b]	Recrystn solvent	Mp, °C	Formula[c]
58	1	-H	MeO	MeO	A	84	EtOH	92–93	$C_{12}H_{16}O_2S_2$
59	1	-H	EtO	MeO	B	85	EtOH	89–90	$C_{13}H_{18}O_2S_2$
60	1	-H	$PhCH_2O$	MeO	A	84	EtOAc	118–119	$C_{18}H_{20}O_2S_2$[d]
61	1	-H	MeO	Me	B	88	EtOH	81–82	$C_{12}H_{16}OS_2$
62	2	$-(CH_2)_3-$	MeO	MeO	C	65	EtOH	117–118	$C_{27}H_{36}O_4S_4$[e]
63	2	$-(CH_2)_4-$	EtO	MeO	C	78	$MeOCH_2CH_2OH$	145–147	$C_{30}H_{42}O_4S_4$[f]
64	2	$-(CH_2)_4-$	$PhCH_2O$	MeO	C	45	$ClCH_2CH_2Cl$-EtOH	177–179	$C_{40}H_{46}O_4S_4$
65	2	$-(CH_2)_4-$	MeO	Me	C	77	$MeOCH_2CH_2OH$	167–168	$C_{28}H_{38}O_2S_4$[g]

[a] See Experimental Section. [b] One recrystallization. [c] Unless indicated, satisfactory analyses were obtained for C, H, and S. [d] C and H analyzed only. [e] S: calcd, 23.20; found, 22.78. [f] C: calcd, 60.56; found, 60.16. [g] C: calcd, 62.87; found, 63.29.

the reaction mixture was packed in ice and stirred overnight while the ice melted. For compounds 9 and 10, stoichiometric amounts of the reactants were used. For compound 17, the solid acid chloride was added as a concentrated solution in tetrachloroethane. The reaction mixture was stored overnight in the refrigerator prior to work-up.

Method B. The procedure[9] for the preparation of 1,6-diphenyl-1,6-hexanedione was adapted for the synthesis of compounds 14 and 15 by substituting *o*-xylene and tetrahydronaphthalene, respectively, for PhH. The reaction mixtures were worked up as described in method A.

Method C. A solution of 75.6 g (0.62 mol) of methylenedioxybenzene and 55 g (0.3 mol) of adipoyl chloride in 750 ml of CS_2 was stirred and maintained at 0–5° while 97 g (0.73 mol) of anhydrous $AlCl_3$ was added in portions over the course of 1 hr. After stirring for an additional 1 hr at 0–3°, the CS_2 was decanted from the dark red-brown gummy complex. The latter was cooled (ice bath) and decomposed by the addition of cracked ice (1 kg) and concentrated HCl (100 ml). After decanting most of the H_2O, the almost black residue was triturated with EtOH, filtered, and washed with EtOH. The resulting dark brown solid was dissolved in 600 ml of $CHCl_3$, washed with 10% Na_2CO_3 (3 × 100 ml, severe emulsions) and then with H_2O, and dried (Na_2SO_4). Evaporation of the $CHCl_3$ left a light brown solid which was recrystallized (Norit).

Method D.[5] With stirring under N_2, yellow HgO (0.3 mol) was added in essentially one portion to a solution of 0.1 mol of the bis(dithiane) in the appropriate solvent. When the HgO was uniformly dispersed, a solution of 0.44 mol of $HgCl_2$ in 250 ml of MeOH–H_2O (9:1 by volume) was added in one portion. The mixture was stirred and refluxed under N_2 for 5 hr. After cooling, the insoluble material was filtered and washed with $CHCl_3$. The combined filtrate and washings were washed successively with 20% aqueous KI, 10% HCl, 10% NaOH, and finally with H_2O. After drying (Na_2SO_4), the $CHCl_3$ was evaporated *in vacuo* to dryness and the residue was recrystallized.

In general, the bis(dithianes) were rather insoluble in common solvents and suitable solvent mixtures had to be determined for each preparation: 62 [2350 ml of boiling MeOH–MeCN–H_2O (9:9:2 by volume)]; 63 [a mixture of 1200 ml of boiling MeOH–MeCN–H_2O (9:9:2 by volume) and 450 ml of boiling PhH]; 64 [3000 ml of boiling 95% aqueous (PhH–EtOH, 2:1 by volume)]; 65 [2000 ml of PhH–MeOH (1:1 by volume)]. For the preparation of 12, an excess (0.9 mol) of HgO was used to avoid hydrolysis of the benzyl groups. The reflux time for this case was 15 hr.

Oximes and Methoximes (Table II). Method A. The ketone (0.1 mol) (Table I) was dissolved in a minimum of 300 ml of hot pyridine–EtOH (2:1 by volume). For the less soluble ketones up to 1400 ml of solvent was required. After adding 0.3 mol of $NH_2OH \cdot HCl$ (or $NH_2OCH_3 \cdot HCl$) the solution was refluxed for 4–5 hr. The solution was cooled and most of the solvent was evaporated *in vacuo*. The residue (oil or solid) was triturated under H_2O and the solid was filtered, washed thoroughly with H_2O, dried, and recrystallized. For the preparation of compounds 18, 28, 31, 32, and 33, the solvent was pyridine–EtOH (1:1 by volume).

Method B. This procedure was used for the preparation of compounds 20, 22, and 34. In these cases the use of method A gave products which either failed to crystallize or did so with great difficulty. To 0.1 mol of the ketone was added 0.4 mol of $NH_2OH \cdot HCl$ dissolved in 60 ml of H_2O, followed by 0.4 mol of NaOAc dissolved in 100 ml of H_2O. While heating the suspension on the steam bath, EtOH (*ca.* 350 ml) was added in portions until solution occurred. The latter was refluxed overnight, and, after cooling, the EtOH was evaporated *in vacuo*. The residue was taken up in *ca.* 800 ml of Et_2O and washed with H_2O. The dried Et_2O layer was concentrated to a small volume and cooled and scratched, if necessary, to start crystallization. The crude solid was isolated as usual and recrystallized.

Amines (Table III). Except where otherwise indicated, the crude free bases (as oils or solids) were converted to their crystalline dihydrochloride salts by dissolving the former in a small amount of absolute EtOH and adding a solution of excess HCl gas (*ca.* 2 times theory) in absolute EtOH. If, on cooling, no precipitate formed or if the amount of solid appeared slight, anhydrous Et_2O or EtOAc was added to complete the precipitation.

Method A. The following procedure is typical of the reaction conditions employed. A solution of 21.5 g (0.050 mol) of the oxime 20 in 225 ml of glacial HOAc was hydrogenated with 2.15 g of 10% Pd/C in a Parr apparatus at room temperature and 45–50 psig. When the uptake of H_2 had ceased (*ca.* 12–36 hr), the catalyst was filtered and washed with solvent. The combined filtrates were treated with 30 ml of concentrated HCl and evaporated *in vacuo* to dryness. A solution of the residue in 250 ml of H_2O was washed with $CHCl_3$ (3 × 30 ml), cooled, and made strongly basic with excess 10 *N* NaOH. After extracting the resulting oil with PhH (4 × 100 ml), the combined extracts were washed with H_2O (3 × 30 ml) and dried (Na_2SO_4). Evaporation *in vacuo* left the crude free base as a pale yellow oil.

Method B.[7] Under N_2, a stirred solution of 0.02 mol of the bis(methoxime) in dry THF (100–300 ml) was cooled in an ice bath and treated dropwise during 0.5–1 hr at 0–3° with 120 ml of a commercial borane–THF solution (*ca.* 1.0 *M*). Stirring was continued for 1 hr at 0–3° and then overnight at room temperature. The resulting solution was cooled in a Dry Ice–Me_2CO bath and carefully treated dropwise with 30 ml of H_2O. After warming to room temperature, the THF was evaporated *in vacuo*. The residual amine–borane complexes were hydrolyzed by various procedures.

Compound 36. The residue was carefully treated with 200 ml of 10% HCl and, after the initial frothing had subsided, the mixture was heated on the steam bath. After 1 hr the turbid solution was cooled, filtered, and made strongly basic with 10 *N* NaOH. The oil which separated was extracted with PhH, and the extracts were washed with H_2O and dried (K_2CO_3). Evaporation left the oily free base.

Compound 44. The residue was carefully treated with 150 ml of 10% KOH and then heated on the steam bath for 1 hr. After cooling, the insoluble oil was extracted with PhH and further worked up as described for compound 36.

Compound 49. The residue was carefully treated with 200 ml of 10% KOH and then refluxed for 5 hr. After cooling, the insoluble oil was extracted with PhH, and the combined extracts were washed with H_2O. Evaporation *in vacuo* and treatment of the residue with 100 ml of 10% aqueous lactic acid gave a turbid solution which was filtered and washed with PhH. The aqueous layer was cooled and made strongly basic with 10 *N* NaOH and the insoluble oil which separated was again extracted with PhH, washed with H_2O, and dried (K_2CO_3). The residue remaining after evaporation of the PhH was dissolved in 20 ml of EtOH and treated with a solution of 5.25 g of 85% aqueous acetic acid in 30 ml of EtOH, followed by the addition of anhydrous Et_2O to the cloud point. On cooling and scratching, a 58% yield of the crude dilactate salt was obtained, mp 167–169°.

Compound 53. The residue was carefully treated with 150 ml of 10% KOH and heated on the steam bath for 2 hr. After cooling, the insoluble gum was extracted with PhH and the PhH evaporated *in vacuo*. The residual oil was taken up in 40 ml of 10% HCl and the turbid solution filtered and washed with PhH. Addition of excess 10 *N* NaOH to the cooled aqueous layer precipitated an oil which was extracted with PhH. After washing the combined extracts with H_2O and drying (Na_2SO_4), the crude free base was isolated by evaporation *in vacuo*.

Method C.[6,7] A mixture of 13.0 g (0.0356 mol) of the oxime 23 and 130 ml of Ac_2O was refluxed for 15 min. The solid which separated on cooling was filtered, washed with a little THF, and dried to yield 14.5 g (0.032 mol) of the corresponding crude oxime acetate. Without further purification, a suspension of the latter in 300 ml of dry THF was reduced as described in method B with 200 ml of 1 *M* BH_3–THF solution. After decomposition of excess diborane with H_2O and evaporation of the THF, the residual complex was hydrolyzed by careful addition of 10% KOH (200 ml) followed by heating for 1 hr on the steam bath. After cooling, the mixture was extracted with PhH, and the combined extracts were washed with H_2O and dried (K_2CO_3). Evaporation left the oily free base.

Method D. A solution of 26.1 g (0.0550 mol) of crude 38 in 150 ml of H_2O was cooled and treated with excess 10 *N* NaOH. After extracting the precipitated oil with PhH, the combined extracts were washed with H_2O and dried. Evaporation *in vacuo* left 17.9 g (0.0445 mol) of the free base as a bright yellow oil. A solution of the latter and 9.9 g (0.098 mol) of Et_3N in 100 ml of dry CH_2Cl_2 was added dropwise during 1.5 hr to a stirred solution of 10.6 g (0.098 mol) of ethyl chloroformate in 200 ml of dry CH_2Cl_2 while the temperature was kept at 0–5°. Stirring was continued for 1.5 hr at 0–5° and then for 2 hr at room temperature. The reaction mixture was washed with H_2O (50 ml), 10% HCl (3 × 50 ml), and finally with H_2O (4 × 50 ml) and dried (Na_2SO_4). Filtration and evaporation *in vacuo* left an orange oil which was triturated under hexane until solid. Filtration and drying gave 17.1 g (71%) of the crude bis(urethane) as a pale yellow amorphous solid. Without further purification, a solution of 16.4 g (0.030 mol) of the

latter in 200 ml of dry THF was added dropwise during 1.5 hr to a stirred suspension (under N_2) of 9.12 g (0.240 mol) of $LiAlH_4$ in a mixture of 250 ml of anhydrous Et_2O and 250 ml of anhydrous THF. After refluxing for 4 hr, the mixture was cooled in an ice bath and excess $LiAlH_4$ was decomposed under N_2 by the successive dropwise addition of 10 ml of H_2O, 10 ml of 15% NaOH, and 30 ml of H_2O. The insoluble oxides were filtered and washed with THF (500 ml) and PhH (500 ml), and the combined filtrates were evaporated *in vacuo*. The residual orange oil was taken up in 100 ml of 10% HCl and the solution was filtered from insolubles. After washing with PhH, the aqueous layer was cooled and made strongly basic with 10 *N* NaOH. The product was extracted with PhH, and the combined extracts were washed with H_2O and dried (Na_2SO_4). Evaporation *in vacuo* left the free base of 56 as an oil which was converted to its dihydrochloride salt in the usual manner.

Compound 57 was prepared from 41 in an analogous manner. The isomeric bis(urethanes) (crude yield, 69%) were only moderately soluble in CH_2Cl_2 and one of the isomers partly precipitated during the course of the reaction. The reduction was carried out by adding a slurry of the isomeric mixture in THF to the $LiAlH_4$. On recrystallization from 95% EtOH, crude 57 yielded (first crop) a comparatively minor amount of crystalline solid, mp *ca.* 290°. This material was assumed to be isomeric (similar ir) with the major component (mp 274–276°) which was obtained by treatment of the EtOH filtrate with anhydrous Et_2O.

Mono- and Bis(dithianes) (Table IV). Method A. Compounds 58 and 60 were prepared according to the method reported for the corresponding 2-phenyl analog.[10]

Method B. A solution of 1.0 mol of aldehyde, 1.0 mol of 1,3-propanedithiol, and 0.01 mol of *p*-TsOH·H_2O in 600 ml of PhH was refluxed (Dean-Stark trap) for 1 hr. After cooling and diluting with an equal volume of PhH, the solution was washed with 10% NaOH (4 × 400 ml) and H_2O (3 × 400 ml) and dried (Na_2SO_4). The crude product (oil or solid) remaining after evaporation *in vacuo* was triturated under hexane, filtered, dried, and recrystallized.

The aromatic aldehydes required in methods A and B either were commercially available or were prepared by known standard literature methods.

Method C.[4] Under N_2, a stirred solution (or suspension) of 0.5 mol of the dithiane (58–61) in 1200 ml of anhydrous THF was kept at −35 ± 5° while adding dropwise during 1.5 hr 345 ml (0.55 mol) of a commercial solution (1.6 *M*) of *n*-BuLi in hexane. After stirring for an additional 1.5 hr at −35° the solution was warmed to −15°. A solution of 0.25 mol of 1,4-dibromobutane (or 1,3-dibromopropane) in 60 ml of anhydrous THF was then added dropwise during 2 hr at −10 ± 5°. After standing overnight in the refrigerator (*ca.* 2–3°) the solution was cooled at −35° and 90 ml of H_2O was added dropwise under N_2 to decompose any excess *n*-BuLi. The residue remaining after evaporation of the solvent *in vacuo* was suspended in 1000 ml of H_2O and the mixture acidified (pH 2–3) by addition of concentrated HCl. The product was extracted with $CHCl_3$ (3 × 500 ml), and the combined extracts were washed with 5% $NaHSO_3$ (3 × 350 ml), 5% KOH (4 × 350 ml), and H_2O (4 × 350 ml) and dried (Na_2SO_4). The $CHCl_3$ was evaporated *in vacuo* and the residue (oil or solid) was triturated under Et_2O or hexane, filtered, dried, and recrystallized.

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Nucleic Acids. 14. Synthesis and Antiviral Activity of Some 5′-Esters of 9-β-D-Arabinofuranosyladenine (Ara-A)[1]

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The synthesis of the 5′-benzoyl and 5′-palmitoyl esters of ara-A is described. Qualitatively, the *in vitro* antiviral activity of 5′-benzoyl-ara-A and ara-A was similar; *i.e.*, both compounds were effective against herpesvirus (a DNA virus) but inactive against several RNA-containing viruses. Ara-A 5′-palmitate was inactive in the plaque inhibition test. In *in vitro* studies comparing the dose of drug with herpesvirus yields, ara-A and the 5′-benzoate had nearly the same activity and were more active than the 5′-palmitate. In *in vivo* studies in mice infected with herpesvirus, ara-A was effective if given intraperitoneally at 125 or 250 mg/kg total daily dose, for 5 days beginning the day after virus inoculation. Both esters of ara-A were devoid of antiviral activity in mice using these conditions of treatment.

The antiviral activity of ara-A was first described by De Rudder and Privat de Garilhe.[2] These authors showed that, *in vitro*, ara-A was inhibitory for the DNA viruses studied (herpes and vaccinia) but was noninhibitory for the RNA viruses (poliomyelitis and measles). Subsequent collaborative studies carried out by the Parke Davis Co. and Southern Research Institute groups expanded and confirmed the *in vitro* studies.[3] These same groups studied the action of ara-A in a variety of model infections in animals and showed that ara-A was active in hamsters and mice infected with herpesvirus[4,5] and in mice infected with vaccinia virus.[6,7]

Recent studies[8,9] comparing the biological activity of ara-C (1-β-D-arabinofuranosylcytosine, cytarabine, Cytosar) with some 5′-esters have provided evidence that the activity of the 5′-esters may be somewhat greater than is ara-C itself. The factors influencing the enhanced biological activity of these derivatives include resistance to pyrimidine nucleoside deaminase, lipophilicity and rate of localization in lipid depots, susceptibility of the ester bond to enzymatic hydrolysis, and dissolution and absorption rates.[9]

We report herein the summary of our findings on the synthesis of two ara-A esters, the 5′-palmitate and the 5′-benzoate, and compare the *in vitro* and *in vivo* antiviral properties of these compounds to that of ara-A.

Methods

Synthesis of 5′-Esters of Ara-adenosine and 5′-Benzoyl-9-β-D-arabinofuranosyladenine. 9-β-D-Arabinofuranosyladenine hydrochloride (5.3 g, 0.017 mol) was dissolved in 50 ml of dimethylacetamide and 4.8 g (0.034 mol) of benzoyl chloride was added. The mixture was allowed to stand at room temperature for 72 hr. The solvent was removed *in*