Overt Behavior in Normal, Free Ranging Cats. Three cats administered compound **5b** were tested for gross behavioral changes. After the animals were dosed, they were simply handled and observed for the ensuing 4–6 h and overt changes in behavior were noted.

Effects on Gross Spinal Reflexes in Cats. The effects of compound **5b** were studied on monosynaptic (patellar) and polysynaptic (flexor) spinal reflexes in intact-chloralose anesthetized cats. The monosynaptic reflex was elicited by tapping the patellar tendon with a solenoid-controlled hammer, and the ensuing knee jerk was recorded. The flexor reflex was recorded as contractions of the tibialis anticus muscle elicited by electrical stimulation of the popliteal nerve.

Cardiovascular Effects in *Cebus* Monkeys. Blood pressure was recorded from two *Cebus apella* monkeys via polyethylene catheters inserted into a carotid artery of each subject. Following surgical implantation of the catheters, the subjects were placed in restraining chairs and allowed to accommodate for 2.5–3.0 h before drug administration. In addition to blood pressure, an EEG was monitored in one subject and an EKG was recorded in the second.

Chemistry. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Silica gel (0.063–0.2 mm) was used in preparing column chromatograms, and analytical thin-layer chromatography was conducted on precoated 40 × 80 mm plastic sheets of silica gel G with fluorescent indicator. In all workup procedures, the drying process involved swirling over $MgSO_4$ and filtering prior to evaporation. Starting materials 1–4 were prepared according to literature methods.[2,3] Compounds of type 5, 6, and 8–11 were prepared according to literature methods A,[9] B,[9,10] C,[11] D,[12] E,[13] F,[14] G,[15] H,[16] I,[17] J,[2] M,[18] N,[19] O,[20] P,[21] and Q.[22] The pertinent data are summarized in Tables I–VI.

Method K. Preparation of 3-Phenyl-5,7-dihydro-5,5,7,7-tetramethylfuro[3,4-*c*]pyridazine Hydrochloride (8c). Using a condenser equipped with a Dean–Stark trap, a mixture of 4-hydroxy-4-(phenylethynyl)-2,5-dihydro-2,2,5,5-tetramethylfuran-3(2*H*)-one (2.58 g, 10 mmol), hydrazine (0.32 g, 10 mmol), and $pTsOH \cdot H_2O$ (0.19 g, 1 mmol) was heated in refluxing toluene (50 mL) for 18 h. After cooling and neutralization with $NaHCO_3$, the solution was evaporated in vacuo and the resulting residue dissolved in Et_2O. Recrystallization of the solid resulting from HCl gas addition to the Et_2O solution from CH_2Cl_2–hexane gave 1.60 g (55%) of pyridazine 8c as a yellow solid, mp 151–152 °C.

Method L. Preparation of 2-Phenyl-5,7-dihydro-5,5,7,7-tetramethylfuro[3,4-*b*]pyrazine 1-Oxide Hydrochloride (8d). A solution of 1-aminoacetophenone hydrochloride (1.71 g, 10 mmol) in toluene (50 mL) was neutralized with concentrated NH_4OH. To the mixture was added 2,2,5,5-tetramethylfuran-3,4-dione monooxime (1.71 g, 10 mmol), and the resulting mixture was heated at reflex for 18 h using a Dean-Stark trap to remove azeotroped water. Evaporation of the solvent and chromatography of the residue over silica gel gave a brown oil. Dissolution in Et_2O and HCl gas addition provided 0.37 g (12%) of pyrazine **8d**, mp 121–125 °C.

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New Analgesic Drugs Derived from Phencyclidine[1]

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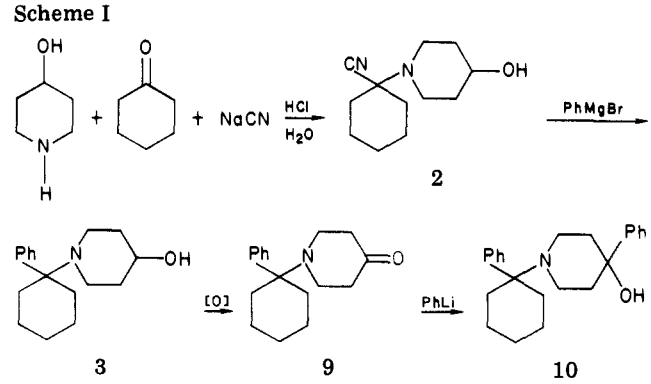
Several esters of 1-(1-phenylcyclohexyl)-4-piperidinol (**3**), 1-(1-phenylcyclohexyl)-4-phenyl-4-piperidinol (**10**) and its propionate (**11**), and 1-(1-phenylcyclohexyl)-4-phenylpiperidine (**13**) were prepared and characterized. The new compounds, which are derived from phencyclidine, exerted analgesic activity in mice. The most potent is **10**, which is twice as active as morphine. The antinociceptive activity of **10**, **11**, and **13** could be well correlated with their potency in the mouse vas deferens bioassay, and both were completely reversed by naloxone.

Phencyclidine [1-(1-phenylcyclohexyl)piperidine, PCP], now a major drug of abuse,[2] held intially the promise of a safe general anesthetic. Indeed, the drug is unique in its lack of depressant effect on the heart and respiration.[3a,b] Its use, precluded in man on account of the acute psychotic syndrome it precipitates, is still practiced with success in veterinary medicine.[4,5] PCP has also been accredited with the exertion of analgesia,[6,7] but no precise data are available on this particular aspect. We assumed that a proper manipulation of the PCP structure might change the balance between its antinociceptive and psychotomimetic properties in favor of the former. This is not unreasonable, in view of the successful precedence offered by ketamine,[8]

Scheme I



(1) Taken from the Ph.D. dissertation of Y.I., 1980.
(2) R. C. Petersen and R. C. Stillman, "Phencyclidine: A Review", National Institute of Drug Abuse: Washington, D.C., May, 1978.
(3) (a) F. E. Greifenstien, M. Devault, J. Yoshitake, and J. E. Gajewski, *Anesth. Analg. (Cleveland)*, **37**, 283 (1958); (b) M. Johnstone, Y. Evans, and S. Baigel, *Br. J. Anesth.*, **31**, 433 (1959).
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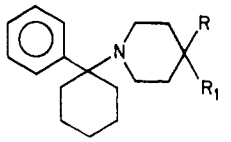
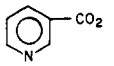
Table I. 4-Substituted 1-(1-Phenylcyclohexyl)piperidines



1 (PCP), R = R_1 = H[a]
3, R = H; R_1 = OH

no.	R	R_1	mp, °C	formula	recrystn solvent[b]	yield, %	anal.
4	H	3,4-$(CH_3O)_2C_6H_3CO_2$	154-155	$C_{26}H_{33}NO_4$	A	62	C, H, N
5	H	$C_6H_5CO_2$	146-148	$C_{24}H_{29}NO_2$	A	85	C, H, N
6	H		114-115	$C_{23}H_{28}N_2O_2$	A	60	C, H, N
7	H	4-$NH_2C_6H_4CO_2$	167-168	$C_{24}H_{30}N_2O_2$	D	60	C, H, N
8	H	CH_3CO_2	195-196	$C_{19}H_{27}NO_2 \cdot HCl \cdot H_2O$	B	72	C, H, N
10	OH	C_6H_5	103-105	$C_{23}H_{29}NO$	E	75	C, H, N
11	$C_2H_5CO_2$	C_6H_5	214-215	$C_{26}H_{33}NO_2 \cdot HCl \cdot 0.5H_2O$	B	60	C, H, N
13	H	C_6H_5	131-132	$C_{23}H_{29}N$	C	57	C, H, N

[a] Reference 13. [b] A = ethyl acetate; B = acetone; C = ethyl acetate–ethanol; D = benzene; E = petroleum ether–hexane.

Table II. Analgesic Activity,[a] Bioassay Results,[b] Relative Potency in Activity Cage,[c] and Acute Toxicity

compd	ED_{50}, mg/kg sc[d] hot-plate test	ED_{50}, mg/kg sc[d] writhing test	IC_{50}, μM[e]	rel potency in act. cage[c]	LD_{50}, mg/kg sc[d]
1	*f*	2.8 (2.2-3.4)	*i*	5.0	37.5 (28.2-49.8)
3	*g*	11.2 (7.5-16.6)	*j*	2.3	nt
4	7.5 (4.7-12.0)	5.2 (3.1-8.4)	*i*	0.5	74.0 (57.1-96.2)
5	15.0 (8.8-25.6)	24.5 (14.4-41.6)	*i*	1.1	>300[k]
6	45.0[h]	16.5 (11.1-24.5)	*i*	1.3	>300[k]
7	40.0[h]	9.3 (5.4-15.8)	*i*	0.7	nt
8	40.0[h]	14.5 (8.0-26.1)	*i*	2.0	nt
10	1.3 (0.9-2.0)	0.27 (0.18-0.40)	0.082 ± 0.008	1.2	82.3 (70.3-96.2)
11	12.1 (8.6-16.9)	5.8 (3.7-8.9)	0.78 ± 0.042	1.1	>300[k]
13	56.0 (43.4-72.2)	42.0 (30.4-57.9)	7.5 ± 0.40	1.0	>300[k]
morphine	2.5 (1.6-3.7)	0.42 (0.22-0.78)	0.50 ± 0.058	1.1	531[l]

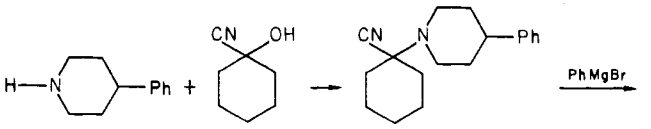
[a] Tested subcutaneously as water-soluble hydrochloride salts. [b] Effect of the compounds on the mouse vas deferens according to ref 17. [c] Values refer to the potency of the compounds to produce hyperactivity in mice. Untreated mice were taken as the control group (potency = 1). [d] Numbers in parentheses are 95% confidence limits by probit analysis;[24] data refer to the free base; nt = not tested. [e] Concentration which produces 50% inhibition of twitches plus or minus SEM. [f] Not active up to 9 mg/kg sc; higher doses produced ataxia. [g] Not active up to 25 mg/kg sc; higher doses produced ataxia. [h] Approximate ED_{20}. [i] Concentrations up to 1.0 μM caused no change in twitches; higher concentrations (up to 100 μM) caused potentiation of twitches (which was concentration dependent). [j] No change in twitches was observed up to 100 μM. [k] No acute toxicity up to 300 mg/kg sc. [l] Reference 25.

which has retained the anesthetic profile of the parent structure but lost much of its psychotomimetic activity. Some of the structural modifications we sought borrowed elements from the well-known analgesic prodine.[9] The relationship between PCP and its new congeners is shown in Table I.

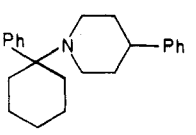
While this work was in progress, disclosure was made[10,11] of a group of analgesics derived from the structurally related (1-phenylcyclohexyl)dimethylamine.

Chemistry. The synthesis of the new compounds was carried out according to Scheme I. 1-(1-Phenylcyclohexyl)-4-piperidinol (3)[12] was obtained by us in 45% yield,

Scheme II



12



13

but silylation of its precursor 2 prior to reaction with PhMgBr increased its yield to 77%. The piperidinol 3 was further esterified to compounds 4–6 and 8 (Table I) with the corresponding acyl chlorides. The 4-aminobenzoate 7 was prepared by transesterification.

1-(1-Phenylcyclohexyl)-4-piperidone (9) was obtained from the alcohol 3 by the Oppenauer oxidation. Attempts to oxidize 3 with chromic trioxide in various media (AcOH,

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H_2SO_4, or pyridine) failed. The piperidone **9** and phenyllithium gave 1-(1-phenylcyclohexyl)-4-phenyl-4-piperidinol (**10**), which with propionic anhydride gave the propionate **11**. In addition, the deoxy analogue **13** was prepared from 4-phenylpiperidine and cyclohexanone cyanohydrin (Scheme II).

Pharmacology. The mouse hot-plate[14] and the writhing tests[15] (using 0.6% acetic acid ip) were used to assess the analgesic activity of the compounds. In the hot-plate test, PCP did not produce any significant change in latency up to 9 mg/kg sc, while higher doses produced marked ataxia. In the writhing test a steep dose–response relationship with an ED_{50} of 2.8 mg/kg sc was observed. Among the 4-monosubstituted derivatives of PCP, only **4**, **5**, and **13** produced analgesia in both tests, while **6–8** exhibited analgesia only in the writhing test (Table II).

The 4,4-disubstituted derivatives of PCP, **10** and **11**, exerted analgesic activity in both tests. **10** was found to be the most potent in this series (almost twice as potent as morphine; Table II). The analgesic activities of **10**, **11**, and **13** were completely antagonized by 2 mg/kg naloxone sc (in the hot-plate test).

In order to assess the opiate-like activity of the new compounds, the mouse vas deferens preparation was used. Opioids were shown to inhibit the contractions induced by electrical-field stimulation of the vas deferens of mice by inhibiting noradrenaline release.[16-18]

Only compounds **10**, **11**, and **13** showed a concentration-dependent inhibition of contractions; all other compounds showed concentration-dependent increases in twitch height (Table II). The maximal inhibition produced by **10**, which was six times as potent as morphine, **11** and **13** could be reversed by 20–50 nM naloxone; the same concentration range was needed to antagonize the effect of morphine in this bioassay.

We have also found[19] that the pA_2 values of naloxone in antagonizing the inhibitory effect of the various compounds were as follows: normorphine, 8.60; **10**, 8.76; **11**, 8.74; **13**, 8.71. However, the regression lines did not have a uniform slope and, therefore, one cannot state with certainty that a single competitive mechanism is involved in the antagonism with naloxone, even though the pA_2 values are very close.

For compounds **10**, **11**, **13**, and morphine, a good correlation was obtained between the relative analgesic potency (hot-plate test) and the relative potency of the inhibitory effect in the mouse vas deferens ($r = 0.95$). When morphine was omitted from the claculation of the regression line, correlation was even better ($r = 0.99$).

It has been suggested that the psychotic effect of PCP is associated with induction of hyperactivity in mice and rats.[20-22] In this respect, as estimated from the results of the activity cage test (Table II), the new compounds are much less active than PCP, but as yet the data are insufficient to draw any conclusions about their psychotic effects.

We presume that different mechanisms are involved in the antinociceptive effect of PCP and the new compounds, particularly **10**, **11**, and **13**. The facts that there is a good correlation between the relative potencies found in the hot-plate test and the mouse vas deferens bioassay, these effects are reversed by naloxone, and the new compounds are structurally similar to the known 4-phenylpiperidine narcotic analgesics,[23] imply that the analgesic effect is mediated by the opiate receptors. This view is supported by preliminary results of the radioreceptor assay (with [^{3}H]morphine) which is being carried out in our laboratory.

Experimental Section

Melting points were determined on a Fisher apparatus and were uncorrected. Infrared spectra (in $CHCl_3$) were taken on a Perkin-Elmer spectrophotometer Model 137 B. Analytical results were within ±0.3% of the theoretical values.

1-(1-Phenylcyclohexyl)-4-piperidinol (3) was prepared by modification of the published procedure.[12] A solution of 28 g (0.35 mol) of the 4-hydroxypiperidinocyclohexylcarbonitrile (**2**) in 200 mL of pyridine was treated with 50 mL of hexamethyldisilazane and 30 mL of trimethylchlorosilane. After stirring for 1 h at room temperature, the solvent was removed, and the residue was taken into $CHCl_3$, filtered, concentrated, and recrystallized from petroleum ether to give 30 g of crystals, mp 90 °C. A solution containing 28 g (0.14 mol) of this nitrile in 200 mL of benzene was added to PhMgBr (prepared from 47 g of bromobenzene and 8 g of Mg in 250 mL of ether), refluxed for 5 h, left overnight at ambient temperature, and then poured into ice–NH_4Cl. The organic layer was separated and washed with water, and the base was extracted with 10% H_2SO_4, liberated with 20% NaOH, reextracted with benzene, dried, and concentrated. The residue which solidified was recrystallized from hexane–ethanol (5:1) to give 20 g of **3**: mp 116–118 °C (lit.[12] mp 117–118 °C).

Esters 4–6. The corresponding aromatic acid was refluxed for 1 h with a considerable excess of freshly distilled thionyl chloride; after concentration, the residue was treated with dry benzene and then distilled again. The residue was treated with piperidinol **3** in 50 mL of pyridine, refluxed for 2–3 h, cooled, diluted with 50 mL of ice–water, extracted with $CHCl_3$, washed with 5% $NaHCO_3$, dried, concentrated, and recrystallized until TLC (alumina, $CHCl_3$–ethyl acetate, 4:1) showed absence of impurities.

1-(1-Phenylcyclohexyl)-4-piperidyl acetate (8) was prepared from 8 g (0.1 mol) of acetyl chloride and 6 g (0.023 mol) of **3** in dry benzene. After refluxing for 2 h, the solvents were removed, and the product was converted into its HCl salt and recrystallized from acetone.

4-Aminobenzoate 7 was prepared as follows: 2.6 g (0.01 mol) of **3** was heated with 0.15 g of sodium (0.065 g-atom) in 30 mL of toluene for 2 h, then a solution of 1.5 g (0.01 mol) of methyl 4-aminobenzoate in 20 mL of toluene was added during 20 min, and methanol was removed by slow distillation during 1.5 h until the temperature reached 110 °C. The mixture was cooled and washed with water, the organic layer was concentrated, and the residue was crystallized from benzene.

1-(1-Phenylcyclohexyl)-4-piperidone (9). A solution of 26 g (0.14 mol) of aluminum isopropoxide in 60 mL of benzene was slowly added to 20 g (0.77 mol) of **3** in 600 mL of benzene and 400 mL of acetone. The mixture was refluxed for 7 h (more prolonged reflux did not improve the yield), concentrated, diluted with CH_2Cl_2, extracted with 3 N H_2SO_4, liberated with 20% NaOH, extracted with benzene, dried, and concentrated. The oily residue was chromatographed on neutral alumina (Fluka) and eluted with 500 mL of petroleum ether–benzene (4:1) and again with 500 mL of benzene. After the solvents were removed, the residue was crystallized from heptane to give 6 g (25%) of **9**: mp

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(23) A. F. Casy, *Prog. Drug Res.*, **22**, 149 (1978).

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).

Acknowledgment. We thank Dr. Y. Sarne and Mrs. O. Keren for their suggestions for the bioassay.

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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

(1) For paper 2 in this series, see G. Maksay, Zs. Tegyey, and L Ötvös, *J. Med. Chem.*, **22**, 1443 (1979).
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(4) S. C. Bell, R. J. McCaully, C. Gochman, S. J. Childress, and M. I. Gluckman, *J. Med. Chem.*, 11, 457 (1968).
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