and the residue was taken up in 120 mL of water. The aqueous solution was washed three times with 40 mL of dichloromethane. The aqueous phase was stirred over 120 mL of dichloromethane, and the pH was adjusted to 8.5 with aqueous disodium hydrogen phosphate and sodium carbonate at 0 °C. The mixture was extracted four times with 120 mL of dichloromethane and washed with brine, and the combined extracts were dried over magnesium sulfate and evaporated to give 1.50 g of product. Purification by flash column chromatography on 80 g of silica gel (ethyl acetate + 1% triethylamine eluent) afforded 1.35 g of **5b**. Recrystallization from dichloromethane/hexanes afforded 1.26 g (85%) of **5b**: mp 221.5–222 °C; $[\alpha]^{23}_D$ −128.5° (CH_3OH, *c* 1.0); EI mass spectrum, *m/e* (relative intensity) 369.1572 (calcd 369.1568); ^1H NMR δ 6.50–6.90 (AB system, J = 8 Hz, 2 H, aromatic), 6.30 (br s, 2 H, OH), 6.12 (t, J = 3 Hz, 1 H, vinyl *E* proton), 6.50 (t, J = 2 Hz, 1 H, vinyl *Z* proton), 4.80 (s, 1 H, C5-H), 1.00–3.35 (m, 16 H), 2.38 (s, 3 H, NCH_3); IR (KBr) 1760 (s, lactone C=O); R_f 0.35 (98% ethyl acetate + 2% triethylamine, two elutions), oxymorphone has an R_f value of 0.26 in this solvent system. Anal. ($C_{21}H_{23}NO_5$) C, H, N.

Opioid Receptor Binding. [^{3}H]Naltrexone (9.8 Ci/mmol) and unlabeled naltrexone were generously supplied by Dr. Richard Hawks of the National Institute of Drug Abuse. [^{3}H-D-Ala-D-Leu]enkephalin (^{3}H-DADLE) (41 Ci/mmol) and [^{3}H]bremazocine (25 Ci/mmol) were purchased from New England Nuclear and [^{3}H-D-Ala^2-MePhe^4-Gly-ol^5]enkephalin (^{3}H-DAGO) (34 Ci/mmol) from Amersham.

Male Sprague–Dawley rats were decapitated, and a crude membrane fraction was prepared from the brains (minus the cerebellum) by a method previously described.[19] The membrane preparation (1:6 w/v) was stored in 0.32 M sucrose at −70 °C until needed. For binding assays the thawed membrane preparations were diluted with 9 volumes of 50 mM Tris buffer, pH 7.4, 1 mM potassium EDTA ± 100 mM NaCl.

Specific binding on control and treated samples was assayed on duplicate 2-mL samples as previously described.[20] Samples were incubated with ^{3}H opioid ± 1 μM unlabeled drug for 45 min at 25 °C and then filtered through GF/B filters. Filters were rinsed twice with 4 mL of buffer, dried, and counted in a toluene-based scintillation cocktail.

Irreversibility of Opioid Receptor Binding. Membrane preparations were incubated with the drug to be tested for 45 min at 25 °C. After incubation, treated membranes were diluted sixfold with 50 mM Tris buffer, pH 7.4, 1 mM potassium EDTA ± 100 mM NaCl and centrifuged for 15 min at 20000*g*. After the supernatant was removed, the pellet was resuspended in 3 times the original volume and incubated at 37 °C for 15 min. Samples were then spum again as above and finally resuspended in the original volume. In a few experiments, additional washes were done to show that the recovery of binding capacity reached a plateau. When a compound showed some degree of irreversibility, the ability of naltrexone to protect against inactivation was also examined. Fractions were preincubated 10–15 min at 25 °C with naltrexone before addition of the potential label.

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Registry No. **1a**, 16590-41-3; **1b**, 76-41-5; **4a**, 92398-20-4; 14-Ac-**4a**, 92398-21-5; **4b**, 92398-22-6; 14-Ac-**4b**, 92398-23-7; **4b**·AcOH, 92398-24-8; **5a**, 92398-30-6; THF-**5a**, 92398-34-0; **5b**, 92398-32-8; THF-**5b**, 92398-35-1; **6a**, 92398-19-1; **6b**, 64643-76-1; **7a**, 92398-25-9; **7b**, 92398-27-1; **8a**, 92398-26-0; **8b**, 92398-28-2; **9**, 92398-17-9; **10a**, 92398-29-3; **10b**, 92398-31-7; 11, 92398-18-0; **12**, 55096-33-8; methyl α-(bromomethyl)acrylate, 4224-69-5; trimethyloxosulfonium chloride, 5034-06-0; O^3-[[β-(trimethylsilyl)ethoxy]methyl]naltrexone, 92398-33-9; O^3-[[β-(trimethylsilyl)ethoxy]methyl]-4,5α-epoxy-3,6α,14-trihydroxy-6β-methyl-17-(cyclopropylmethyl)morphinan, 92398-36-2.

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1-Aryl-3,3-dimethyltriazenes: Potential Central Nervous System Active Analogues of 5-(3,3-Dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC)

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A series of 19 aryldimethyltriazenes were synthesized as potential central nervous system (CNS) active analogues of 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC). The compounds were screened in mice against both intraperitoneally (ip) and intracerebrally (ic) implanted L1210 leukemia. Select compounds were further screened against ic implanted ependymoblastoma, and one compound was additionally screened against ic implanted B16 melanoma. Although several compounds were as effective as DTIC at prolonging the life span of mice bearing ip implanted L1210 leukemia, only 4-(3,3-dimethyl-1-triazeno)benzamide (DTB) and 4-(3,3-dimethyl-1-triazeno)benzoic acid (DTBA) were significantly active against the ic implanted tumor. DTB, unlike DTIC, was equally effective against both the ip and the ic implanted tumor, clearly indicating that it penetrated into the CNS in therapeutic concentration. DTB was also active against ic implanted ependymoblastoma and ic implanted B16 melanoma. Aryldimethyltriazenes, particularly DTB, may have a role in the treatment of tumors metastatic to the CNS. They may also be effective against primary brain tumors.

DTIC [5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide, imidazole carboxamide, Dacarbazine, DIC, NSC 45388] is the most active single agent in the palliative management of human disseminated malignant melanoma.[1-3] However, it is usually not effective either in the therapy or the prophylaxis of cerebral metastases of this tumor.[2,3] In fact, patients with melanoma undergoing chemotherapy with DTIC, or a DTIC-containing regimen, frequently relapse in the CNS while their peripheral tumor is under good control.[2] Paradoxically, the patients at greatest risk from CNS relapse are those who respond best to chemotherapy. Although comprehensive tissue distribution studies of DTIC have not been reported in man, it seems likely that the poor responsiveness of cerebral tumors to the drug is due to its limited ability to penetrate into the CNS after parenteral administration. Low CNS

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drug levels have been reported in experimental animals treated with this agent.[4-6] For example, after intravenous administration of DTIC to the dog, either by rapid bolus injection or by continuous infusion, the maximum drug concentration observed in the cerebrospinal fluid is only about one-eighth of that of the corresponding plasma-free drug concentration.[4,5] The inability of DTIC to penetrate significantly into the CNS in man would be expected to severely compromise its efficacy in the treatment of malignant melanoma, since this tumor exhibits a propensity to metastasize to the CNS.[2] In fact, the autopsy incidence of CNS metastases in patients with disseminated melanoma has been variously reported[2,7-9] as 44–90%. In the majority of patients, CNS disease was considered to be the primary cause of death. Further improvement in the chemotherapeutic management of patients with metastatic melanoma, therefore, appears to be critically dependent on the availability of agents that can penetrate readily into the CNS.

The physicochemical and physiologic determinants of CNS drug penetrability have been reviewed.[10-14] Briefly, molecular properties that correlate with CNS drug entry are as follows: moderate to high lipid solubility, nonionic character at physiologic pH (7.4), and a molecular weight of less than approximately 700. The apparent limited ability of DTIC to penetrate into the CNS after parenteral administration is most likely due to its low lipophilicity ($\log P = -0.24$,[15] where P is the water/1-octanol partition coefficient), which, in turn, probably stems from the polar character of the imidazole ring. Previously, we[5,16-18] and others[19-23] have reported that 1-aryl-3,3-dimethyltriazenes are as effective as DTIC at prolonging the life span of mice bearing intraperitoneally (ip) implanted tumors.

Aryldimethyltriazenes are structural analogues of DTIC in which the imidazole moiety has been replaced with a benzene ring. In addition to antitumor activity, aryldimethyltriazenes and DTIC have other biologic properties in common. For example, both classes of drug are mutagenic,[24,25] teratatogenic,[26,27] and carcinogenic.[28-31] Moreover, they probably share a common mechanism of action; thus, both are oxidatively N-demethylated, in vitro, by P-450 dependent hepatic mixed function oxidases[32,33] to generate highly reactive intermediates which are capable of methylating biological macromolecules.[34-36] In addition, 7-methylguanine has been isolated from the tissues of rodents treated with DTIC[36,37] and 1-phenyl-3,3-dimethyltriazene.[38,39] Since aryldimethyltriazenes are, in general, more lipophilic than DTIC, we hypothesized that they might be able to penetrate more facilely into the CNS after parenteral administration and, therefore, be more effective in the treatment of CNS malignancies.

A further indication that aryldimethyltriazenes might gain ready entry into the CNS comes, paradoxically, from the distribution of tumors induced in experimental animals by chronic administration of these compounds. Thus, rats treated orally with DTIC developed tumors mainly in the peripheral system,[30,31] particularly mammary adenocarcinomas and thymic lymphosarcomas, although a few ependymomas were also observed. By contrast, similar administration of aryldimethyltriazenes resulted in tumors predominately of the brain and spinal cord.[28,29] The obvious conclusion from these findings is that either the parent aryldimethyltriazenes or their active metabolites penetrate into the CNS after parenteral administration. In this paper, we report the synthesis of a series of aryldimethyltriazenes and describe their antitumor activity against both intracerebrally (ic) and ip implanted neoplasms in mice. Preliminary accounts of this work have appeared.[5,18]

Results and Discussion

The data reported here extend our previous observations on the antitumor activity of aryldimethyltriazenes.[5,16-18] Of the 19 congeners evaluated, nine increased the life span of mice bearing ip implanted L1210 leukemia by at least 25% over that of controls (Table II). The most active compounds were those bearing a carbonyl-containing substituent (i.e., CO_2H, $COCH_3$, CO_2CH_3, $CONH_2$) located meta or para to the dimethyltriazeno group. The ortho-substituted analogues were ineffective. The six mono-

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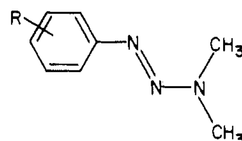
Table I. Physicochemical Properties of Aryldimethyltriazenes



no.	R	% yield	mp, °C	recryst solvent[a]	ref	log P^b	empirical formulae
1	o-$CONH_2$	25	130-134	A	19	1.73	$C_9H_{12}N_4O$
2	m-$CONH_2$	70	143-144	B	16	1.21	$C_9H_{12}N_4O$
3	p-$CONH_2$	75	175-177	B	19	1.20	$C_9H_{12}N_4O$
4	o-CO_2CH_3	91	liquid		46	2.72	$C_{10}H_{13}N_3O_2$
5	m-CO_2CH_3	67	43-45	B	16	2.77	$C_{10}H_{13}N_3O_2$
6	p-CO_2CH_3	91	99-100	B	16	2.77	$C_{10}H_{13}N_3O_2$
7	o-$COCH_3$	92	liquid			2.19	$C_{10}H_{13}N_3O$
8	m-$COCH_3$	86	liquid			2.19	$C_{10}H_{13}N_3O$
9	p-$COCH_3$	59	88-90	C		2.19	$C_{10}H_{13}N_3O$
10	o-CO_2H	41	124-126	A	46	-2.66	$C_9H_{11}N_3O_2$
11	p-CO_2H	58	174-176	B	47	-1.77	$C_9H_{11}N_3O_2$
12	o-Cl	95	liquid		48	2.97	$C_8H_{10}N_3Cl$
13	m-Cl	97	liquid		48	3.30	$C_8H_{10}N_3Cl$
14	p-Cl	27	56-57	B		3.30	$C_8H_{10}N_3Cl$
15	p-F	73	33-35	B	49	2.73	$C_8H_{10}N_3F$
16	p-Br	89	58-60	B	50	3.45	$C_8H_{10}N_3Br$
17	p-I	60	76-77	B	49	3.71	$C_8H_{10}N_3I$
18	o,o-Cl_2	74	liquid			4.01	$C_8H_9N_3Br_2$
19	o,o-Br_2	88	liquid			4.31	$C_8H_9N_3Br_2$
20	DTIC					-0.24	$C_6H_{10}N_6O$

[a] Recrystallization solvent: A, benzene-hexane; B, methanol; C, ethanol. [b] Log P values are calculated from ref 23 (Table I and eq 7).

Table II. Antitumor Activity of Aryldimethyltriazenes against ip Implanted and ic Implanted Murine Leukemia L1210[a]

		% increase in life span[b] (maximum)		opt dose,[c] mg/(kg day) (qd 1-9)	
no.	R	ip	ic	ip	ic
1	o-$CONH_2$	10	10	65	40
2	m-$CONH_2$	50	22	39	40
3	p-$CONH_2$	40	45	39	160
4	o-CO_2CH_3	11	14	65	40
5	m-CO_2CH_3	30	10	39	160
6	p-CO_2CH_3	40	7	39	160
7	o-$COCH_3$	0	9	108	40
8	m-$COCH_3$	55	6	65	40
9	p-$COCH_3$	16	5	108	20
10	o-CO_2H	12	6	65	20
11	p-CO_2H	41	25	39	80
12	o-Cl	21	5	65	80
13	m-Cl	11	7	108	40
14	p-Cl	26	2	108	80
15	p-F	16	ND[d]	300	ND
16	p-Br	0	ND	300	ND
17	p-I	5	ND	300	ND
18	o,o-Cl_2	39	12	108	160
19	o,o-Br_2	44	14	108	160
20	DTIC	50	18	108	160

[a] L1210 leukemia cells were implanted intracerebrally (ic, 10^4 cells) or intraperitoneally (ip, 10^5 cells) in groups of six $B_6D_2F_1$ mice. [b] Percentage increase in median survival time over untreated controls at optimal drug dosage. [c] The aryldimethyltriazenes, formulated as a suspension in Klucel, or in physiological saline containing a few drops of Tween 80, were administered ip daily for 9 consecutive days beginning 24 h after tumor implantation. At least five dose levels covering the dose range 10-300 mg/(kg day) were used for each drug. [d] ND: not determined.

Table III. Antitumor Activity of Aryldimethyltriazenes against ic Implanted Murine Ependymoblastoma[a]

no.	R	% increase in life span[b]	opt dose,[c] mg/(kg injection)
3	p-$CONH_2$	62	32
5	m-CO_2CH_3	62	128
6	p-CO_2CH_3	64	64
10	o-CO_2H	2	8
11	p-CO_2H	18	32
12	o-Cl	38	128
20	DTIC	60	64

[a] The tumor was inoculated ic in groups of six $B_6C_3F_1$ mice. [b] The percentage increase in life span of treated animals over controls at optimal dosage. [c] The drugs, formulated as described in Table II, were administered ip daily, for 5 consecutive days beginning 24 h after tumor implantation. Five dose levels covering the dose range 4-256 mg/(kg day) were used.

halogenated compounds screened were only marginally active, regardless of the position of the halogeno atom. The two o,o-dihalogeno analogues, by comparison, were as active as DTIC. This result is surprising in view of the marginal activity of the monosubstituted compounds. However, considered as a whole, the data in Table II clearly indicate that the L1210 tumor is relatively insensitive both to the aryldimethyltriazenes and to DTIC. This finding precluded systematic quantitative structure-activity analyses of the data. Nevertheless, it is apparent that a well-defined relationship does not exist between the lipophilicities of these compounds and their antitumor activities.

Of the 16 compounds evaluated against ic implanted L1210 leukemia, only the p-amide (DTB) and the p-carboxylic acid (DTBA) were significantly active (Table II). Although, at first sight, an increase in life span of 45% appears unremarkable, it is probably the optimal result that can be achieved with this class of compounds against the L1210 tumor. Thus, the maximum increase in life span obtained with DTB against the ip implanted tumor, where there is obviously no pharmacologic barrier to drug/tumor cell interaction, is 40% over that of controls. Since DTB, unlike DTIC, is equally effective against both the ic and ip implanted tumor, the obvious conclusion is that either the parent drug or its active metabolite(s) gains entry into the CNS in therapeutic concentration after ip administration. The marginal (18%) increase in life span observed with DTIC against the ic tumor is consistent with limited drug entry into the CNS.

Select aryldimethyltriazenes were screened against ic implanted ependymoblastoma, a transplantable murine brain tumor. Several compounds were significantly active (Table III), but none were superior to DTIC. Although

Table IV. Antitumor Activities of Dimethyltriazenobenzamide (3) and DTIC against ic Implanted B16 Melanoma[a]

compd	% increase in life span,[b] ic	opt dosage,[c] mg/(kg day), ic
3	30	40–80
DTIC	8	10–40

[a] The tumor was implanted ic in $B_6D_2F_1$ mice. [b] The percentage increase in median survival time over controls at optimal dosage. [c] The drugs, formulated as described in Table II, were administered intraperitoneally, every other day, for 17 days (i.e., q2d × 9). six dose levels covering the dose range 10–320 mg/(kg day) were used.

at first sight surprising, this result most likely reflects the exquisite sensitivity of the tumor to alkylating agents. In fact, several aryldimethyltriazenes that were ineffective against ic implanted L1210 leukemia (Table II) were significantly active against the ependymoblastoma. Several other alkylating agents that are generally considered to be ineffective against human CNS neoplasms (e.g., cyclophosphamide, uracil mustard) are also active against the ependymoblastoma.[40] This tumor, therefore, might not be the ideal model for predicting CNS-active alkylating agents in man.

Because of the promising activity of DTB against ic implanted L1210 leukemia, it was also screened against ic implanted B16 melanoma (Table IV). Again, this compound was more effective than DTIC. However, since the best result obtained with DTIC, in multiple screenings, against ip implanted B16 melanoma is about a 30% increase in life span (data not shown), the results are, once more, compromised by the inherent insensitivity of the tumor to the drugs. Nevertheless, the data in Table IV are consistent with facile entry of DTB or its active metabolites into the CNS.

Several interesting points emerge from a consideration of the data presented in this paper. In particular, anticancer drugs with an established role in the management of human malignancies (such as DTIC) occasionally are only marginally active against experimental tumors. This shortcoming constitutes a serious limitation to congener development since it is obviously difficult to select the most active member of a series of compounds that, collectively, show limited activity in the biologic test system. Hansch et al. conducted a comprehensive QSAR structure–activity analysis of aryldialkyltriazenes as potential antitumor agents and concluded that limited opportunity existed to improve their therapeutic activity through rational structural modification.[15,41] However, these investigators did not address the CNS drug penetration problem that appears to limit realization of the full therapeutic potential of DTIC. Our data show that DTB, unlike DTIC, is equally effective against both ic and systemically implanted tumors and, therefore, penetrates into the CNS in therapeutic concentration after parenteral administration. As already emphasized, the propensity of malignant melanoma to metastasize to the CNS, together with the paucity of CNS-active drugs, constitutes a serious problem in the chemotherapeutic management of patients with this tumor. It is indeed tragic that the patients at greatest risk for the development of CNS metastases are those whose peripheral tumor is best controlled by chemotherapy (because they survive longer).

A further consideration that should be addressed here is the well-known carcinogenic properties of aryldimethyltriazenes.[28,29] Although obviously detracting from the appeal of these compounds as therapeutic agents, this biologic property is manifested by many clinically effective antineoplastic drugs including DTIC,[42] Procarbazine,[42] the nitrosoureas,[42] and the anthracycline antibiotics.[43] In this context, it must be emphasized again that disseminated malignant melanoma with CNS involvement usually carries a grim prognosis. In fact, the average life expectancy of patients with this complication is only 2.75 months.[2] Under these circumstances, the risk of drug-induced secondary malignancies, which normally have a long latency period, is of relatively minor concern.

On the basis of our findings, it is reasonable to speculate that aryldimethyltriazenes may be effective in the therapy of CNS metastases of malignant melanoma and, therefore, may aid significantly in the overall chemotherapeutic management of patients with this disease. These compounds may also have potential in the treatment and prophylaxis of other CNS neoplasms including primary brain tumors such as gliomas and ependymoblastomas. Further studies with aryldimethyltriazenes as potential CNS-active drugs are in progress and will be the subject of a future communication.

Experimental Section

1. **Drugs.** The aryldimethyltriazenes were prepared by coupling the appropriate diazotized aromatic amine with dimethylamine according to the method of Lin et al.[16] as modified by Audette et al.[20] The crude reaction products were purified to homogeneity on TLC (silica gel F 254, benzene-ethyl acetate, 95:5, or chloroform–methanol, 3:1) either by recrystallization or by chromatography on magnesia–silica gel (Florisil) with chloroform as eluent. The structure of each compound was verified by NMR and MS. Elemental analyses (C, H, and N) were obtained for all new compounds; the observed values were within ±0.4% of the theoretical values. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The physicochemical properties of each compound are given in Table I.

2. **Tumors.** The compounds were screened against both ip and ic implanted L1210 leukemia in mice. Additionally, select congeners were screened against ic implanted ependymoblastoma and ic implanted B16 melanoma. These studies were performed by the Drug Evaluation Branch of the Division of Cancer Treatment at the National Cancer Institute according to standard protocols.[40,44,45] A brief summary of the experimental procedures follows. **Leukemia L1210:** The ascites tumor was inoculated ip (10^5 cells) or ic (10^4 cells) into $B_6D_2F_1$ mice. The aryldimethyltriazenes were formulated immediately before injection either as a suspension in aqueous Klucel [(hydroxypropyl)cellulose] or as a suspension in sterile saline containing a few drops of Tween 80. DTIC was formulated as a suspension in aqueous (carboxymethyl)cellulose. The drugs were administered ip for 9 consecutive days beginning 24 h after tumor implantation. A control group of mice received only the drug vehicle. **Ependymoblastoma:** The tumor was implanted ic in $B_6C_3F_1$ mice as reported.[40] The drugs, formulated as described above, were administered ip for 5 consecutive days beginning 24 h after tumor

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inoculation. **B16 melanoma** was implanted ic in $B_6D_2F_1$ mice according to the standard protocol.[44] The drugs, formulated as described, were administered ip every other day for 17 days beginning 24 h after tumor implantation. Antitumor activity was determined by comparing the median survival time of treated animals (T) with that of a control group (C), which received only the drug vehicle, and is expressed as a percentage increase in life span (% ILS), where % ILS = $(T/C - 1) \times 100$. A % ILS of at least 25% was considered significant. The optimum dose shown in Tables II–IV is that which produced the maximum % ILS in the screen.

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Registry No. **1**, 33330-89-1; **2**, 36120-57-7; **3**, 33330-91-5; **4**, 35967-28-3; **5**, 35972-50-0; **6**, 29168-87-4; **7**, 91860-71-8; **8**, 52416-17-8; **9**, 52416-18-9; **10**, 20119-28-2; **11**, 7203-91-0; **12**, 20241-00-3; **13**, 20241-05-8; **14**, 7203-90-9; **15**, 23456-94-2; **16**, 7239-21-6; **17**, 23456-93-1; **18**, 52388-42-8; **19**, 91860-72-9.

Notes

Opioid Agonists and Antagonists. 6,6-Hydrazi and 6-Oximino Derivatives of 14-Hydroxydihydromorphinones

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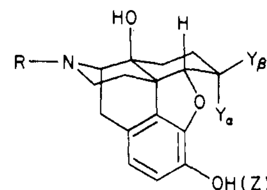
Naloxone (**1a**), naltrexone (**1b**), and oxymorphone (**1c**) were converted to the corresponding 6,6-diaziridines (**4a–c**), oximes (**5a–c**), and oxime *O*-methyl ethers (**6a–c**). The antagonist derivatives (R = $CH_2CH{=}CH_2$ and R = CH_2-c-C_3H_7) were less active than the parent ketones in the tail-flick assay vs. morphine, by 2–10-fold, except for **6a**, which was much less active. The agonist analogues (R = Me) were more active than morphine but less active than dihydromorphine in standard agonist assays. None were significantly longer in duration of action. Thus structural changes at the C-6 position to produce diaziridines, oximes, and oxime *O*-methyl ethers provide compounds retaining expected opioid activity.

The 14-hydroxy-7,8-dihydromorphinone nucleus has provided many pharmacologically interesting compounds that have been important in opiate research. Among them are the important opioid antagonists naloxone (**1a**) and naltrexone (**1b**) and the useful analgesics oxymorphone (**1c**) and oxycodone (**1d**). More recently, mixed agonist–antagonist analogues butorphanol (**1e**) and nalbuphine (**1f**) have been proven to be clinically useful analgesics.[1] A large number of derivatives with this nucleus have been made, which clearly indicates functional group changes may be made in the C ring, particularly at the 6-, 7-, and 8-positions while still retaining significant activity as opioid agonists or antagonists.[2,3] Among these are the 6-desoxy-6-methylene compounds and their corresponding 6α-epoxides, which are highly potent.[3]

The 6-position has been the locus of funtional group changes that have produced several potential alkylating



1a, R = $CH_2CH{=}CH_2$; Y = O
1b, R = CH_2-c-C_3H_7; Y = O
1c, R = Me; Y = O
1d, R = Me; Y = O; Z = Me
1e, R = CH_2-c-C_4H_9; Y = H_2
1f, R = CH_2-c-C_4H_9; Y_α = OH; Y_β = H
2a,b, R = CH_2-c-C_3H_7; Y_β or Y_α = $N(CH_2CH_2Cl)_2$
2c,d, R = CH_2-c-C_3H_7; Y_β or Y_α = HNC(=O)CH=CHCOOMe
2e,f, R = CH_2-c-C_3H_7; Y_β or Y_α = N=C=S
3a, R = $CH_2CH{=}CH_2$; Y = N=N- (dimeric)
3b, R = $CH_2CH{=}CH_2$; Y = NNH_2
4a–c, Y_α, Y_β = NHNH
5a–c, Y = NOH
6a–c, Y = NOMe
a, R = $CH_2CH{=}CH_2$
b, R = CH_2-c-C_3H_7
c, R = Me

agents that have been used to aid in characterization of opioid receptors. Among them are *N,N*-bis(β-chloroethyl) derivatives of 6α- and 6β-naltrexamine and -oxymorphamine (**2a,b**) and the fumaramide methyl ester (**2c,d**) and isothiocyanate derivatives (**2e,f**) of these amines.[4] Nal-

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