**Registry No.** 1, 83726-78-7; 1·Hbr, 83726-79-8; 2, 109628-21-9; 2·HBu, 113669-42-4; 3, 109628-22-0; 3·HBr, 113669-43-5; 4, 113669-44-6; 4·HBr, 113669-45-7; 5, 83726-76-5; 6, 83726-82-3; 7, 83726-81-2; 8, 113669-46-8; 8·HBr, 113669-47-9; 9, 109658-78-8; 9·HBr, 113669-48-0; 10, 113669-49-1; 10·HBr, 113669-50-4; 11, 109628-19-5; 12, 113669-51-5; 12·2HBr, 113669-52-6; 13, 100565-47-7; 13·HBr, 113669-53-7; 14, 51344-10-6; 14·HBr, 113669-54-8; 15, 52402-78-5; 15·HBr, 100565-45-5; 16, 109628-23-1; 17, 108772-84-5; 18, 113669-55-9; 19, 113669-56-0; 20, 113669-57-1; 22, 103191-90-8; 23, 90-43-7; 24, 580-51-8; 25, 92-69-3; 26, 1134-35-6; 27, 81998-05-2; 2-chloro-4-methylpyrimidine, 13036-57-2; sodium 2-(dimethylamino)ethanethiolate, 55931-94-7; 2-chloro-5-methylpyrimidine, 22536-61-4; 2-(dimethylamino)ethanol, 108-01-0; 2-chloropyrimidine, 1722-12-9; thiophene, 110-02-1; furan, 110-00-9; 1-methylpyrrole, 96-54-8; phenyllithium, 591-51-5; *N,N*-dimethylethylenediamine, 108-00-9; 2-(dimethylamino)-ethylchloride hydrochloride, 4584-46-7; bleomycin $A_2$, 11116-31-7; bleomycin $B_2$, 9060-10-0.

# Synthesis and Testing of Quinone-Based Bis(2,2-dimethyl-1-aziridinyl)phosphinyl Carbamates as Radiation-Potentiating Antitumor Agents

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Two new drug candidates, in which a quinonoid moiety is linked to the reactive bis(2,2-dimethyl-1-aziridinyl)phosphinyl function, have been prepared and tested in vivo for antitumor activity and in vitro as potentiators of the cytotoxic effect of X-irradiation. Without irradiation only moderate effectiveness against leukemia P-388 in mice was exhibited by one of the quinonoid compounds that had sufficient water solubility to be used in the in vivo screening. However, both compounds were shown to potentiate the effect of X-irradiation in vitro by a colony-forming cell culture assay under hypoxic conditions.

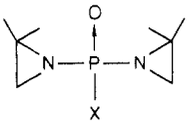
Several quinone compounds have shown useful anticancer activity, the best known of these being the antitumor antibiotics adriamycin, daunorubicin, mitomycin C, and streptonigrin. Other antineoplastic quinones include the naphthoquinone lapachol,[1] Sartorelli's bioreductively activated alkylating quinones (2-(halomethyl)-3-phenyl-1,4-naphthoquinones),[2] Driscoll's series of aziridinyl quinones,[3,4] and certain aminoquinones.[5] Also the *o*-hydroquinones levodopa and dopamine, when activated via oxidation to *o*-quinones by tyrosinase, have been shown to be cytotoxic to human and murine cancer cells, in part due to their ability to inactivate such sulfhydryl-dependent enzymes as DNA polymerase $\alpha$ and reverse transcriptase.[6]

Most of these antineoplastic drugs containing a quinoid moiety appear to exert their major effects via participation in oxidation–reduction reactions, with the active species believed to be the relatively stable semiquinone radical. This species might act directly on DNA[5] or DNA polymerase[6] by transfer of an electron, or by binding to a susceptible group (alkylating activity), or may act by intervening in oxygen-metabolizing processes,[7] promoting the formation of superoxide, hydroxyl, and peroxide radicals.[8]

The quinone antitumor drugs also possess some other characteristics that may contribute to their effectiveness as antineoplastic agents. Because of their planar ring structures, many of the known quinone drugs bind to DNA via intercalation;[7] this binding activity may induce single or double strand breaks in the DNA of carcinoma cells.[5] Moreover, the affinity of these drugs for the DNA helix directs the reactivity of the semiquinone radical toward this target. Many quinones also exhibit good lipid solubility and low levels of ionization, required for penetration of the blood–brain barrier, making them potentially effective agents against tumors of the central nervous system.[4]

Although most of the quinonoid antineoplastic drugs may be transformed to their active semiquinone forms intracellularly via the action of such enzymes as NADPH cytochrome P450 reductase,[9] a second known method of forming the semiquinone form is by irradiation.[10] Thus, the quinones as a group may act as radiation sensitizers, as has been shown in vitro for menaquinone.[10,11] However, the potential radiation sensitizing activity of quinones in vivo has not been so far tested or reported in the literature.

A different class of antineoplastic agents, the multifunctional bis(2,2-dimethyl-1-aziridinyl)phosphinic esters,[12] amides,[13] carbamates,[14] and hydroxycarbamates[15] termed "dual antagonists" (**1**–**3a**), has previously shown the ability




**1**, X = *O*-alkyl (X=OEt, AB-163)
**2**, X = $NR^1R^2$; $R^1$,$R^2$=H or alkyl
**3**, X = $NHCO_2$-alkyl (X = $NHCO_2Et$, AB-132)
**3a**, X = $ONHCO_2$-alkyl (X = $ONHCO_2Et$, AB-183)

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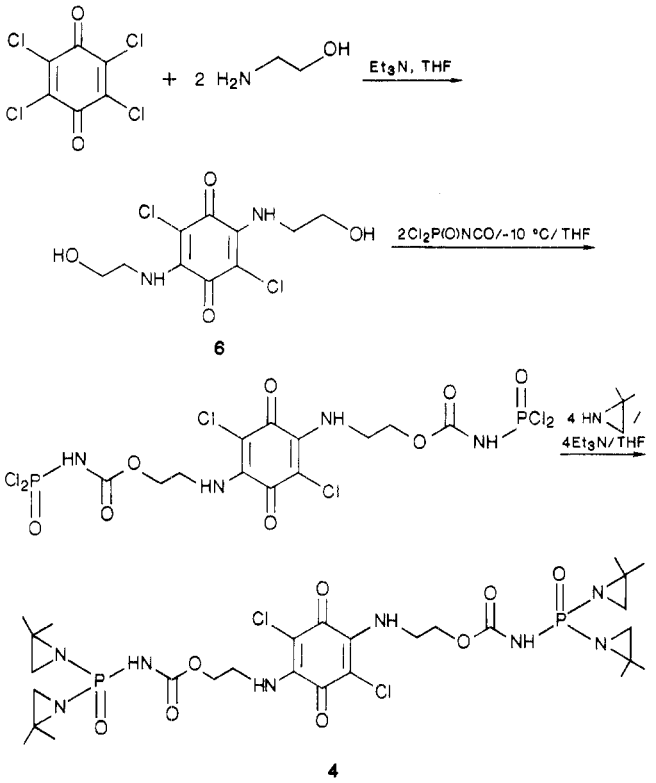
**Scheme I**




to enhance the in vivo antitumor effect of X-irradiation[16-23] in experimental animals as well as in humans, by a mode of action apparently not based on electron affinity as in the case of most other radiosensitizing agents (quinones, nitroimidazoles, nitrobenzene derivatives). A postulated mechanism for radiopotentiation by this group of compounds involves the inhibition of repair of radiation-induced damage to DNA, possibly through hydrolytic intermediates that act as phosphorylating agents.[24] However, it is conceivable that the (2,2-dimethylaziridinyl)phosphinyl moiety may also form a reasonably stable tertiary radical ion via uptake of an electron from the irradiated aqueous medium.

On the basis of these considerations, the bis(2,2-dimethylaziridinyl)phosphinyl moiety has been combined with a quinonoid nucleus to form the dual-acting agents **4** and **5**, allowing the different modes of action of each moiety to contribute additively or synergistically to the overall chemotherapeutic effect of the drug, either alone or in combination with X-irradiation. The syntheses of **4** and **5** and the results of their initial biological testing are here described.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**Scheme II**

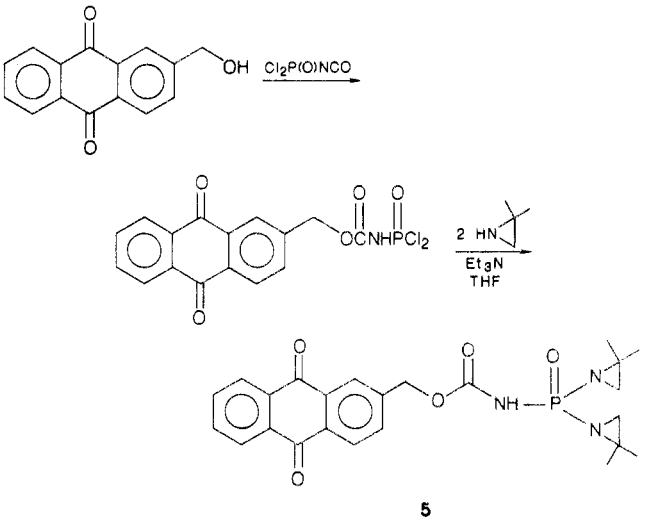


**Table I.** Screening of Compound **4** against P-388 Leukemia in Mice

| compound | dose,[a] mg/kg (mmol/kg) | AWC,[b] g | % T/C[c] |
|---|---|---|---|
| **4** | 256 (0.34) | −2.1 | 165 |
| | 128 (0.17) | −0.9 | 135 |
| | 64 (0.085) | −1.2 | 124 |
| | 32 (0.042) | −0.6 | 129 |
| | 16 (0.021) | −1.1 | 124 |
| | 8 (0.011) | −0.4 | 118 |
| **3** (AB-132) | 400 (1.45) | −1.3 | 244 |
| | 200 (0.73) | −0.2 | 231 |
| | 100 (0.36) | −0.4 | 181 |
| | 50 (0.18) | −0.7 | 163 |
| cyclophosphamide | 250 (0.96) | −2.5 | 511 |
| | 125 (0.48) | −1.1 | 311 |

[a] Given as a single ip injection on day 1 following tumor implant. [b] Median survival times (MST) of treated animals as percent of the MST of untreated controls. [c] Average weight change on day 5 of the experiment.

## Chemistry

The synthesis of **4**, the first quinone phosphoraziridine studied, is outlined in Scheme I. Tetrachlorobenzoquinone (Chloranil) was reacted with 2-aminoethanol, as described by Asahara et al.,[25] to give the intermediate 2,5-bis[(2-hydroxyethyl)amino]-3,6-dichloro-1,4-benzoquinone. This intermediate was then condensed with 2 equiv of dichloroisocyanatophosphine oxide, and the product of the biscarbamoylation was treated immediately with 2,2-dimethylaziridine in the presence of triethylamine to give **4**.

Compound **5** was obtained in an analogous manner from the commercially available 2-(hydroxymethyl)anthraquinone, by carbamoylation followed by reaction with 2,2-dimethylaziridine (Scheme II).

**Antitumor Activity.** Compound **4** was screened against P-388 leukemia implanted intraperitoneally in CDF-1 female mice. Intraperitoneal administration of **4** in water/Tween 80 solution in a single dose on day 1 resulted in significant (albeit moderate) antitumor activity, with T/C values greater than 120% for all doses above 8 mg/kg and T/C of 165% at 256 mg/kg, the maximum dose tested. By comparison, in an earlier experiment using essentially identical conditions, the experimental drug AB-132 (**3**) showed a T/C of 231% at 200 mg/kg. The difference between the potencies of these two drugs is less


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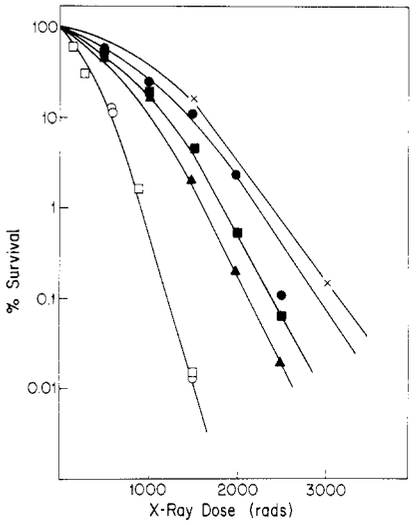


**Figure 1.** Survival curves for V-79 cells irradiated under oxic and hypoxic conditions when treated with 4. Drug/atmosphere combinations are as follows: no drug/$N_2$ (x), 0.05 mM 4/$N_2$ (●), 0.1 mM 4/$N_2$ (■), 0.5 mM 4/$N_2$ (▲), no drug/air (○), 0.5 mM 4/air (□).

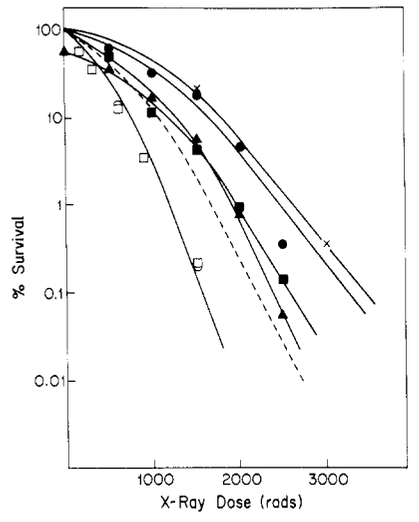


**Figure 2.** Survival curves for V-79 cells irradiated under oxic and hypoxic conditions when treated with 5. Drug/atmosphere combinations are as follows: no drug/$N_2$ (x), 0.001 mM 5/$N_2$ (●), 0.005 mM 5/$N_2$ (■), 0.01 mM 5/$N_2$ (▲), no drug/air (○), 0.005 mM 5/air (□). Dotted line: Misonidazole, 1.0 mM/$N_2$.

significant when considered in terms of mole equivalent doses, since there is a great disparity in the molecular weights of 3 (275.3 g/mol) and 4 (753.6 g/mol). The data for these two experiments are given in Table I.

Compound 5 was not tested in this in vivo screening assay because of its insolubility in water.

## Radiation Sensitization

Both 4 and 5, as well as the known radiosensitizing drug Misonidazole, were tested for their ability to potentiate the cytotoxic effect of X-irradiation under oxic and hypoxic condition in a cell culture assay employing Chinese hamster lung fibroblast line V-79. The data thus obtained are presented for 4 and 5 as survival curves (see Figures 1 and 2) conforming to the multitarget model described by the equation[26] $S = 1 - (1 - e^{kD})^n$, where $S$ is the surviving fraction of cells, $k$ is the slope of the linear portion of the curve when $S$ is plotted semilogarithmically against the radiation dosage $D$. The extrapolation number $n$ is the intercept of the extrapolation of the linear (exponential) portion of the survival curve on the ordinate when using a fractional (0–1.0) rather than a percent scale. This extrapolation number $n$ indicates the number of unrepairable events needed to kill a cell,[27] although in mammalian cells there may be some deviation from the simple model described by the equation.[28] For these quinone derivatives, as for Misonidazole, a common extrapolation number of approximately 10 was found.

**Table II.** Sensitizer Enhancement Ratios (SER) for Compounds 4, 5, Misonidazole, and $O_2$

| drug/atmosphere condition during irradiation | SER (1%) |
|---|---|
| 0.05 mM 4/$N_2$ | 1.07 |
| 0.10 mM 4/$N_2$ | 1.30 |
| 0.50 mM 4/$N_2$ | 1.47 |
| $O_2$ | 2.60 |
| 0.10 mM Misonidazole/$N_2$ | 1.10 |
| 1.00 mM Misonidazole/$N_2$ | 1.46 |
| $O_2$ | 1.93 |
| 0.001 mM 5/$N_2$ | 1.05 |
| 0.005 mM 5/$N_2$ | 1.33 |
| 0.01 mM 5/$N_2$ | 1.37[a] |
| $O_2$ | 2.17 |

[a] This curve is eccentric due to chemical toxicity of 5 at this dose. Thus SER is not constant throughout the exponential part of the curve.

The survival curves may be compared by use of a sensitizer enhancement ratio (SER) defined here as

$$\text{SER} = \frac{\text{radiation dose at 1\% survival in absence of drug}}{\text{radiation dose at 1\% survival in presence of drug}}$$

SER values at 1% survival for compounds 4, 5, Misonidazole, and $O_2$ are given in Table II.

The survival curves generated for 4 (Figure 1) show no cytotoxicity in the absence of radiation at the doses employed. In the presence of air, no radiation potentiation (beyond that caused by $O_2$) was observed, just as in the case of the typical "hypoxic" radiosensitizers such as Misonidazole.[29] Like the latter, 4 was effective in potentiating the lethality of X-irradiation under hypoxic conditions. The survival curves for 4 shown in Figure 1 are quite similar to those obtained for Misonidazole (not shown). In fact, the curves for 0.05 and 0.5 mM 4 virtually are overlapping with those for 0.1 and 1.0 mM Misonidazole, respectively. Thus, on a molar concentration basis, 4 appears to be twice as potent as Misonidazole, but when compared at their highest nontoxic concentrations tested, the two compounds produced the same radiation-sensitizing effect.

The anthraquinone derivative 5, as shown by the survival curves (Figure 2), does exhibit cytotoxicity against hypoxic V-79 cells at a concentration of 0.01 mM in the absence of radiation. The curves generated for 5 at doses of 0.001 and 0.005 mM are comparable to those of Misonidazole at doses of 0.1 and 1.00 mM, respectively, but at the latter concentration, the survival curve for Misonidazole (dotted line) is steeper than that for compound 5 at 0.005 mM. In other words, 5 shows significant radiosensitizing activity at 100 times lower molar concentrations than Misonidazole does, but the latter is the more

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effective radiosensitizer if the two compounds are compared at their maximum nontoxic concentrations and at a higher than 1000-rad X-ray dose. Again, as in the cases of both 4 and Misonidazole, no potentiation of the radiation effect by 5 was detected under oxic conditions.

## Discussion

The preliminary evaluation of 4 and 5 suggests that the concept of the combination of a quinonoid moiety with the bis(2,2-dimethyl-1-aziridinyl)phosphinyl moiety does bear some promise. The benzoquinone derivative 4 shows at least moderate activity in vivo against murine P-388 leukemia and is able to potentiate the effect of X-irradiation in vitro. It may be postulated that each of these effects is due to a different half of the combined-modality drug 4. Driscoll[3] noted that all of the 3,6-dihalo-2,5-aziridinyl quinones evaluated against L1210 leukemia in a 1976 study proved to be inactive and speculated that an electronic effect, affecting the quinones' redox potentials, might be the cause of this. (A second speculative explanation, that a lipophilic transport effect may have caused inactivity, does not apply in the case of 4, since the in vivo activity against P-388 indicates that 4 did reach the target sites.) If the electronic effect of dihalo substitution does prevent the metabolic activation of the benzoquinone moiety, then the activity of 4 against the P-388 leukemia must be primarily an effect of the bis(2,2-dimethyl-1-aziridinyl)-phosphinyl group. Conversely, in the hypoxic radiosensitization study, the effects observed may be attributed specifically to the benzoquinone half of the molecule, since this cell-culture assay has been previously found to be unable to detect hypoxic radiosensitization by the bis-(2,2-dimethyl-1-aziridinyl)phosphinyl derivatives AB-132 and AB-163 at any noncytotoxic doses[30] although the latter compounds had been demonstrated to possess significant radiation potentiating abilities in vivo.[16-23] Further testing of 4, in an experimental model capable of detecting radiation potentiation by phosphoraziridines as well as by electron-affinic moieties such as quinones, would be desirable, in order to establish whether both modes of action of this dual-modality radiation potentiator will operate additively or synergistically.

The anthraquinone 5 is itself not a promising drug candidate because of its extremely low solubility in aqueous media. However, its potent cytotoxicity and radiation-potentiating activity at very low concentrations suggest that more soluble analogues of 5 could be worthy candidates for study, especially as radiation-sensitizing agents.

## Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA, and by Galbraith Laboratories, Knoxville, TN. NMR spectra were obtained on a Varian T-60 spectrometer and values are reported in parts per million ($\delta$) from TMS.

The 2,2-dimethylaziridine was supplied by Polyscience, Inc. Dichloroisocyanatophosphine oxide was prepared by the method described by Papanastassiou and Bardos.[31]

**2,5-Bis[(2-hydroxyethyl)amino]-3,6-dichloro-1,4-benzoquinone (6).** A solution of 122.2 mg of 2-aminoethanol (2 mmol) in 15 mL of THF was added dropwise over a 30-min period to a mixture of 246 mg of choranil (1 mmol) in 15 mL of THF at 10–15 °C. After complete dissolution of the chloranil, the reaction mixture was stirred for 4 h at room temperature and then chilled to −10 °C and filtered, and the solid product was washed with cold water. The 280 mg of crude brown product thus obtained was recrystallized from ethanol to yield 250 mg (72.8% yield) of purple crystalline 6: mp 169 °C dec; NMR (DMSO-$d_6$) $\delta$ 7.8 (s, 2, NH), 4.9 (t, 2, OH), 3.8 (m, 8, $CH_2$). Anal. ($C_{10}H_{12}Cl_2N_2O_4$) C, H, N.

**2,5-Bis[[2-[[[bis(2,2-dimethyl-1-aziridinyl)phosphoryl]-carbamoyl]oxy]ethyl]amino]-3,6-dichloro-1,4-benzoquinone (4).** A suspension of 295 mg (1 mmol) of 6 in 25 mL of dry THF, under a dry atmosphere, was treated with 363 mg (2.5 mmol) of dichloroisocyanatophosphine oxide at −15 to −20 °C. Stirring was continued for 3 h at 0–5 °C, with solution achieved after 1 h. A solution of 320 mg (4.5 mmol) of 2,2-dimethylaziridine and 0.85 mL (6.1 mmol) of triethylamine in 20 mL of THF was added dropwise at 0–3 °C and stirring continued for 3 h at 0–5 °C. Filtration, concentration of the filtrate to 15 mL, and addition of 15 mL of isopropyl ether gave crude 4 as a purple-pink solid. Recrystallization of 4, by dissolving in THF, addition of isopropyl ether to turbidity, and cooling at −20 °C for 5 h gave 308 mg (41% yield) of the pure compound as a purple-pink powder: mp 125–127 °C; NMR ($CDCl_3$) $\delta$ 7.3 (br, 4, NH), 4.3 (m, 8, $CH_2$), 2.28 (d, 8, aziridine $CH_2$, $J$ = 14.5 Hz), 1.45 (s, 24, $CH_3$). Anal. ($C_{28}H_{44}Cl_2N_8O_8P_2$) C, H, N, P.

**2-[[[[Bis(2,2-dimethyl-1-aziridinyl)phosphoryl]carbamoyl]oxy]methyl]-9,10-anthraquinone (5).** Compound 5 was prepared by the same method as was 4 (vide supra), with 476.5 mg (2 mmol) of 2-(hydroxymethyl)anthraquinone (Aldrich) in 25 mL of THF, 360 mg (2.4 mmol) of dichloroisocyanatophosphine oxide, and 342 mg (4.8 mmol) of 2,2-dimethylaziridine plus 0.5 mL of triethylamine in 20 mL of THF. The reaction mixture was chilled to −10 °C, filtered, concentrated to 15 mL, combined with 10 mL of dry ethyl ether, and filtered again. Solvent removal afforded 0.72 g of yellow solid, which was washed three times with 10:1 ethyl ether/THF to leave 0.51 g (55% yield) of yellow 5: mp 140–141.5 °C; NMR ($CDCl_3$) $\delta$ 8.30 (m, 4, aryl 1,4,5,8 H), 7.83 (m, 4, aryl 3,6,7 H, NH), 5.34 (s, 2, $CH_2$), 2.31 (d, 4, aziridine $CH_2$, $J$ = 14 Hz), 1.43 (d, 12, $CH_3$, $J$ = 2 Hz). Anal. ($C_{24}H_{26}N_3O_5P$) C, H, N.

**In Vivo Testing against P-388 Murine Leukemia.** P-388 leukemia was maintained in ascitic form in DBA/2 mice. At the initiation of testing procedures, $10^6$ cells were injected into $CDF_1$ female mice (16–20 g), with six mice for each dose level and 10 mice as a leukemia control group.

Compounds 3 and 4 were dissolved in $H_2O$ with the aid of Tween 80, to give total injection volumes of 0.5 mL, and were administered to the mice within 15 min of dissolution. A single drug treatment, by ip injection the first day, was used, and the mice were observed until death to determine their survival times and T/C values.

**Radiation-Sensitization Studies. Cell Culture.** All radiation-sensitization experiments used V-79 Chinese hamster lung fibroblast cells, maintained in an asynchronous monolayer in a humidified, $CO_2$-enriched incubator, at 37 °C, with RPMI 1640 medium plus 50 g/mL gentamicin and 5% v/v fetal celf serum as a growth medium. Immediately prior to testing, drugs were dissolved in cold RPMI 1640 medium, with use of DMSO (up to 5% of final volume) with the RPMI 1640 for some insoluble compounds.

**Irradiation under Oxic Conditions.** V-79 cells grown in 35 × 15 mm tissue culture dishes were given fresh medium and treated with the freshly prepared drug solution, incubated for 30 min, and then X-irradiated with Westinghouse Coronado 250 kvp X-ray source for 0–15 min at 150–220 rads/min. One hour after the addition of the drug, the medium was replaced, and the dishes were incubated for a short time. The cells were then trypsinized, detached, and made into a single-cell suspension in 5 mL of fresh medium. Cell concentration was determined with an Electrozone-Celloscope electronic particle counter and the suspension was diluted to $10^4$ cells/mL. From this suspension tissue culture dishes were plated with 100–100 000 cells, depending on the radiation dose, and given fresh medium; plating efficiencies were at least 85%. The dishes were incubated in a $CO_2$ incubator for 1 week or until visible colonies were formed. The cells were then fixed with formalin and stained with methylene blue. The stained colonies were counted manually.

**Irradiation under Hypoxic Conditions.** Radiation treatment under hypoxic conditions was accomplished as above, except that

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pretreatment cultures of cells were grown in 25-$cm^2$ disposable plastic tissue culture flasks, and before drug and X-ray treatment, the flasks received fresh complete medium and were ventilated with humidified gas consisting of 95% $N_2$ and 5% $CO_2$ for 4 h at 37 °C with very gentle agitation. Drug was then added via a syringe so as to introduce no $O_2$. Irradiation procedures and the subsequent colony-forming assay were as described above for oxic conditions.

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**Registry No.** 4, 113811-39-5; 5, 113811-41-9; chloranil, 118-75-2; 2-aminoethanol, 141-43-5; 2,5-bis[(2-hydroxyethyl)amino]-3,6-dichloro-1,4-benzoquinone, 28857-12-7; 2,5-bis[[(dichlorophosphinyl)[(carbamoyloxy)ethyl]amino]-3,6-dichloro-1,4-benzoquinone, 113811-38-4; 2,2-dimethylazinidine, 2658-24-4; 2-(hydroxymethyl)anthraquinone, 17241-59-7; 2-[(dichlorophosphinyl)carbamoyloxymethyl]anthraquinone, 113811-40-8.

# Synthesis and Analgesic Activity of Pemedolac (*cis*-1-Ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic Acid)†

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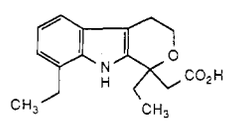
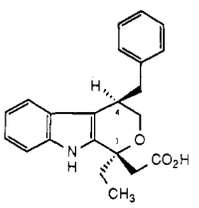
The synthesis of *cis*-1-ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic acid, pemedolac (USAN), is described. This compound has been found to be a potent analgesic agent in primary screening. Pemedolac has been resolved and the active (+)-enantiomer assigned a 1*S*,4*R* absolute configuration on the basis of a crystallographic analysis of its (*S*)-(−)-borneol ester.

In 1976 we disclosed the discovery of a novel antiinflammatory agent, 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-*b*]indole-1-acetic acid, etodolac.[1] Since then, etodolac has progressed successfully through clinical studies and has been demonstrated to be an effective agent possessing an exceptional gastrointestinal safety profile in humans.[2] Like many other nonsteroidal antiinflammatory drugs, etodolac also possesses analgesic properties.[3] Continued investigations of the pyrano[3,4-*b*]indole-1-acetic acids have now led to a new series of agents exhibiting a marked separation of the levels of these activities. One member, *cis*-1-ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano-[3,4-*b*]indole-1-acetic acid, pemedolac (**13**), a highly potent analgesic with relatively weak antiinflammatory properties, has been chosen for further study and is currently being evaluated in humans. We report the synthesis, primary pharmacology, and X-ray structural determination of pemedolac (**13**) and its enantiomers.



etodolac

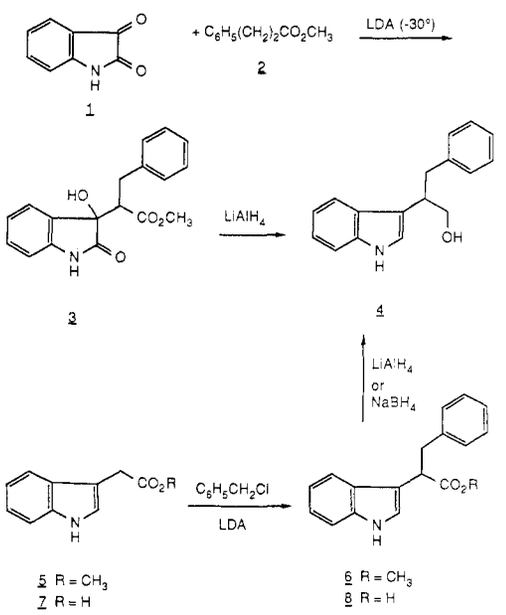


pemedolac 13

## Chemistry

Synthesis of pemedolac (**13**) was achieved as shown in Scheme I. The enolate of methyl phenylpropionate (**2**) was trapped by isatin (**1**) to form adduct **3**. Quantitative conversion was not observed; even when large excess of the enolate of **2** was utilized, unreacted isatin remained after workup. The crude adduct **3**, a mixture of diastereomers,

**Scheme I**




was treated with excess $LiAlH_4$ in tetrahydrofuran to afford β-(phenylmethyl)indole-3-ethanol (**4**) in a 72% yield. Indole, resulting from reduction of unreacted isatin, was obtained as a byproduct.

An alternate approach to β-(phenylmethyl)indole-3-ethanol (**4**) has been devised. The dianion of methyl indole-3-acetate (**5**), formed by treatment with lithium diisopropylamide (LDA) in tetrahydrofuran at −30 °C, was alkylated with benzyl chloride to afford adduct **6**. Upon reduction with sodium borohydride in methanol, β-(phenylmethyl)indole-3-ethanol (**4**) was obtained together with tryptophol. The latter presumably could have come from

† This paper is dedicated to Prof. E. C. Taylor by one of us (A.H.K.) on the occasion of his 65th birthday.
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