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Synthesis and Antitumor Properties of Some Isoindolylalkylphosphonium Salts

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Antitumor evaluation of 2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyltriphenylphosphonium bromide (1) revealed significant activity in P-388 lymphocytic leukemia (T/C = 160%). As a follow-up to this chemical lead, a series of closely related phosphonium salts was prepared in which the 1,3-dihydro-1,3-dioxo-2*H*-isoindole ring system was maintained or in which it was replaced by other moieties such as maleimido, bromo, methoxy, and isoindoline. Syntheses generally involved treatment of the appropriate *N*-(bromoalkyl)phthalimide with the required phosphine or condensation of the K salt of the substituted imide with β-(bromoethyl)triphenylphosphonium bromide (12). From the biological data obtained for these compounds, several requirements can be defined for substantial antileukemic activity. Of utmost importance is the presence of a triarylphosphonium halide moiety, coupled to an alkyl chain of two or three carbon atoms. The preferred terminus of the alkyl chain is the 1,3-dihydro-1,3-dioxo-2*H*-isoindole ring system, although the observed activity of β-(bromoethyl)triphenylphosphonium bromide (12) (T/C = 127%) would suggest that a superior carrier molecule could be developed.

In the course of our antitumor agents synthesis program, it became necessary to prepare 2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyltriphenylphosphonium bromide (1)

$NCH_2CH_2\overset{+}{P}(C_6H_5)_3Br^-$

1

as a synthetic intermediate. This material was routinely submitted for biological evaluation and unexpectedly displayed substantial activity in the P-388 lymphocytic leukemia screen. As a follow-up to this chemical lead, a series of closely related phosphonium salts was prepared and biologically screened in an attempt to elucidate the minimum structural requirements necessary for antitumor activity, information which could then be utilized in the development of a more active second generation drug. These compounds are listed in Tables I–III. Their methods of preparation and antileukemic activity are the subjects of this report.

Chemistry. Compounds 1–4 which represent variations in the length of the carbon side chain were prepared by treatment of the appropriate *N*-(bromoalkyl)phthalimide with triphenylphosphine in refluxing mesitylene (benzene in the case of **2**). In a similar manner, reaction of *N*-(2-bromoethyl)phthalimide with the required phosphine in DMF at 50–90 °C generated analogues **5–11** with altered substituents at the phosphorus atom. Under the conditions of refluxing DMF, *n*-butoxydiphenylphosphine reacted with *N*-(2-bromoethyl)phthalimide to yield phosphine oxide **24**, via an Arbusov rearrangement of the intermediate phosphonium salt.

Due to the commercial unavailability of the appropriately substituted *N*-(2-bromoethyl)imides, compounds **13–18** and **23** were synthesized by an alternate procedure which involved condensation of **12** with the K salt of the substituted imide. Intermediate **12** was isolated from the reaction of phosphorus tribromide with β-(hydroxyethyl)triphenylphosphonium bromide, itself obtained from treatment of 2-bromoethanol with triphenylphosphine.[1]

Attempted reaction of **12** with the K salt of 1,8-naphthalimide did not result in the preparation of the desired naphthalimido phosphonium salt but unexpectedly generated the methoxy derivative **22**, a product originating from the methanol solvent.

Synthesis of phosphonium chloride **19** was achieved by treatment of **1** with Amberlite IRA-400 ion-exchange resin (Cl^- form).

Reduction of phthalimide with diborane resulted in the preparation of isoindoline which was converted to **20** by reaction with phosphonium salt **12**. The free base **21** was obtained from **20** by neutralization with $NaHCO_3$.

Biological Results and Discussion. The antimitotic activity of all compounds (see Tables I–III) was measured in lymphocytic leukemia P-388 by standard protocols of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.[2] Compounds are considered significantly active if they give reproducible T/C activity[2] values in the P-388 leukemia system equal to or greater than 125% where T/C represents the ratio of the mean or median survival times of the treated an-

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Table I. Physicochemical and Antitumor Screening Data

R– (phthalimide) $N(CH_2)_nP^+(R_1)_3Br^-$

Compd no.	R	*n*	R_1	Yield, %	Mp, °C	Mol formula	Analyses	P-388 lymphocytic leukemia[a-c] Dose[d]	T/C[e,f]
1	H	2	C_6H_5	60	242-243	$C_{28}H_{23}BrNO_2P$	C, H, P	12.5[g]	160
2[h]	H	1	C_6H_5	68	270-274	$C_{27}H_{21}BrNO_2P\cdot 0.25H_2O$	C, H, N	18.8[i]	136
3[h]	H	3	C_6H_5	44	241-245,[j] wetting at 120	$C_{29}H_{25}BrNO_2P\cdot H_2O$	C, H, N	12.5[g]	151
4	H	4	C_6H_5	60	148-150 dec	$C_{30}H_{27}BrNO_2P$	C, H, N, P	9[k]	121
5[h]	H	2	$(CH_2)_3CH_3$	26	Oil	$C_{22}H_{35}BrNO_2P\cdot H_2O$	C, H, N	100[i]	116
6[h]	H	2	CH_2CH_2CN	30	142, wetting at 110	$C_{19}H_{20}BrN_4O_2P\cdot H_2O$	C, H, N	25[i]	117
7	H	2	$CH_2C_6H_5$	31	240-242	$C_{31}H_{29}BrNO_2P$	C, H, N	25[k]	112
8	H	2	c-C_6H_{11}	63	282-285	$C_{28}H_{41}BrNO_2P$	C, H, N	25[i]	118
9[h]	H	2	-C_6H_4-4-OCH_3	39	138-143	$C_{31}H_{29}BrNO_5P\cdot H_2O$	C, H, N	6[i]	134
10[h]	H	2	-C_6H_4-4-CH_3	54	218-220, wetting at 150	$C_{31}H_{29}BrNO_2P\cdot H_2O$	C, H, N	6.25[i]	134
11[h]	H	2	-C_6H_4-4-Cl	18	168-172	$C_{28}H_{20}BrCl_3NO_2P\cdot 1.5H_2O$	C, H, N	6.25[i]	110
13[h]	4-NO_2	2	C_6H_5	37	240-244 dec, wetting at 194	$C_{28}H_{22}BrN_2O_4P\cdot 0.5H_2O$	C, H, N	50[i]	109
14	4-CH_3	2	C_6H_5	48	180-185	$C_{29}H_{25}BrNO_2P$	C, H, N	3.13[i]	140
15	5-CH_3	2	C_6H_5	91	208-210	$C_{29}H_{25}BrNO_2P$	C, H, N	6.25[i]	139
16[h]	5-NO_2	2	C_6H_5	43	135-140 dec	$C_{28}H_{22}BrN_2O_4P\cdot 1.5H_2O$	C, H, N	25[i]	107

[a] Protocol and tumor system described in ref 2. [b] QD 1-9 treatment. [c] Drug given intraperitoneally. [d] In mg/kg. [e] T/C = (treated survival)/(control survival) × 100. [f] All T/C results reported for the significantly active compounds (see text for definition of significant activity) have been reproduced in a minimum of one additional experiment to give values not more than 8.6% lower than the value shown. All significantly active compounds have been confirmed as such by at least one additional test. [g] Hydroxypropylcellulose as vehicle. [h] As a hydrate. [i] H_2O as vehicle. [j] Lit.[3] mp 158-160 °C for the anhydrous compound. [k] H_2O + Tween 80 as vehicle.

Table II. Physicochemical and Antitumor Screening Data

$RCH_2CH_2P^+(C_6H_5)_3X^-$

Compd no.	R	X	Yield, %	Mp, °C	Mol formula	Analyses	P-388 lymphocytic leukemia[a-c] Dose[d]	T/C[e,f]
12	Br	Br	89	191-193[g]	$C_{20}H_{19}Br_2P$	C, H, Br	3.13[h]	127
17	N-	Br	16	235-240 dec	$C_{24}H_{21}BrNO_2P$	C, H, N	25[h]	120
18[i]	N-	Br	53	203-206, wetting at 185	$C_{28}H_{27}BrNO_2P\cdot H_2O$	C, H, N	25[h]	115
19[i]	N-	Cl	69	240-242	$C_{28}H_{23}ClNO_2P\cdot 0.5H_2O$	C, H, Cl	6.25[h]	133
20[i,j]	N-	Br	61	256-260 dec	$C_{28}H_{27}BrNP\cdot HBr\cdot H_2O$	C, H, N	6.25[k]	118
21	N-	Br	78	173-176 dec	$C_{28}H_{27}BrNP$	C, H, N	6.25[l]	114
22	CH_3O	Br	38	192-196[m]	$C_{21}H_{22}BrOP$	C, H, P, Br	12.5[h]	123

[a-f] See corresponding footnotes in Table I. [g] Lit.[1] mp 198-200 °C. [h] H_2O as vehicle. [i] As a hydrate. [j] As an HBr salt. [k] H_2O + Tween 80 as vehicle. [l] Saline as vehicle. [m] Lit.[4] mp 216 °C.

imals over those of the control animals expressed as a percentage.

All T/C results reported for the significantly active compounds have been reproduced in a minimum of one additional experiment to give values not more than 8.6% lower than the value shown.

Our initial structure–activity investigations involved only minor modifications of the active lead compound 1. The

Table III. Physicochemical and Antitumor Screening Data

Compd no.	Structure	Yield, %	Mp, °C	Mol formula	Analyses	P-388 lymphocytic leukemia[a-c] Dose[d]	T/C[e,f]
23	RN / NR[i] (pyromellitic diimide)	35	175–178 dec, wetting at 165	$C_{50}H_{40}Br_2N_2O_4P_2\cdot 2H_2O$	C, H, N	25[g]	18 (toxic)
24	$NCH_2CH_2P(O)(C_6H_5)_2$ (phthalimide)	12	164–167	$C_{22}H_{18}NO_3P$	C, H, N, P	25[h]	106

[a-f] See corresponding footnotes in Table I. [g] H_2O as vehicle. [h] H_2O + Tween 80 as vehicle. [i] $R = CH_2CH_2P^+(C_6H_5)_3Br^-\cdot H_2O$.

first series of compounds, **1**–**4**, represent a variation in the length of the carbon side chain. From the observed antitumor response, it would appear that two methylene units optimize the activity. For this reason, all further analogues were designed to retain this feature.

Alterations in the substituent at phosphorus (**5**–**11**) in all cases led to decreased P-388 activity. This was less drastic in the case of the aromatic derivatives **9** and **10** where significant results were still observed. Retention of the phenyl group substituted at phosphorus was thus suggested.

Substituents on the isoindole ring in either the 4 or 5 position resulted in almost complete loss of activity with the electron-withdrawing NO_2 group (**13** and **16**). The electron-donating methyl group (**14** and **15**), however, was instrumental in maintaining substantial anticancer activity.

As expected, replacement of the counterion of **1** with chloride (compound **19**) did not cause an appreciable change in antitumor action.

The interesting molecule **23**, synthesized as a dimeric form of the parent compound, unfortunately displayed only host toxicity.

Compounds **18**, **20**, and **21**, which are reduced forms of the parent, and the maleimide derivative **17** all exhibited a substantial decrease in antitumor effect.

The importance of the triphenylphosphonium halide moiety was revealed by the almost complete absence of activity of the phosphine oxide **24** and the surprising activity of **12** and **22** which lack the isoindole functionality.

It is also significant to note that analogue **3**, which was substantially active in vivo, was completely inactive when tested in the KB cell culture. This observation, coupled with the apparent requirement of the triphenylphosphonium halide moiety, suggests an in vivo activation of **3** (a potential Wittig reagent precursor) to its corresponding ylide. This reactive intermediate could possibly interfere with vital cell functions. It is hoped that further synthetic analogues will clarify the mechanism of action of **3** and its related phosphonium salts.

From the data presented it is apparent that several requirements can be defined for substantial antileukemic activity. Of utmost importance is the presence of a triarylphosphonium halide moiety, coupled to an alkyl chain of two or three carbon atoms. The preferred terminus of the alkyl chain is the 1,3-dihydro-1,3-dioxo-2*H*-isoindole ring system, although the observed activity of **12** and **22** would suggest that a superior carrier molecule could be developed. Our subsequent analogues' program will hopefully uncover such a moiety.

Experimental Section

All melting points are uncorrected and were recorded on a Thomas-Hoover capillary melting point apparatus. Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn. When several compounds were prepared by comparable procedures, only one representative example is included in this section. Reference should be made to Tables I–III for supplementary information on the reported compounds. Satisfactory elemental analyses (±0.4% of calculated values) are indicated by elemental symbols in Tables I–III.

2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyltriphenylphosphonium Bromide (1). A solution of 10.48 g (40 mmol) of triphenylphosphine and 10.16 g (40 mmol) of *N*-(2-bromoethyl)phthalimide in 100 mL of mesitylene was refluxed for 22 h. The solvent, when cooled to room temperature, was removed from the crystalline reaction product by filtration and the crystals were washed successively with benzene and pentane to provide 12.33 g (60%) of **1**. Recrystallization from 2-propanol gave the analytical sample, mp 242–243 °C.

Compounds **5**–**11** were prepared in DMF solution at 50–90 °C. On completion of the reaction, the solvent was evaporated under vacuum and the residue triturated with benzene or dioxane or chromatographed over silica gel Woelm (dry column grade, activity III).

β-(Bromoethyl)triphenylphosphonium Bromide (12). A mixture of 42.8 g (0.11 mol) of β-(hydroxyethyl)triphenylphosphonium bromide[1] and 20.6 g (0.076 mol) of PBr_3 was heated on a steam bath with occasional shaking for 1.25 h. The syrup obtained was suspended in H_2O and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent gave 44.4 g (89%) of **12**. Recrystallization from 2-propanol gave an analytical sample, mp 191–193 °C (lit.[1] mp 198–200 °C).

2-(4-Methyl-1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyltriphenylphosphonium Bromide (14). To a solution of 10.0 g (22 mmol) of **12** in 200 mL of CH_3CN was added 4.4 g (22 mmol) of the K salt of 3-methylphthalimide (prepared by the procedure of Sah and Ma[5]) and 0.2 g (0.54 mmol) of dicyclohexyl-18-crown-6 in 10 mL of CH_3CN. Then 200 mL of MeOH was added to give a solution and the reaction stirred at room temperature for 24 h. Evaporation of solvent gave a solid which was treated with boiling $CHCl_3$ and filtered. Evaporation of solvent gave a solid which was recrystallized from EtOH, then 2-propanol–ethanol, and finally H_2O and dried at 60–75 °C under high vacuum for 5 h. This gave 5.6 g (48%) of **14**, mp 180–185 °C.

Compound **23** was prepared from 2 mol of **12** and 1 mol of the dipotassium salt of pyromellitic diimide. The latter was obtained by treatment of pyromellitic diimide in DMF with KOH in EtOH, followed by heating on a steam bath for 15 min. The salt was filtered after cooling.

Compound **22** was inadvertently prepared when **12** was allowed to react with the K salt of 1,8-naphthalimide. The reader is referred to ref 4 for an alternate procedure to **22**.

2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyltriphenylphosphonium Chloride Hemihydrate (19). A 25-mL portion of Amberlite IRA-400 ion-exchange resin was washed three times with 1 N HCl (75-mL portions) in a beaker. It was then packed in a column (1.5 cm in diameter × 15 cm in length) with 1 N HCl and washed again with 100 mL of 1 N HCl, followed by distilled water until the washings were neutral. The column was

then rinsed with 150 mL of MeOH–H_2O (1:1).

A 1.5-g (2.91 mmol) sample of 1 was then dissolved in 10 mL of MeOH and diluted with 10 mL of H_2O. This solution was added to the above column and 2-mL fractions were collected at a flow rate of 1.5 mL/min. A total of 20 fractions was collected. Fractions 3–14 were combined and evaporated to a solid which was recrystallized from 2-propanol and dried at 60 °C for 8 h under high vacuum to give 0.96 g (69%) of **19**, mp 240–242 °C.

***N*-[2-(Triphenylphosphonium bromide)ethyl]isoindoline Hydrobromide Monohydrate (20).** To 171 mL of 0.8 M BH_3 in THF (0.14 mol) at 0–5 °C under N_2 atmosphere was added dropwise a solution of 5.0 g (0.034 mol) of phthalimide in 130 mL of THF. The mixture was warmed gradually, then refluxed 1 h, and stirred overnight at room temperature. It was then cooled to 5 °C and 6 N HCl was added dropwise until pH 2. The mixture was warmed gradually, then refluxed 1 h, and filtered (solid discarded), and the solvent was removed under vacuum. To the residue was added 100 mL of H_2O and the solution was basified with NH_3(g) to pH 9, then extracted with $CHCl_3$, and dried over K_2CO_3. Evaporation gave a solid–liquid mixture which was filtered. The filtrate was then vacuum distilled to give 1.8 g (44%) of isoindoline, bp 75–82 °C (7.5 mm) [reported[6] bp 96–97 °C (10 mm)].

To a solution of 6.4 g (14 mmol) of **12** in 60 mL of DMF was added a solution of 1.7 g (14 mmol) of the above isoindoline in 10 mL of DMF. The reaction mixture was heated at 64 °C under N_2 for 4 h, and the solvent was then evaporated to an oil. This was triturated with EtOAc to a solid which was recrystallized from EtOH and then H_2O and dried under high vacuum at 60 °C for 10 h. This gave 5.0 g (61%) of **20**, mp 256–260 °C dec.

2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyldiphenylphosphine Oxide (24). To a solution of 4.92 g (19 mmol) of *N*-(2-bromoethyl)phthalimide in 10 mL of DMF under N_2 atmosphere was added 5.0 g (19 mmol) of *n*-butoxydiphenylphosphine. The reaction mixture was heated on a steam bath for 10 h and then refluxed for 12 h. The solvent was evaporated to an oil which was treated with benzene and filtered. The filtrate was evaporated to another oil which was chromatographed over silica gel Woelm (dry column grade, activity III) with benzene, followed by $CHCl_3$. The $CHCl_3$ fractions were combined and evaporated to a white solid which was recrystallized from EtOAc and dried at 60 °C under high vacuum for 6 h. This gave 0.85 g (12%) of **24**, mp 164–167 °C.

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A Ureido Group Containing Analogue of Oxytocin Comprising Eight Amino Acid Residues

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A new analogue of oxytocin was constructed from L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-lysyl-L-prolyl-L-leucylglycinamide. Reaction of this 8-peptide amide with di-*p*-nitrophenyl carbonate yielded a cyclic compound, in which the $-CH_2SSCH_2-$ bridging portion of oxytocin formed by the oxidative linking of the two cysteine side chains was replaced by the $-CH_2CH_2CH_2CH_2-$ group of lysine, while the ϵ-NH_2 group of the same residue took the place of the α-CH of cysteine-1. The N-terminal amino group of oxytocin, which is not necessary for its hormonal activities, was omitted. The new analogue, referred to as [1,6-N^{ϵ}-carbonyl-L-lysine]oxytocin, possessed a rat uterotonic activity in vitro of 3.9 ± 0.3 units/mg, less than 0.5 unit/mg of rat antidiuretic activity, and caused a marked tachyphylaxis in the rat pressor assay. Moreover, the analogue was a strong competitive inhibitor, with a pA_2 value of 7.27 ± 0.13 of the oxytocin induced vasodepressor response in chickens.

In the paper[1] announcing the first synthesis of a peptide hormone, du Vigneaud and his associates considered oxytocin an octapeptide. Yet, both in biosynthesis and in the laboratory procedures two cysteine residues are incorporated rather than the disulfide cystine. Therefore it is probably more appropriate to call oxytocin a cyclic nonapeptide (or a 9-peptide[2]). A numbering system has been proposed[3] accordingly (Figure 1). The recognition by Rudinger and his collaborators[4] that the disulfide bridge is not an essential feature of the molecule opened the way to the construction of new analogues in which the sulfur atoms were replaced by CH_2 groups.[5,6] An inspection of the structure of deamino-dicarbaoxytocin[6] suggested to us that if the cysteine residue in position 6 of the C-terminal 8-peptide of oxytocin would be replaced by lysine (compound I in Figure 2), then the insertion of a –CO– group could close a ring of 20 atoms. The resulting compound, II, would be quite analogous to deamino-dicarbaoxytocin,[6] except that in II an –NH– group takes the place of a $-CH_2-$ group in the potent oxytocin analogue. The possible perturbations caused by a urea grouping in the ring of II on the conformation of the molecule and/or the influence on its interaction with specific oxytocin receptors has not been overlooked, but it seemed to be worthwhile to prepare compound II and examine its biological activities.

Synthesis of [6-lysine]oxytocin$_{2-9}$ (compound I) has been described earlier.[7] In our first attempts to prepare compound II we tried to acylate one of the two free amino groups of I with *p*-nitrophenyl chlorocarbonate[8] in the

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