TABLE II

1,3-DI(ARYLACETYL)INDOLES (II)

Compd[a]	R_1, R_5, and R_7	R_2	R_3	R_4	R_6	Mp, °C	Yield, %[b] (pure)	Infrared, μ (C=O)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
c	H	MeO	H	H	H	135.5–136	20	5.72, 5.92	$C_{26}H_{23}NO_4$	75.53	5.60	3.39	75.72	5.99	3.71
h	H	Me	Me	H	H	136–137	32	5.80, 5.95	$C_{28}H_{27}NO_2$	82.11	6.64	3.42	82.20	6.83	3.46
i	H	Cl	Cl	H	H	200–202	75	5.76, 5.95	$C_{24}H_{15}Cl_4NO_2$	58.68	3.08	2.85	58.73	3.13	2.85
k	H	MeO	MeO	Cl	Br	219–220.5	52[c]	5.51, 5.90	$C_{28}H_{24}BrCl_2NO_6$	54.13	3.89	2.25	54.17	4.06	2.27
m	H	Me	Me	H	Br	143–144	19	5.77, 5.96	$C_{28}H_{26}BrNO_2$	68.85	5.36	2.86	68.77	5.28	2.87

[a] Letter designations and substituent distribution are consistent in Table I and II. [b] Yield based on arylacetyl chloride. [c] Recrystallized from aqueous acetone, the others from 95% ethanol.

TABLE III

SOME PHENYLACETIC ACID DERIVATIVES

$ArCH_2COX$

Ar	X	Bp (mm) or mp °C[a]	% yield	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
5-Chloro-3,4-dimethoxyphenyl	OH	94–95	56[b]	$C_{10}H_{11}ClO_4$	52.07	4.81	52.28	4.97
5-Chloro-3,4-dimethoxyphenyl	OMe	114–115.5 (0.05)	61[b]	$C_{11}H_{13}ClO_4$	54.00	5.36	54.28	5.46
2-Chloro-3,4-dimethoxyphenyl	OH	138–140	44[b]	$C_{10}H_{11}ClO_4$	52.07	4.81	52.22	4.90
2-Chloro-3,4-dimethoxyphenyl	OMe	125–125.5 (0.12)	47[b]	$C_{11}H_{13}ClO_4$	54.00	5.36	54.21	5.39
2-Chloro-4,5-dimethoxyphenyl	OH	121–123	63[b]	$C_{10}H_{11}ClO_4$	52.07	4.81	52.18	4.98
2-Chloro-4,5-dimethoxyphenyl	OMe	111–111.5 (0.05)	69[b]	$C_{11}H_{13}ClO_4$	54.00	5.36	54.28	5.85
2-Chloro 4,5-dimethoxyphenyl	Cl	73.5–75	84	$C_{10}H_{10}Cl_2O_3$	48.22	4.05	48.50	3.83
2-Methyl-3,4-dimethoxyphenyl	OH	109–110	66	$C_{11}H_{14}O_4$	62.84	6.71	62.80	6.83

[a] All acids were crystallized from benzene–petroleum ether (bp 60–70°), and the acid chloride from petroleum ether. [b] Yields based on azlactone.

162° (3 mm);[14c] 3,4-methylenedioxyphenyl-, 79, 101–102° (1 mm);[14e] 3-methoxyphenyl-, 70, 104–109° (2 mm).[14f]

Acylation of Indoles *via* the Oddo Reaction. General Procedure.—A solution of 0.05 mole of indole (or 5,6-methylenedioxyindole or 5-bromoindole) in 25 ml of anhydrous benzene was added dropwise during 10 min to a vigorously stirred solution of 0.05 mole of phenylmagnesium bromide, prepared in the usual way, in 50 ml of anhydrous ether. The resulting mixture was refluxed for 2 hr, then cooled to −10° in a Dry Ice–methanol bath. A solution of 0.05 mole of the arylacetyl chloride in 20 ml of benzene was then added dropwise during 45 min while the temperature was maintained at −8 to −10°. The cooling bath was then removed, the mixture was stirred for another 30 min, and finally hydrolyzed by addition of 25 ml of 10% aqueous NH_4Cl. The resulting solid product was collected by filtration, washed several times with ether, and air dried. Further treatment of the crude product followed one of the three following procedures. Properties of the final pure products are summarized in Table I (3-arylacetylindoles) and Table II (1,3-di(arylacetyl)-indoles).

Method A. Direct Formation of a 3-Arylacetylindole.—This situation occurred only in the case of 3-(2-methyl-3,4-dimethoxyphenylacetyl)indole (Ia), which was directly purified by recrystallization from 95% ethanol.

Method B. Predominant Formation of 1,3-Di(arylacetyl)indoles.—The crude products were purified by recrystallization from 95% ethanol (except where otherwise noted) and had the properties collected in Table II. These pure diacyl compounds (II) were hydrolyzed as illustrated by the following explicit example.

3-(3,4-Dichlorophenylacetyl)indole (Ii).—One gram (0.0021 mole) of (IIi) was refluxed for 5 min with a solution of 5 ml of 10% NaOH in 15 ml of 95% ethanol. The resulting solution was diluted with 20 ml of water and cooled. The precipitate was collected by filtration, washed with water, air dried, then recrystallized from 95% ethanol to yield 0.60 g (98%) of pure (Ii) (*cf.* Table I).

Method C. Formation of Gross Mixtures of Mono- and Diacylindoles.—In these cases the crude products, although distinctly crystalline, did not yield either pure 3-arylacetyl- or 1,3-di(arylacetyl)indoles even after repeated recrystallization. Such mixtures were therefore directly hydrolyzed with aqueous alcoholic NaOH, as described under method B, to yield the pure 3-arylacetylindoles.

Method D. Seka's Reaction.—The reactions of 2-methylindole with 3,4-methylenedioxyphenyl-,[15] 3,4-dimethylphenyl-,[16] 3,4-dichlorophenyl-,[16] and 2,4-dichlorophenylacetonitriles[17] in anhydrous ethereal HCl solution were all accomplished by essentially the same procedures previously reported.[6]

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Derivatives of 4-Phenyl-$\Delta^{\beta,\gamma}$-butenoides[1]

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In our efforts to prepare physiologically active compounds we have prepared a series of α-arylidene-γ-substituted $\Delta^{\beta,\gamma}$-butenolides[2-6] (see Table I on following page).

These compounds were tested for antitumor, antischistosome, antiviral, and antibacterial activities. The lactones were inactive in these tests except that compounds 1, **9**, and **12**, which contain the nitrogen mustard group, showed slight antileukemia activity.[7]

Experimental Section

The α-arylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides were prepared by heating 0.05 mole of the appropriate β-aroylpropionic acid, 0.055 mole of aldehyde, 8.2 g of sodium acetate, and 16 ml of acetic anhydride on a hot plate until homogeneous. The heating was continued on a steam bath until crystals separated. The reaction mass was allowed to cool, filtered, washed with water and sodium bicarbonate, and recrystallized from ethanol.

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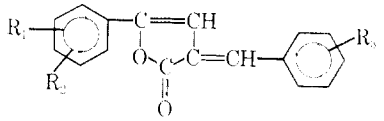
(7) The antileukemia tests were arranged through CCNSC and were carried out at the Department of Medicine, University of Miami, Miami, Fla.

TABLE I



No.	R_1	R_2	R_3	Mp, °C (cor)	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Found, % C	Found, % H	Found, % Cl
1	4-Cl	H	*p*-(ClCH$_2$CH$_2$)$_2$N	177–180	61	$C_{20}H_{18}Cl_3NO_2$	59.67	4.29	25.56	59.55	4.37	25.32
2	4-Cl	H	*a*	242–243	73	$C_{16}H_{14}ClNO_2$	67.79	3.56	12.50	67.54	3.73	12.91
3	4-Cl	H	2-Chloro	244–246	85	$C_{17}H_{10}Cl_2O_2$	64.37	3.18	22.35	64.34	3.37	22.53
4	4-Cl	H	4-Methoxy	228–229	77	$C_{18}H_{13}ClO_3$	69.14	4.19	11.34	69.30	4.36	11.65
5	4-Cl	H	2-Acetoxy	192–194	65	$C_{19}H_{13}ClO_4$	66.97	3.84	10.41	66.89	3.88	10.64
6	4-Cl	H	2,3-Dimethoxy	179–180	50	$C_{19}H_{15}ClO_4$	66.57	4.41	10.34	66.42	4.51	10.57
7	4-Cl	H	3-Acetoxy	169–171	48	$C_{19}H_{13}ClO_4$	66.97	3.84	10.41	66.90	3.89	10.75
8	4-Cl	H	*b*	184–188	38	$C_{15}H_9ClO_3$	66.05	3.33	13.00	66.08	3.61	13.42
9	4-Ethoxy	H	*p*-(ClCH$_2$CH$_2$)$_2$N	142–143	64	$C_{23}H_{23}Cl_2NO_3$	63.90	5.36	16.40	63.81	5.49	16.58
10	4-Ethoxy	H	2-Chloro	136–137	87	$C_{19}H_{15}ClO_4$	69.80	4.63	10.85	70.08	4.86	11.02
11	4-Ethoxy	H	*c*	165–167	93	$C_{17}H_{14}O_3S$	68.43	4.73	10.75	68.30	4.76	10.98
12	2-Ethoxy	5-Ethoxy	*p*-(ClCH$_2$CH$_2$)$_2$N	105–107	48	$C_{25}H_{27}Cl_2NO_4$	63.03	5.72	14.89	63.52	5.91	15.25
13	2-Ethoxy	5-Ethoxy	4-Methoxy	175–177	71	$C_{22}H_{22}O_5$	72.11	6.05		72.08	6.24	
14	4-Methoxy	H	2,3-Dimethoxy	165–166	63	$C_{20}H_{18}O_5$	71.01	5.36		71.19	5.48	
15	4-Methoxy	H	4-Dimethylamino	175–177	47	$C_{20}H_{19}NO_3$	74.51	5.95	4.35	74.72	6.11	
16	4-Methoxy	H	3-Ethoxy-4-acetoxy	135–137	55	$C_{22}H_{26}O_6$	69.46	5.30		69.40	5.54	
17	4-Methoxy	H	*c*	175–176	90	$C_{16}H_{12}O_3S$	67.60	4.26	11.27	67.55	4.39	11.52

[a] Phenyl replaced by 3-pyridyl. [b] Phenyl replaced by 2-furyl. [c] Phenyl replaced by 2-thienyl.

Synthesis of 1,1′-Trimethylene-4,4′-Substituted Pyridinium and 1,3′-Halopropyl-4-Substituted Pyridinium Compounds[1]

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Various nucleophilic agents, particularly oximes, have been employed in antagonizing the highly toxic anticholinesterase alkyl phosphates, *e.g.*, chemical warfare agents and insecticides. One of the most effective agents for antagonizing alkyl phosphate intoxication is 1,1′-trimethylenebis(4-aldoximinopyridinium) dibromide.[3,4] The metabolic disposition of this antagonist is being investigated in our laboratory both *in vitro*[5] and *in vivo*.[6] The report herein describes the synthesis of some known or potential biological metabolites of this antagonist and their intermediates, which are being employed to facilitate the investigation of the biochemical transformation of 1,1′-(rimethylenebis(4-aldoximinopyridinium) dibromide.

Experimental Section[7]

General.—All reactions were performed under anhydrous conditions and in stoppered flasks protected from light. It should be stressed that the cyano derivatives of types I and II are extremely labile, especially if anhydrous conditions are not carefully maintained. Isonicotinic acid was obtained from Eastman Organic Chemicals. Pyridine-4-aldoxime, 4-cyanopyridine, 1,3-diiodopropane, and 1,3-dibromopropane were purchased from the Aldrich Chemical Co. Care should be exercised in the use of 4-cyanopyridine due to its high vapor pressure and toxic properties. All other reagents and starting materials were of the highest grade and purity commercially available.

The Menschutkin reaction has been employed in the synthesis of these quaternary pyridinium compounds.[8] Minor modification of this reaction was utilized in the synthesis of this antagonist and in the preparation of the compounds presently described. The 4-aldoximino and the 4-cyano derivatives of type I were synthesized by treating the corresponding 1,3-dihalopropane with the substituted pyridine derivative. The 4-pyridone of types I and II was prepared by the alkaline hydrolysis of the corresponding 4-cyano derivative.[9] Bisquaternary derivatives of type II were prepared by treating type I with the appropriate monosubstituted pyridine, with the exception of the biscyano and the pyridone derivatives. The biscyano was prepared by the same procedure as for type I derivatives.

1,3′-Bromopropyl-4-aldoximinopyridinium Bromide (I).—A solution of 12.21 g (0.1 mole) of pyridine-4-aldoxime and 121 g (0.6 mole) of 1,3-dibromopropane in 750 ml of anhydrous nitrobenzene was allowed to stand at room temperature for 90 days. The yellow crystals which formed were collected, washed with ether, and dried *in vacuo;* yield 31.8 g (99%) of product, mp 188–189° dec. Recrystallization from methanol yielded as yellow needles 30.2 g (94%) of the quaternary salt, mp 189–190° dec. Compounds II and III were made with appropriate modification of the general method described above. The results are listed in Table I.

1,3′-Bromopropyl-4-pyridone Picrate (IV).—A solution of 6.35 g (0.021 mole) of 1,3′-bromopropyl-4-cyanopyridinium bromide and 20 ml of 1.0 *N* NaOH in 35 ml of distilled water was allowed to stand at 0–5° for 10 min, was adjusted to pH 9.0 with 1.0 *N* HCl, and was extracted with 1 l. of benzene in a liquid–liquid extractor for 24 hr. The benzene extract was dried ($MgSO_4$) and concentrated *in vacuo*. The yellow oil was crystallized as the picrate salt from benzene.

(1) This work was supported in part by U. S. Public Health Service Grants NB 04541 and MH 10109.

(2) These data are from a thesis to be presented by C. N. Corder in partial fulfillment of the requirements for a Ph.D. degree in pharmacology.

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(7) Analyses were performed by Weiler and Strauss, Oxford, England, and by Huffman Laboratories, Inc., Wheatridge, Colo. All melting points were determined with a Thomas–Hoover apparatus and are corrected. Ultraviolet spectra were measured in a Beckman DB and/or Beckman DU spectrophotometer using distilled water as the solvent. Infrared spectra were determined with a Beckman IR-5 spectrophotometer using either KBr pellet, or Nujol mull. Legend for interpretations of principle absorbance bands are: s, strong; m, medium; w, weak. A Cahn Electrobalance was used to weigh spectral samples.

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