1.69 g (70%) of **10** was obtained with **12** (0.13 g, 5%) as a by-product, while in formic acid 1.80 g (70%) of **12** with some amount of **10** (0.05 g, ~2%) was isolated. ^{1}H NMR and mass spectra are identical with those obtained in Scheme I.

Antitumor Evaluation. F_1 hybrid ($DBA_2 \times C$ 57 BL 6) mice (23–25 g) were ip inoculated with 10^5 L_{1210} cells on day 0. The compounds **9**/**12** as aqueous solution and CNCC as suspension in olive oil were intraperitoneally or intravenously administered on days 1, 5, and 9. The average median survival times were measured for each group. The control animals survived 10.0 days on average. The long term survivors in treated groups (90.0 days) were recorded.

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Registry No. **1**, 96413-07-9; **2**, 96413-08-0; **3**, 96413-09-1; **4**, 96413-10-4; **5**, 96413-11-5; **8**, 55661-43-3; **9**, 96413-12-6; **10**, 96413-13-7; **11**, 96413-14-8; **12**, 79955-36-5; $MeS(CH_2)_2NH_2$, 18542-42-2; $OCN(CH_2)_2Cl$, 1943-83-5; p-$O_2NC_6H_4OCOCl$, 7693-46-1; $Cl(CH_2)_2NH_2 \cdot HCl$, 870-24-6.

In the Search for New Anticancer Drugs. 13. Phosphonic and Phosphinic Analogues of Ornithine

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Phosphonic (**4a,b**) and phosphinic (**5a–d**) analogues of ornithine were synthesized and evaluated for their inhibitory activity against ornithine decarboxylase and against the lymphocytic leukemia P388. The title compounds possess a low degree of inhibition against rat liver ornithine decarboxylase as compared to α-(difluoromethyl)ornithine. Thus, compounds **4a** and **5a** inhibit by 40% the ornithine decarboxylase activity at a 5 mM concentration. The other derivatives are less potent. Compounds **4a**, **4b**, **5b**, and **5d** are inactive against P388 tumor in CD_2F_1 mice at doses of 50 and 150 mg/kg.

In the past 20 years, the polyamines putrescine, spermidine, and spermine have been extensively investigated because of their involvement in cell growth.[1-4] The elevated levels of polyamines in cancer patients have been associated with increased cell proliferations in rapidly growing tissues.[5] Elevated levels of ornithine decarboxylase and/or of putrescine, spermidine, and spermine have been correlated with the rate of proliferation of cancer cells.[6] On the basis of these results it was proposed to use the polyamines as sensitive cancer markers[7] that could be conveniently monitored by specific assays. It can also be hypothesized that by administering suitable inhibitors of ornithine decarboxylase the proliferation of cancer cells may be retarded, and hence a successful chemotherapy might be developed. The most effective inhibitors of polyamine formation that have been synthesized to date belong to various structural analogues of ornithine (**1a**) and methylglyoxal hydrazones such as α-(difluoromethyl)ornithine (α-DFMO, **1c**),[8-10] α-methylornithine (**1b**),[9,11] 2-hydrazino-5-aminopentanoic acid,[12] DL-2-hydrazino-2-methyl-5-aminopentanoic acid,[13] *N*-(5-phosphopyridoxyl)ornithine,[14] DL-(*E*)-2,5-diamino-3-pentenoic acid,[15] and methylglyoxal bis(guanylhydrazone), MGBG (**2**).[16,17] The most widely investigated of these inhibitors are α-DFMO and MGBG. Specifically, the administration of either α-DFMO[8,9] or MGBG[16,17] to rapidly proliferating cells retards their further growth. The data obtained with cell cultures indicated that α-DFMO exerts a cytostatic rather than a cytocidal effect.[18] In vivo experiments with α-DFMO using L1210 leukemia bearing mice produced moderate prolongation of their survival time.[19-21] α-DFMO has also shown activity against solid tumors such as murine mammary sarcoma,[20,22] glioma,[23] rat hepatoma,[20] and gliosarcoma.[23] Clinical trials with α-DFMO[24] and MGBG[25] apparently have not fulfilled the high expectation. Therefore, the search for new inhibitors is continuing, and in the present investigation a somewhat

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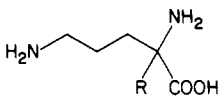
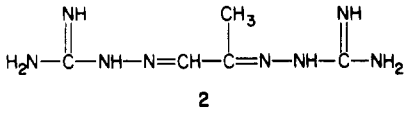
new approach is described, using phosphinic and phosphonic derivatives. To the best of our knowledge, no attempt has been reported of the synthesis of ornithine decarboxylase inhibitors by replacing the carboxyl function in ornithine with phosphonic and phosphinic moieties. This type of approach appeared to be promising on the basis of the following rationale. The replacement of the carboxyl group in amino acids by the phosphinic or phosphonic groups leads to phosphorus analogues of amino acids that are known to possess competitive inhibiting activity against certain enzymes such as rat liver glutamine synthetase,[26] aminoacyl-tRNA synthetases,[27,28] and angiotensin-converting enzyme (ACE).[29] Some phosphorus analogues of amino acids have been also reported to act as enzyme substrates.[30,31] Replacement of the carboxyl group in ornithine by phosphinic or phosphonic moieties is not expected to result in changes in the distance between the two nitrogen atoms. This distance of about 6 Å in ornithine (**1a**) is considered to be crucial for binding to the



1a, R = H
b, R = CH_3
c, R = CHF_2



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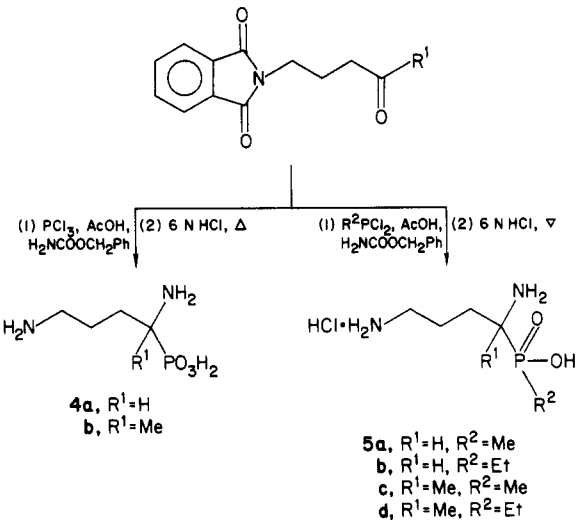
ornithine decarboxylase.[11] It was also reported[11] that the site of this enzyme that accommodates the terminal amino group of the substrate is very sensitive to steric hindrance, whereas the site that accommodates the carboxyl group is insensitive to changes of the steric requirements of the ligand. Thus, it was shown that the replacement of the carboxyl group in ornithine by the tetrazolyl group causes no decrease in affinity of such an analogue toward the bull prostate ornithine decarboxylase.[11] It was further found that phosphonic functions are a good replacement for the carboxyl group in certain ACE inhibitors.[29]

On the basis of these results, the idea to evaluate phosphinic and phosphonic analogues of ornithine as potential ornithine decarboxylase inhibitors appears to have some merit. Therefore, in this paper we describe the preparation of the phosphonic (**4a,b**) and phosphinic

Scheme I



4a, R^1 = H
b, R^1 = Me

5a, R^1 = H, R^2 = Me
b, R^1 = H, R^2 = Et
c, R^1 = Me, R^2 = Me
d, R^1 = Me, R^2 = Et

(**5a–d**) analogues of ornithine (**1a**) and α-methylornithine (**1b**) and the results of their evaluations as possible rat liver ornithine decarboxylase inhibitors. In addition, results of in vivo testing against P388 lymphocyte leukemia in mice are reported for four derivatives.

Results and Discussion

Chemistry. Among the six derivatives that were prepared in this work (Scheme I), only **4a** was reported in literature.[32] It was prepared[32] from tetraethyl 2-phosphonoadipate by the Curtius rearrangement followed by acid hydrolysis of the intermediate carbamate. This method lacks versatility, since all desired functions must be introduced into the structure of the starting materials before a transformation of the carboxylic groups into the amino groups can be made. In the search for a more general method that would permit the use of similar and also more readily accessible starting materials, it was decided to make an adaptation of the methods.[37,38] reported by Oleksyszyn and co-workers.[33] Thus, starting from an aldehyde or ketone of the general formula **3** and phosphorus trichloride or alkyldichlorophosphines, a series of phosphorus analogues of ornithine (**1a**) were synthesized. This approach clearly represents an advance over the method involving the Curtius rearrangement.[32] The required 4-phthalimido-*n*-butyraldehyde **3a**[34] and *N*-(4-oxopentyl) phthalimide **3b**[35] were synthesized by two-step literature procedures starting from the commercial available 4-aminobutyraldehyde diethyl acetal and 2-acetylbutyrolactone, respectively. The general procedure for the synthesis of **4a,b** and **5a–d** consisted of a portionwise addition of the carbonyl component **3a** or **3b** to a stirred acetic acid solution of benzyl carbamate and the appropriate phosphorus component at 0–25 °C followed by 1 h of stirring of the resultant reaction mixture at 100–110 °C and subsequent hydrolysis with 4 N hydrochloric acid under reflux. After removal of the phthalic acid by filtration and extraction, the crude products were purified by ion-exchange chromatography. Phosphonic

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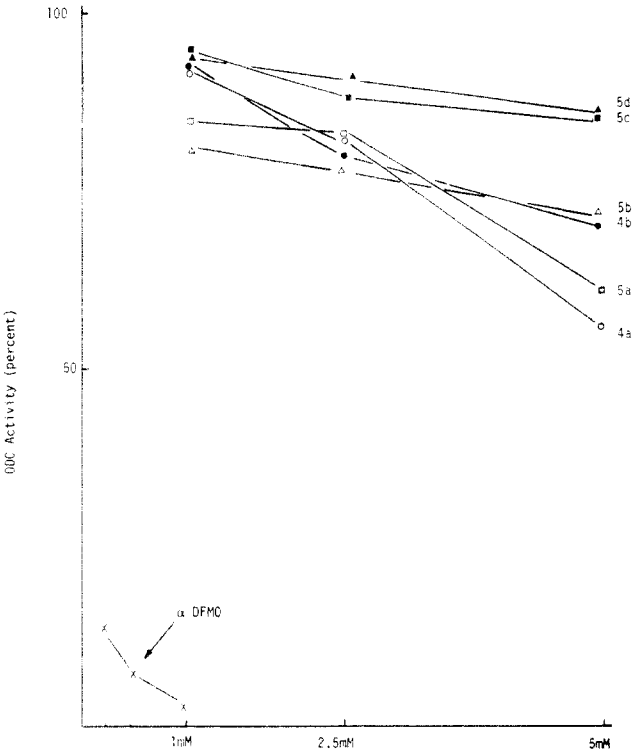

Figure 1. Inhibition of the ornithine decarboxylase activity by phosphonic and phosphinic analogues of ornithine. Absolute values of enzyme activity ranged between 2 and 3 nmol of CO_2/mg of protein per hour. Each point is the mean of two duplicate experiments.

derivatives **4a** and **4b** were isolated in the form of the free acids, whereas the phosphinic derivatives **5a**, **5b**, and **5d** were isolated as monohydrochlorides.[36] Compound **5c** was too hygroscopic for reliable microanalysis, and therefore, it was transformed into the corresponding monohydrobromide that could be analyzed. All compounds were prepared in 47–56% overall yields, and the applied synthetic procedure proved to be convenient and versatile. All amino acids were characterized by microanalyses, and ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopies.

Biology. The amino acids, **4a,b** and **5a–d** were tested as inhibitors of rat liver ornithine decarboxylase. Experiments were carried out on the thioacetamide-induced liver ornithine decarboxylase. Thus, male Wistar rats were treated with 150 mg/kg of thioacetamide and sacrificed after 18 h to obtain the liver cytosol. The compounds **4a,b** and **5a–d** as well as α-(difluoromethyl)ornithine used as the standard were added to the cytosol 15 min before the determination of the ornithine decarboxylase activity, according to literature methods.[37,38] It was found that the phosphorus analogues of ornithine do not inhibit ornithine decarboxylase at low concentrations. Thus, under our experimental conditions α-(difluoromethyl)ornithine inhibits by 90% the ornithine decarboxylase activity at a 0.25 mM concentration, whereas compounds **4a** and **5a** inhibit by 40% the ornithine decarboxylase activity at 5 mM concentration. The other derivatives **4b** and **5b–d** are less active (Figure 1). Compounds **4a**, **4b**, **5b**, and **5d** were evaluated in vivo for potential anticancer activity by using the lymphocytic leukemia P388 in accordance with the NCI protocol.[39] On the basis of the following results it is concluded that all four compounds are devoid of anticancer activity against the P388 leukemia [compound, T/C at 50 mg/kg, T/C at 150 mg/kg]: **4a**, 98, 100; **4b**, 98, 100; **5b**, 100, 100; **5d**, 98, 98.

Experimental Section

Materials and Methods. Mice. The male CD_2F_1 mice for antitumor testing (average weight 18–21 g) and DBA/2 mice for tumor propagation (6–7 weeks old)[39] were supplied by Hawley Sprague–Dawley (Indianapolis, IN). The mice were fed rodent laboratory chow 5001 (Ralston Purina Co.) and water ad libitum. The compounds were administered ip as saline solutions in two doses of 50 and 150 mg/kg per day for 9 days.

Antitumor Testing. Antileukemic experiments were initiated on day 0 by implanting ip into the male CD_2F_1 mice 10^6 of P388 ascites cells according to the NCI protocol.[39] Drug treatment was commenced on day 1 and consisted of nine daily ip injections (days 1–9). All treated groups consisted of six mice, and the leukemia control group consisted of 10 mice. The mice were observed daily, and the antileukemic activity of each compound was compared on the basis of the T/C criterion, where T represents the mean survival time of the treated group and C the mean survival time of the tumor-bearing control group. The percent of increase in life span (%ILS) was calculated by the formula $[(T - C)/C] \times 100$. Compounds with T/C values below 125 (25% ILS) are considered to be inactive.[39]

Analytical Procedures. All melting points (decomposition) were obtained with a Thomas Hoover melting point apparatus, Model 6406-K, using a calibrated thermometer. The IR spectra were recorded on a Perkin-Elmer spectrophotometer, Model 735B. Microanalyses were performed either on a Perkin-Elmer elemental analyzer, Model 240C, or by the Atlantic Microlab, Inc., Atlanta, GA. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a 250-MHz Bruker NMR spectrometer, Model WM-250, using Me_4Si and/or phosphoric acid standards and D_2O lock. The purity control of products was performed on silica gel 60 F_{254} precoated TLC sheets (EM Reagents), layer thickness 0.20 mm. TLC plates were developed in a solvent system composed of 95% ethanol and concentrated aqueous ammonia (7:3, v/v). Visualization was achieved by iodine and/or by spraying the plates with a diluted solution of ninhydrin and pyridine in methanol.

Ornithine Decarboxylase Activity. ODC activity was tested in accordance with the previously published methods.[37,38]

Preparation of the Phosphonic (4a,b) and Phosphinic (5a–d) Analogues of Ornithine. General Procedure. To a stirred solution of benzyl carbamate (Aldrich Chemical Co.) (1.51 g, 10.0 mmol) in acetic acid (2.5 mL) was added in one portion either phosphorus trichloride (1.37 g, 10.0 mmol), methyldichlorophosphine (1.17 g, 10.0 mmol), or ethyldichlorophosphine (1.31 g, 10.0 mmol), followed by a portionwise addition of aldehyde **3a**[34] (2.17 g, 10.0 mmol) or ketone **3b**[35] (2.31 g, 10.0 mmol) during a period of 3 min at 25 °C. After the addition, the resultant dense oil was heated with stirring at 100–105 °C for 1 h. Hydrochloric acid (4 N, 50 mL) was then added, and the reaction mixture was boiled with reflux for 8 h. After the mixture was cooled to 20 °C, concentrated hydrochloric acid (50 mL) was added and the resultant solution cooled to 5 °C. The crystalline precipitate of the phthalic acid was collected by filtration and washed with concentrated hydrochloric acid (2 × 10 mL). The combined filtrates and washings were extracted with chloroform (3 × 25 mL) and the extracts discarded. The aqueous layer was concentrated on a rotating evaporator at 80 °C (20 torr). The residue was dissolved in water (10 mL) and passed through a column filled with Amberlite IRA-400 anion-exchange resin in acetate (AcO^-) form, eluting with 1 N aqueous acetic acid. The fractions with a positive ninhydrin test were combined and concentrated at 80 °C (20 torr). The remaining oily residue was mixed with water (10 mL) and the resultant solution concentrated at 80 °C (20 torr). This operation was repeated three times to ensure the removal of the excess acetic acid. The isolation procedures for phosphonic acids **4a** and **4b** were different from those of phosphinic acids

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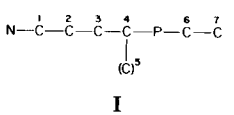
Table I. Phosphonic (**4a,b**) and Phosphinic (**5a–d**) Analogues of Ornithine

compd	yield, %	mp (dec), °C	mol formula[a] (mol wt)	IR (KBr) ν, cm^{-1}	^1H NMR(D_2O) δ	^{13}C NMR (D_2O)[b] δ	^{31}P NMR δ
4a	51	299–300[c]	$C_4H_{13}N_2O_3P$ (168.13)	980, 1070, 1550, 1610, 2500–330	1.51–1.73 (m, 4 H, $C(CH_2)_2C$), 2.80–2.85 (m, 3 H, $-CH_2NH_2$ + C*H*P)	52.18 + 50.08 (d, C4, J = 132.3 Hz), 40.21 (C1), 27.52 (C3), 25.45 + 25.36 (d, C2, J = 6.0 Hz)	11.82
4b	55	259–260	$C_5H_{15}N_2O_3P$ (182.16)	980, 1050, 1150, 1540, 1610, 2500–3300	1.23 (d, 3 H, CH_3, J = 13 Hz), 1.61–1.65 (m, 4 H, C ($CH_2)_2$C), 2.80 (bs, 2 H, NCH_2)	57.61 + 55.41 (d, C4, J = 138.7 Hz), 40.73 (C1), 33.70 (C3), 22.86 + 22.79 (d, C2, J = 4.1 Hz), 20.85 (C5)	15.15
5a	47	272–274	$C_5H_{16}ClN_2O_2P$ (202.63)	860, 1020, 1140, 1490, 1540, 1580, 2050, 2550–3050	1.18 (d, 3 H, PCH_3, J = 13.5 Hz), 1.53–1.92 (m, 4 H, $C(CH_2)_2C$), 2.89 (bs, 2 H, NCH_2), 3.00–3.13 (bs, 1 H, CHP)	52.68 + 51.22 (d, C4, J = 91.9 Hz), 40.25 (C1), 26.28 (C3), 25.40 + 25.31 (d, C2, J = 6.0 Hz), 15.62 + 14.09 (d, C6, J = 6.4 Hz)	34.87
5b	53	255–257	$C_6H_{18}ClN_2O_2P$ (216.66)	1040, 1150, 1510, 1610, 2050, 2500–3100, 3350	0.83 + 0.80 (2 t, 3 H, PCH_2CH_3, J = 17.5 Hz), 1.33–1.55 (m, 2 H, PCH_2–), 1.56–1.85 (m, 4 H, $C(CH_2)_2C$), 2.85 (bs, 2 H, NCH_2), 3.00–3.11 (m, 1 H, CHP)	51.28 + 49.89 (d, C4, J = 86.5 Hz), 40.35 (C1), 26.22 (C3), 25.43 (C2), 22.86 + 21.32 (d, C6, J = 6.7 Hz), 6.47 (C7)	38.27
5c	58	218–220	$C_6H_{18}BrN_2O_2P$ (261.11)	880, 1050, 1160, 1390, 1600, 1600, 2050, 2850, 3400	1.12–1.26 (m, 6 H, CH_2, CCH_3), 1.65 (bs, 4 H, $C(CH_2)_2C$), 2.84 (bs, 2 H, NCH_2)	57.68 + 56.16 (d, C4, J = 95.2 Hz), 40.67 (C1), 32.53 (C3), 22.56 + 22.48 (d, C2, J = 5.3 Hz), 19.53 (C5), 13.93 + 12.43 (d, C6, J = 94.6 Hz)	38.61
5d	56	204–206	$C_7H_{20}ClN_2O_2P$ (230.68)	1040, 1160, 1520, 1590, 1615, 2050, 2500–3100, 3420	0.88 + 0.85 (2 t, 3 H, PCH_2CH_3, J = 16.5 Hz), 1.25 (d, 3 H, CCH_3, J = 12 Hz), 1.41–1.49 (m, 2 H, PCH_2), 1.66–1.70 (m, 4 H, $C(CH_2)_2C$), 2.85 (bs, 2 H, NCH_2)	57.78 + 56.34 (d, C4, J = 90.7 Hz), 40.67 (C1), 32.59 (C3), 22.52 + 22.44 (d, C2, J = 5.0 Hz), 20.58 + 19.06 (d, C6, J = 95.8 Hz), 19.64 (C6), 6.12 + 6.00 (d, C7, J = 7.1 Hz)	41.21

[a] Satisfactory microanalyses were obtained: C, ±0.31; H, ±0.06; N, ±0.10. [b] Peaks of the ^{13}C NMR spectra are numbered in accordance with I. The assignments of signals for C2 and C3 are based on the fact that a large downfield shift is observed for signals C3 when this carbon is attached to a quaternary C4 (II) as in **4b**, **5c**, and **5d**, as compared to signals for C3 when this carbon is attached to a tertiary C4 as in **4a**, **5a**, and **5b** (III).



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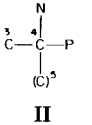
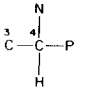


II



III

[c] Lit.[32] mp 284 °C dec, 293 °C dec.

5a–d. Thus, during the preparation of phosphonic acids, as a result of evaporation procedures, solid, crude products were obtained. Crystallization from a mixture of water and ethanol afforded analytically pure phosphonic acids **4a** and **4b**. In the case of the preparations of phosphinic acids **5a**, **5b**, **5c**, and **5d**, as a result of evaporation procedures, oily materials were obtained. These products were dissolved in water (25 mL), acidified with concentrated hydrochloric acid to pH 1, and concentrated on a rotating evaporator at 80 °C (20 torr). In each case, the residue was mixed with water (10 mL) and concentrated under preceding conditions, repeating this operation three times. Finally, the oily residues were dissolved in anhydrous ethanol (25 mL), and the pH was adjusted with pyridine to the point at which the Congo Red paper no longer changed to blue. The resultant solutions were then set aside for crystallization, which required several days for completion. Filtration and washing of the crystals with anhydrous ethanol and subsequently with ethyl ether afforded analytically pure compounds **5a**, **5b**, and **5d**, as the monohydrochloride salts. Since hydrochloride **5c** did not crystallize from ethanol solution, this solution was concentrated on a rotating evaporator at 50 °C (20 torr) and the oily residue dissolved in water (10 mL) and passed through a column filled with Dowex 50X2-100 ion-exchange resin in hydrogen (H^+) form, eluting with 2 N aqueous ammonia. The fractions with a positive ninhydrin test were combined and concentrated on a rotating evaporator at 80 °C (20 torr) followed by addition of water (10 mL) to the oily residue and repeating the evaporation under the preceding conditions. The remaining oily residue was then dissolved in water (15 mL) and the pH adjusted to 3.8 with 2 N hydrobromic acid. The resultant solution was concentrated to dryness on a rotating evaporator at 80 °C (20 torr) and the solid, crude product recrystallized from anhydrous ethanol to give pure **5c** monohydrobromide. The yields and analytical data for all compounds are shown in Table I.

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Registry No. **1a**, 70-26-8; **1b**, 48047-94-5; **3a**, 3598-60-5; **3b**, 3197-25-9; **4a**, 20820-73-9; **4b**, 96616-24-9; **5a**, 96616-25-0; **5a**·HCl, 96616-26-1; **5b**, 96616-27-2; **5b**·HCl, 96616-28-3; **5c**, 96616-29-4; **5c**·HBr, 96616-30-7; **5d**, 96616-31-8; **5d**·HCl, 96616-32-9; ornithine decarboxylase, 9024-60-6; phosphorus trichloride, 7719-12-2; methyldichlorophosphine, 676-83-5; ethyldichlorophosphine, 1498-40-4; benzyl carbamate, 621-84-1.

Structure–Activity Relationships for Prazosin and WB 4101 Analogues as α_1-Adrenoreceptor Antagonists[1]

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Several α-adrenoreceptor antagonists were prepared by coupling one of the two moieties of WB 4101 (**1**) with one of the two moieties of prazosin (**2**). Their blocking activity and relative selectivity on α_1- and α_2-adrenoreceptors were evaluated in the isolated rat vas deferens. Although retaining a significant selectivity toward α_1-adrenoreceptors, all the drugs were weaker antagonists than the parent compounds **1** and **2**. Opening the piperazine ring of **2** gave **3**, which displayed a very high activity and selectivity toward α_1-adrenoreceptors (α_1/α_2 = 3890). This may have relevance in understanding the mode of action of prazosin. In addition, **3** may represent a valuable tool in the characterization of α-adrenoreceptor subtypes.

Knowledge of receptor structure and function requires not only accessibility to selective ligands (both agonists and antagonists) but at the same time understanding of their mode and site of action. Adrenoreceptors play a fundamental role in human pharmacology for their involvement in many vital functions. Thus knowledge of both the chemical and biochemical nature of these receptors is of paramount importance. A great amount of research has led to a clearer picture for β-adrenoreceptors compared to α-adrenoreceptors. This may be explained by the fact that β-adrenoreceptor ligands can be structurally related to the endogenous catecholamines leading to relevant structure–activity relationships. On the contrary, different classes of α-adrenoreceptor ligands cannot be easily correlated with one another, owing to their different unrelated chemical structures.[2] As a consequence, we know only little about antagonist binding sites at α-adrenoreceptors. Furthermore, the situation is even more complex when one considers that the α-adrenoreceptor is not an homogeneous population.[3–8] In fact, it can be divided into α_1- and α_2-types according to their selectivity toward agonists and antagonists.[9,10] Since many unrelated structures are active at both types of α-adrenoreceptors,[2,11] we have recently undertaken a study aimed at correlating different classes of α-adrenoreceptor antagonists.[12]

Among α-adrenoreceptor antagonists, WB 4101 (**1**) and prazosin (**2**) have a prominent role in the characterization of α_1-adrenoreceptors owing to their specificity and selectivity.[13] Furthermore, **2** is used in treating patients with hypertension and congestive heart failure.[14] Although many structure–activity relationship studies among derivatives of **1** and **2** are available,[2,13] none, to our knowledge,

(1) Some aspects of this work were presented in preliminary form at the 8th International Symposium on Medicinal Chemistry, August 27–31, 1984, Uppsala, Sweden, Abstract, p 22.
(2) For example, see: Melchiorre, C.; Belleau, B. "Adrenoceptors and Catecholamine Action", Part A; Kunos, G., Ed.; Wiley: New York, 1981; p 181.
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(11) For example, see: Ruffolo, R. "Adrenoceptors and Catecholamine Action", Part B; Kunos, G., Ed.; Wiley: New York, 1983; p 3.
(12) Melchiorre, C.; Gulini, U.; Giardinà, D.; Gallucci, P.; Brasili, L. *Eur. J. Med. Chem.* **1984**, *19*, 37.
(13) For example, see: U'Prichard, D. C. "Adrenoceptors and Catecholamine Action", Part A; Kunos, G., Ed.; Wiley: New York, 1981; p 131.
(14) Colucci, W. S. *Ann. Intern. Med.* **1982**, *97*, 67.

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