85–86 °C; IR 1720 (C=O) cm^{-1}. Further elution of the column with $CHCl_3$ (300 mL) and then CH_3OH (200 mL) yielded about 8 g of the starting material **3**.

1-(1-Phenylcyclohexyl)-4-phenyl-4-piperidinol (10). A solution of 5 g (0.019 mol) of the ketone **9** in 10 mL of benzene was added dropwise to phenyllithium (from 6.3 g of bromobenzene and 0.56 g of lithium ribbon in 40 mL of ether). After 1 h of reflux, the mixture was poured into ice–water–AcOH, ammonia was added, and the basic substance was extracted with benzene, dried, and concentrated. The residue was recrystallized: yield 5.0 g (77%).

1-(1-Phenylcyclohexyl)-4-phenyl-4-piperidyl Propionate (11). A solution of 2 g of the piperidinol **10** in 3 mL of pyridine was refluxed for 5 h with 5 mL of propionic anhydride, diluted with 50 mL of $CHCl_3$, washed with aqueous $NaHCO_3$, dried, concentrated, and converted to the hydrochloride, which was recrystallized from acetone: IR 1750 cm^{-1}.

1-(1-Phenylcyclohexyl)-4-phenylpiperidine (13). 1-(4-Phenylpiperidino)cyclohexanecarbonitrile (**12**) was prepared from 24.5 g (0.152 mol) of 4-phenylpiperidine (Aldrich) and 18.7 g (0.15 mol) of cyclohexanone cyanohydrin by refluxing azeotropically in 60 mL of benzene for 3 h. The residue was recrystallized from methanol–ethyl acetate (1:1), mp 106–107 °C. A solution of 12 g (0.044 mol) of **12** in 50 mL of benzene was added dropwise to PhMgBr (from 2.0 g of Mg and 12.5 g of bromobenzene in 20 mL of ether). The mixture was decomposed after 2 h of reflux and then treated as described for **3**.

Pharmacology. All compounds as hydrochloride salts were dissolved in saline or twice distilled water (for bioassay). Male ICR mice weighing 24–28 g were used for analgesic tests, and mice weighing approximately 30 g were used for bioassay.

Hot-Plate Test. The method of ref 14 was used. Mice were put on a hot plate at 57 ± 0.5 °C. The reaction time (jumping or licking the hind paws) was observed once before and then after administration of the compound sc.

$$\% \text{ analgesia} = \left(\frac{T_t - T_0}{T_{max} - T_0}\right)100$$

T_0 = control time; T_t = latency time at the peak; T_{max} = 30 s

Writhing Test. Mice were injected ip with 0.6% acetic acid (0.1 mL/10 g) after administration of the compound sc, and the number of writhing movements were noted in control mice (W_c) and in treated mice (W_x).

$$\% \text{ inhibn of acetic acid induced stretching response} = 100 - \left[\left(\frac{W_x}{W_c}\right)100\right]$$

ED_{50} and 95% confidence limits were obtained from probit analysis, according to Litchfield and Wilcoxon.[24] At least 40 mice were used for each determination of ED_{50}.

Bioassay. Effects of the compounds on the mouse vas deferens were examined according to Hughes et al.[17] Mice were killed by cervical dislocation. Both vasa deferentia were dissected out as a single unit. The tissue was bathed in an organ bath of 50 mL volume at 37 °C in modified Krebs solution and gassed with 95% O_2 and 5% CO_2. Contractions were recorded by an isotonic transducer. The intramural nerves were stimulated (0.2 Hz, 2-ms duration, supramaximal voltage) through a pair of platinum electrodes around the tissue. When twitches were constant, 0.1–0.3 mL of a solution of the compound tested was injected into the organ bath.

IC_{50}, the concentration which produced 50% inhibition of twitches, was determined from probit analysis. At least three dose–response curves (four to six concentrations) were obtained. Complete reversal of the maximal inhibitory effect (80–90%) was obtained with 20–50 nM naloxone, for compounds **10**, **11**, **13**, and morphine hydrochloride.

Determination of Locomotion Activity in Mice. The locomotor activity was measured in the animal Activity Monitor "Varimex" (Columbus, Ohio). Three male ICR mice weighing 25–30 g were injected sc with the compound tested (ED_{50} from the analgesic assay) and three with saline (controls). Each group was transferred to a cage, and counts were recorded at 6-min intervals. The counts at the peak effect of each compound was divided by the value found for its control group (taken as 1.0). At least nine mice were tested for each compound. (The tests were carried out between 8:00 and 12:00).

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Oxazepam Esters. 3.[1] Intrinsic Activity, Selectivity, and Prodrug Effect

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Antimetrazol and muscle-relaxant activities of 11 aliphatic esters of oxazepam were studied as a function of time in mice. The esters given intravenously retained antimetrazol activity, while muscle-relaxant activity was generally decreased. The administration of a dose equivalent to the antimetrazol ED_{50} resulted in constant oxazepam brain levels for most esters; therefore, the intrinsic anticonvulsant activity of the intact ester is insignificant. The dimethylphenylpropionyl ester appeared to antagonize the effect of oxazepam, since it elevated the free oxazepam level required to achieve the ED_{50} in the antimetrazol assay. The administration of doses equivalent to the muscle-relaxant ED_{50} values resulted in no correlation with total brain benzodiazepine levels, suggesting that changes in the selectivity of action are the consequence of different sites of action.

Oxazepam (7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepin-2-one) is a widely used centrally acting drug.[2] Although it had been concluded that 3-substitution diminished the activity of 1,4-benzodiazepines,[3] several 3-substituted derivatives of oxazepam were synthetized and investigated.[4-7] The hemisuccinate ester of oxazepam and its enantiomers were extensively

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Table I. Antimetrazol and Muscle-Relaxant Effects of Oxazepam Derivatives

no.	compd[b]	pretreatment, min:	ED_{50} (95% fiducial limits), mg/kg iv[a] antimetrazol 120[c]	antimetrazol 240	muscle relaxant 120	muscle relaxant 240
1	oxazepam		0.49 (0.21-1.38)	0.62 (0.41-0.93)	2.4 (1.6-6.0)	6.6 (3.3-15.3)
2	Ox-OAc		0.47 (0.29-0.92)	1.17 (0.68-2.97)	2.6 (1.4-3.4)	4.8 (3.2-7.4)
3	Ox-OPr		0.33 (0.10-0.54)	0.98 (0.28-1.67)	6.6 (3.8-13.8)	20.2 (4.7-33.9)
4	Ox-OBu^n		0.22 (0.11-0.67)	1.89	5.4 (3.5-9.0)	11.3 (6.9-29.9)
5	Ox-OBu^i		0.27 (0.09-0.67)	0.60	4.9 (2.8-7.5)	10.1 (5.5-33.0)
6	Ox-pivaloate		0.61 (0.35-1.14)	0.80	5.6 (3.7-7.4)	9.0 (7.0-13.1)
7	Ox-Et_2OAc		0.32 (0.19-0.64)	1.97	4.7 (2.7-9.0)	9.1 (5.8-21.2)
8	Ox-β-Phe-OPr		0.66 (0.31-1.42)	0.63 (0.40-0.98)	4.1 (2.8-5.3)	7.5 (5.2-10.9)
9	Ox-(±)-α-Me-β-Phe-OPr		0.59 (0.47-1.44)	1.92	6.4 (4.7-8.2)	7.8 (5.8-20.4)
10	Ox-(+)-α-Me-β-Phe-OPr		0.81	1.11	4.6 (3.3-6.6)	5.0 (3.5-7.6)
11	Ox-(−)-α-Me-β-Phe-OPr		0.33 (0.18-0.52)	1.13	2.4 (0.5-3.9)	4.3 (2.6-7.1)
12	Ox-α,α-Me_2-β-Phe-OPr		1.57 (1.01-3.82)	1.14 (0.56-1.78)	19.2 (13.1-49.4)	17.1 (10.8-32.3)

[a] Doses are expressed in oxazepam equivalents. [b] Ox = oxazepam; OAc = acetate; OPr = propionate; OBu^n = n-butyrate; OBu^i = isobutyrate. [c] For activities at 30 and 60 min, see in ref 13.

Table II. Short-Time Antimetrazol and Muscle-Relaxant Activities of Oxazepam Derivatives

no.	pretreatment, min:	ED_{50} (95% fiducial limits), mg/kg iv[a] antimetrazol 5	antimetrazol 10	antimetrazol 20	muscle relaxant 5	muscle relaxant 10	muscle relaxant 20
1		0.18 (0.09-0.36)	0.16 (0.07-0.50)	0.21 (0.06-0.40)	0.96 (0.51-1.51)	0.86 (0.64-1.69)	0.80 (0.65-1.38)
7		1.07 (0.77-2.06)	0.46 (0.28-1.66)	0.31 (0.19-1.23)	0.95 (0.66-4.92)	0.61 (0.35-0.92)	0.36 (0.25-0.48)
12		9.6 (6.6-14.9)	14.8 (11.4-23.2)	6.2 (4.3-8.3)	13.1 (10.3-20.6)	11.7 (7.8-25.4)	13.1 (10.1-18.6)

[a] Expressed in oxazepam equivalents.

studied.[8,9] These ester derivatives may act as prodrugs; i.e., the pharmacological activity can be attributed to the hydrolysis products. The hydrolysis of oxazepam esters was demonstrated for the hemisuccinate ester[10] and for the acetate ester.[11] Pharmacokinetic studies of the hemisuccinate and pivaloate esters[6] were limited to the measurement of either the intact ester or oxazepam, probably because the gas–liquid chromatographic method used does not allow simultaneous determination of both compounds.

We studied the time course of anticonvulsant and muscle-relaxant activities of several oxazepam esters and determined the brain levels of both the derivative and the parent oxazepam.

Results and Discussion

Antimetrazol and Muscle-Relaxant Effects. Prodrugs may increase or prolong the pharmacological activity of the parent drug or they may improve its selectivity of action.[12] We examined these possibilities for oxazepam esters with six aliphatic and five phenylpropionate esters. The chain length and the steric hindrance in the α position of the acyl group were varied. Long-time (2 and 4 h) antimetrazol and muscle-relaxant activities are summarized in Table I. Small differences in activity at longer times can be explained with the extensive hydrolytic conversion of the esters. Phenyl-substituted esters are generally inferior to the aliphatic esters, probably because of their slower hydrolysis rate[1] (especially compound **12**). A certain selectivity of action results from the fact that some of the esters have a prolonged antimetrazol effect, but most of them are inferior in their muscle-relaxant effects.

We compared the short-time activity of two characteristic esters (compounds **7** and **12**) with that of oxazepam at 5–20 min (Table II), when the contribution to activity of the esters themselves or their different hydrolysis rates can be better evaluated. The bulky and sterically hindered phenyl-substituted ester **12** is much less potent than **7** in both tests. Compound **7** is not a potent anticonvulsant, but it is approximately as active as oxazepam in the muscle-relaxant test. Steric hindrance of the acyl group, described by the Taft E_S constant, was demonstrated to decrease the rate of the hepatic microsomal hydrolysis of oxazepam esters[13,14] and, consequently, to decrease the brain accrual of oxazepam.[15] Thus, a decrease in the rate of brain appearance of oxazepam results in decreased activity, apparently without the contribution to activity of the esters themselves.

Comparison of the Time Profiles of Pharmacological Effects with Brain Levels. Anticonvulsant effect of some benzodiazepines was demonstrated to correlate with brain levels of the compound.[16-18] We have previ-

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Table III. Time Profile of Pharmacological Effects and Brain Levels of Fixed Doses

	dose, mg/kg	pretreatment, h 0.5	1	2	4
Oxazepam β-Phenylpropionate (8)					
antimetrazol act.[a]	0.8	40	90	50	30
oxazepam level[b]	5.0	10.7	13.6	12.2	6.6
ester level		3.5	1.6	0.5	
muscle relaxant act.[c]	5.0	70	50	40	0
Oxazepam (+)-α-Methyl-β-phenylpropionate (10)					
antimetrazol act.	1.0	70	90	60	30
oxazepam level[b]	5.0	9.6	12.8	11.7	7.2
ester level		7.7	4.0	1.4	0.6
muscle relaxant act.	5.0	40	30	10	0
Oxazepam (−)-α-Methyl-β-phenylpropionate (11)					
antimetrazol act.	1.0	30	60	80	40
oxazepam level[b]	5.0	9.5	14.8	13.7	12.2
ester level		12.4	4.0	1.2	0.6
muscle relaxant act.	5.0	60	80	60	30

[a] Percentage of 10 mice protected against seizures. [b] Taken from ref 13, in nanomoles per gram brain. [c] Percentage of 10 mice falling off the rod.

Table IV. Brain Levels of Oxazepam and Its Esters after Administration of Compounds 1, 7, and 12

compd	time after administration, min	dose, mg/kg[a]	brain levels, pmol/g ± SEM oxazepam	ester
(a) Antimetrazol ED_{50}				
1	30	0.18	351 ± 34	
(n = 5)[b]	60	0.39	342 ± 79	
	240	0.62	309 ± 52	
7	5	1.07	374 ± 98	1250 ± 270
(n = 10)	10	0.46	339 ± 62	383 ± 66
	30	0.28	286 ± 50	187 ± 51
	120	0.32	344 ± 69	95 ± 31
12	30	2.74	1890 ± 220	2510 ± 280
(n = 5)	60	1.28	1590 ± 390	710 ± 280
	240	1.13	870 ± 200	230 ± 40
(b) Muscle Relaxant ED_{50}				
1	5	0.96	3010 ± 370	
(n = 7)	10	0.86	3120 ± 130	
	30	0.75	3090 ± 180	
	60	1.60	4820 ± 530	
7	5	0.96	480 ± 60	1440 ± 170
(n = 12)	30	2.82	5160 ± 810	1820 ± 520

[a] Expressed in oxazepam equivalents. [b] n represents the number of mice at each time.

ously studied oxazepam brain levels,[15] and the lack of correlation between the pharmacological data and the time profile of oxazepam brain levels was explained with the substantial difference of the dose ranges. In the present study, when the time profiles of the pharmacological effect of fixed and comparable doses of some phenyl-substituted esters were examined, the results indicated measurable changes of the two activities tested (Table III). The time profile of the antimetrazol and muscle-relaxant effects seems to parallel the brain levels of oxazepam.

Marcucci et al. demonstrated[16,17] that antimetrazol ED_{50} values were associated with a constant oxazepam brain level of 334 pmol/g. We measured the brain levels following the administration of the anticonvulsant ED_{50} values of three compounds to evaluate their own contribution to activity (Table IV). The average oxazepam brain level after the administration of compounds 1 and 7 was 335 ± 29 pmol/g, which excellently agrees with that of Marcucci et al.[17] According to their data,[16] the introduction of a 3-hydroxyl group into demethyldiazepam slightly increases the brain concentration required for the anticonvulsant activity. Similarly, oxazepam has a smaller affinity to the benzodiazepine receptors than demethyldiazepam.[19] Further, the rather bulky 3-(diethylacetoxy) group in compound 7 abolishes all antimetrazol activity, since varying concentrations of 7 do not significantly affect the constant oxazepam concentration required for the anticonvulsant activity (Table IV). The oxazepam esters displaced [^{3}H]diazepam from the high-affinity binding sites of the brain synaptosomal fraction with a much smaller potency than oxazepam.[20] This also suggests that the esters are prodrugs in relation to oxazepam. While the prodrug effect of the esters and, consequently, the brain accrual of oxazepam are mainly determined by the steric hindrance of the acyl group to hydrolysis (E_S), the reduced intrinsic activity of the esters seems to result from the size of the 3-substituent, because affinity of the esters to receptors decreases with the molar refractivity (MR) of the acyl substituent.[20]

The presence of compound 12 requires a significantly higher oxazepam brain level ($p < 0.001$) to induce the same anticonvulsant effect. This effect depends on the ester concentration (Figure 1a) and shows the antagonizing effect of this ester. An inhibitory affinity constant of approximately 10^{-7} M can be determined from the Schild plot of the data (Figure 1b). Thus, very low activity of compound 12 can be explained not only by its slow oxa-

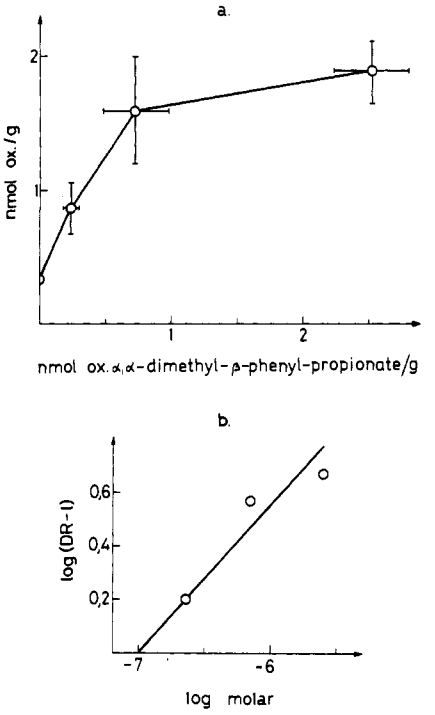

Figure 1. (a) Brain levels of oxazepam and its dimethylphenylpropionyl ester (12) after administration of the antimetrazol ED_{50} values. (b) Schild plot of the brain levels. DR is the ratio of oxazepam levels in the presence and in the absence of the ester.

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zepam liberation but also by its specific antagonizing effect to oxazepam.

The parallel time profile of the antimetrazol effect and the brain levels of oxazepam lead to the same conclusion as the constant oxazepam levels following administration of antimetrazol ED_{50} values: the esters of oxazepam do not appear to contribute to the anticonvulsant effect. Compound 12 seems to antagonize the antimetrazol effect of oxazepam.

Comparison of the muscle-relaxant ED_{50} values at 5 min (Table II) shows that compound 7 is still equipotent to oxazepam, while the bulky compound 12 is much less potent. However, since the muscle-relaxant ED_{50} values are not accompanied with constant oxazepam brain levels (Table IV, part b), total brain levels do not properly represent the site of the muscle-relaxant effect of the benzodiazepines and conclusions cannot be drawn for this intrinsic activity. Instead, the results for the dissociation of muscle-relaxant and anticonvulsant effects support the notion that the sites of action are different.[21]

Experimental Section

Materials. Oxazepam-2-^{14}C was synthetized as previously described.[22] Its labeled and nonlabeled esters were prepared by known methods.[15] Specific radioactivity of the compounds ranged between 1.9 and 3.2 mCi/mmol. Metrazol (pentylenetetrazol) was purchased from Fluka.

Drug Administration. Oxazepam and its esters were administered intravenously to male mice of the CFLP strain (outbred albino, 19–21 g of body weight) 5–240 min prior to investigation. Respective doses were diluted with distilled water from a solution, the composition of which was as follows: 5 mg of test compund, 2 mL of propylene glycol, 1 mL of Chremofor EL (propylene glycol sicin oleate), and 7 mL of distilled water.

Antimetrazol Activity.[23] Test compounds were injected iv 5–240 min prior to sc administration of 125 mg/kg of metrazol in distilled water. Animals were classified as protected if tonic-extensor convulsions did not occur within 60 min of observation.

Muscle Relaxant Effect.[24] Animals were selected and trained to maintain on a rotating rod (diameter, 20 mm; revolution frequency, 12 min^{-1}) for 120 s. The number of animals falling down was expressed as a percentage of the dose group totals. Respective ED_{50} values and their confidence limits were determined according to Litchfield and Wilcoxon.[25]

Brain levels of oxazepam and its esters were determined as previously described.[15]

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Characterization of α-Adrenoceptor Populations. Quantitative Relationships between Cardiovascular Effects Initiated at Central and Peripheral α-Adrenoceptors

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The agonist selectivities of central (medullary) and peripheral (vascular) α-adrenoceptors were compared in order to investigate a possible similarity among these two α-adrenoceptor populations. Linear regression equations were derived between the α-adrenergic potencies, mediated by these two types of α-adrenoceptors for 21 structurally dissimilar α-adrenoceptor agonists. Hypotensive potency after intravenous administration to anesthetized, normotensive rats was determined as a measure of central α-adrenergic activity and expressed as pC_{25}, obtained from log dose–response curves. Peripheral α-adrenergic potency was quantified by means of the hypertensive effect elicited in pithed, normotensive rats after intravenous injections, yielding pC_{60} as the biological variable. A most significant linear relationship was generated between central hypotensive activity (pC_{25}) and peripheral hypertensive potency (pC_{60}), provided that log P' (octanol/buffer; pH 7.4, 37 °C) was included into the regression in a parabolic form. This result indicates that the central (medullary) α-adrenoceptors and the peripheral (vascular) α-adrenoceptor sites, which are excited by the drugs in question, make identical demands upon their agonists. The difference in accessibility to these peripheral and central α-adrenoceptor populations is adequately accounted for by a parabolic description in log P'. The apparent contradiction of this finding with the suggestion that central, hypotensive α-adrenoceptors are of the α_2 type and peripheral, vascular α-adrenoceptors belong to the α_1 subpopulation is discussed. The recent identification of an additional subclass of postsynaptic, vascular α_2-adrenoceptors and the lack of pronounced differential stimulating activity of the agonists at peripheral α-adrenoceptors may explain the present findings and clarify the paradox.

In our studies on quantitative structure–activity relationships in α-adrenergic drugs, we have attempted to characterize α-adrenoceptor populations in more detail. A possible similarity between peripheral (vascular) and central (medullary) α-adrenoceptors has been investigated. These two particular types of α-adrenergic receptors play a major role in the acute circulatory effects of α-adrenergic drugs. Their participation in blood-pressure control is illustrated by the action of the antihypertensive drug clonidine (catapres) injected intravenously. Being an α-adrenoceptor stimulant, clonidine initially triggers peripheral, vascular α-adrenoceptors, which results in a transient hypertensive effect. Subsequently, a long-lasting hypotensive phase is observed, which is caused by cloni-

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