The compounds were dissolved in Hams (F-10, 1X) medium containing up to 1% Me_2SO to give concentrations between 10^{-2} and 10^{-6} M. Chick embryo fibroblasts were grown as monolayer cells at 5×10^5 cells/60 mm petri dish. The medium was removed by suction. Virus was diluted to give approximately 200 focus-forming units/0.1 mL. To the cells were added 2.6 mL of fresh medium, 0.3 mL of drug, and 0.1 mL of virus so that final drug concentrations were between 10^{-3} and 10^{-6} M. Three controls were used: cell control (no virus, no drug); virus control (no drug); cytotoxicity control (no virus). The cells were incubated at 37 °C for 8–16 h, and the medium was removed by suction. The cells were overlaid with 4.5 mL of agar medium and 0.5 mL of drug solution and incubated for 4 days. A second agar overlay (5 mL) was performed. The foci were counted between days 7 and 10.

The % inhibition of transformation was calculated as follows:

$$\% \text{ inhibition} = (1-(T/C)) \times 100\%$$

where T = number of foci in treated samples and C = number of foci in control samples.

The results were calculated by using probit analysis.[19,20]

Inhibition of RSV Replication. The medium used in this experiment is the same as for the focus assay.

Compounds were prepared in Hams 1 × F10 medium so that the final concentrations were their approximate ID_{50}s in the viral transformation assay. Chick embryo cells were grown at 5×10^5 cells/60-mm petri dish. The old medium was removed by suction and replaced with 4.5 mL of new medium, 0.5 mL of drug solution, and virus. The control consisted of medium and virus only. On days 3 and 6, the medium was removed by suction and replaced with another 4.5 mL of new medium and 0.5 mL of drug solution. Two days later, the medium was harvested. The virus titers in each harvest were then tested by standard focus assays as described above, without the presence of any drug.

The virus titers in the treated samples were compared to that in the control. A decrease in number points to an inhibition of viral replication. The results are summarized in Table IV.

In Vivo Acute Toxicity (LD_{50}) Studies. The toxicities of two of the compounds (**3**, **9**) were studied in Swiss-Webster male mice. The compounds were suspended with 2.5% acacia in normal saline. Six mice were used for each dose. The mice were weighed and the appropriate doses injected intraperitoneally. Control mice were injected ip with a 2.5% acacia suspension in normal saline. The LD_{50} of each compound was calculated by using probit analysis.[19,20]

In Vivo Anticancer Activity against P388 Leukemia. The activities of the compounds against P388 leukemia in vivo in mice were studied by the National Cancer Institute, Bethesda, Md. The drugs were given by the intraperitoneal injection. The activity was expressed as the percentage increase in median survival time of treated cancer-bearing mice over control cancer-bearing mice.

Acknowledgment. This paper was taken in part from the Ph.D. dissertation of A.T., University of Southern California, 1984. The study was supported in part by Grant BRSG 507 RR05792 (NIH) to E.J.L. and A.T. and by U.S. Public Health Service Grant CA 16113 from the National Cancer Institute to M.M.C.L. A summary of the synthesis and the anticancer activity of some of the compounds has been presented at the 131st APhA Annual Meeting, Medicinal Chemistry and Pharmacognosy Section, Montreal, Quebec, Canada, May 5–10, 1984.

Supplementary Material Available: Appendix 1, thin-layer chromatography R_f values, and Appendix 2, proton NMR chemical shifts in Me_2SO-d_6 (Varian 200 MHz) (6 pages). Ordering information is given on any current masthead page.

Substituted 2-Pyrones, 2-Pyridones, and Other Congeners of Elasnin as Potential Agents for the Treatment of Chronic Obstructive Lung Diseases†

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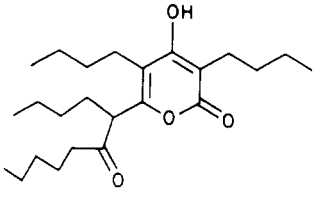
Department of Chemistry, Wichita State University, Wichita, Kansas 67208. *Received August 17, 1984*

Several congeners of elasnin (I) have been synthesized and shown to inhibit human leukocyte elastase (HLE). The C-3 alkyl substituted 2-pyrones **11** and **12** were found to be the most effective inhibitors of the enzyme. These compounds are highly specific in their inhibitory activity.

More than 48 000 people die each year in the U.S. from chronic obstructive lung disease (emphysema and bronchitis).[1] Furthermore, the disabling nature of these diseases results in a formidable economic cost in terms of lost wages and other medical expenses. The destruction of lung tissue by leukocyte elastase has been postulated to occur whenever a proteinase–proteinase inhibitor imbalance exists.[2] This imbalance can, in principle, be overcome either by replenishing the amount of α-1-proteinase inhibitor (α-1-PI) or by inhibiting selectively human leukocyte elastase (HLE).

We have recently reported preliminary findings related to the use of substituted α-pyrones as selective inhibitors of HLE.[3] These compounds resemble elasnin (I), a 2-pyrone elaborated by *Streptomyces noboritoensis*.[4-7] Elasnin has been reported to exhibit selective inhibitory activity toward HLE and to be devoid of toxic side effects.[4] In pursuing our objectives in this general area,[8,9] we have synthesized several congeners of elasnin and have examined their inhibitory activity toward HLE.



I

Chemistry. The substituted 2-pyrones and 2-pyridones were prepared according to Scheme I. Alkylation of the

† A portion of this work was presented at the 19th National Symposium in Medicinal Chemistry, University of Arizona, Tucson, AZ, June 17–21, 1984.

(1) U.S. Department of Health and Human Services, Public Health Service (1980), National Institutes of Health, Publication No. 81-2105.
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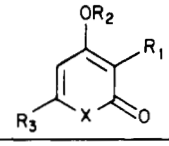
0022-2623/85/1828-1106$01.50/0

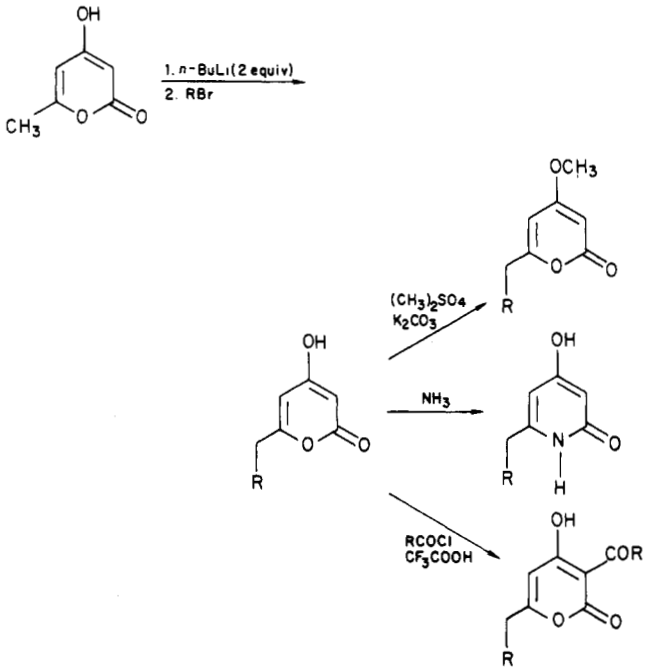
Table I



compd	R_1	R_2	R_3	X	IC_{50},[a] M
1	H	H	$CH_3(CH_2)_2$	O	inactive
2	H	H	$CH_3(CH_2)_3$	O	inactive
3	H	H	$CH_3(CH_2)_4$	O	inactive
4	H	H	$CH_3(CH_2)_6$	O	inactive
5	H	H	$CH_3(CH_2)_{10}$	O	31.5×10^{-4}
6	H	H	$C((CH_2)_3CH_3)H(CH_2)_5CH_3$	O	16.2×10^{-4}
7	H	CH_3	$C((CH_2)_3CH_3)H(CH_2)_5CH_3$	O	
8	$COCH_2CH_3$	H	CH_3	O	inactive
9	$CO(CH_2)_2CH_3$	H	CH_3	O	inactive
10	$CO(CH_2)_4CH_3$	H	CH_3	O	inactive
11	$CO(CH_2)_{10}CH_3$	H	CH_3	O	2.68×10^{-5}
12	$CO(CH_2)_{14}CH_3$	H	CH_3	O	3.58×10^{-5}
13	H	H	$CH_3(CH_2)_6$	NH	inactive
14	H	H	$CH_3(CH_2)_{10}$	NH	15.3×10^{-5}

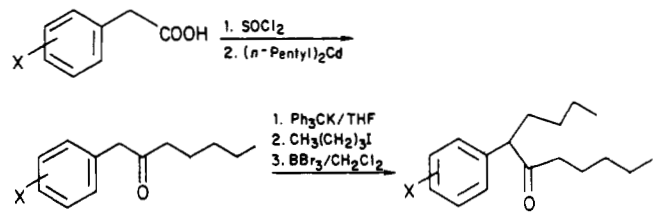
[a] All IC_{50} values represent the average of two determinations.

Scheme I



dianion of 6-methyl-4-hydroxy-2-pyrone with the appropriate alkyl halide yielded compounds **1–6** readily.[10] Compound **6** was methylated with dimethyl sulfate by refluxing in the presence of anhydrous potassium carbonate and acetone.[10] Formation of the corresponding 2-pyridones was accomplished by refluxing with concentrated ammonia.[11] 6-Methyl-4-hydroxy-2-pyrone was readily acylated with the appropriate acid chloride or anhydride in trifluoroacetic acid to yield compounds **8–12**.[12]

Scheme II



Scheme III

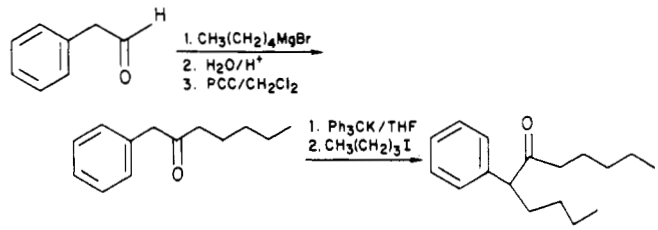
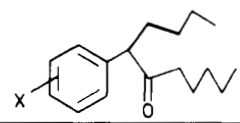


Table II



compd	X	compd	X
15	H	18	*p*-OCH_3
16	*o*-OCH_3	19	*m*-OH
17	*m*-OCH_3		

Compounds **16–19** were synthesized according to Scheme II. In the case of compound **15**, the capriciousness of the di-*n*-alkylcadmium reaction and the presence of a persistent impurity necessitated the use of an alternative synthetic pathway (Scheme III).[13]

Results and Discussion

The results of the in vitro inhibitory activity of the synthesized compounds are listed in Table I. It is apparent from Table I that the nature of the ring, the nature of the alkyl chain, and the position of the alkyl chain on the ring all influence the inhibitory activity of these com-

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pounds. The 3-acyl-substituted 2-pyrones bearing an alkyl chain of at least 11 carbon atoms (compounds **11** and **12**) were found to be the most active, while shorter alkyl chains at C-3 yielded inactive compounds. In comparing compounds **5** and **14** it is clear that the 2-pyridone ring enhances the inhibitory activity of these compounds. Replacement of the 2-pyrone ring with a phenyl ring gave inactive compounds (**15–19**) irrespective of the nature and position of the alkyl chain. Of the compounds that were found to be active, namely, **6**, **7**, **11**, **12**, and **14**, none of them had any effect on porcine pancreatic elastase or α-chymotrypsin under comparable conditions, attesting to the highly specific action of these compounds. Some of the compounds had rather limited solubility in aqueous and nonaqueous solvents.

In summary, the present study has shown that the nature of the ring and of the alkyl chain as well as the position of the alkyl chains in elasnin, all play a significant role with respect to its inhibitory activity. It also demonstrates that elasnin can serve as a "lead" compound in developing more potent inhibitors of human leukocyte elastase.

Experimental Section

Human leukocyte elastase was obtained from Elastin Products, St. Louis, Boc-L-Ala-p-nitrophenol, α-chymotrypsin, and methoxysuccinyl-L-Ala-Ala-Pro-Val-*p*-nitroanilide were purchased from Sigma Co. The infrared spectra of the compounds were recorded on a Perkin-Elmer 1330 infrared spectrophotometer and the ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer spectrometer using tetramethylsilane as an internal standard. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. A Beckman Acta III UV/visible spectrophotometer was used in the enzyme assays. Elementary analyses were performed by Galbraith Labs, Knoxville, TN, and M-H-W Laboratories, Phoenix, AZ.

***m*-Methoxyphenylacetyl Chloride (20).** *m*-Methoxyphenylacetic acid (24.9 g, 0.15 mol) in 200 mL of methylene chloride was reacted with thionyl chloride (17.8 g, 0.15 mol). After the mixture was refluxed overnight, the solvent was removed in vacuo and the residue was vacuum distilled, yielding 21.0 g (76%) of product [bp 104 °C (0.50 mm)]: IR (neat) 1800 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 7.0 (5 H, m), 4.3 (2H, s, Ar CH_2), 3.75 (3 H, s, OCH_3). Anal. ($C_9H_9ClO_2$) C, H, Cl.

1-(*m*-Methoxyphenyl)-2-heptanone (21). 1-Bromopentane (17.22 g, 0.114 mol) was reacted with magnesium turnings (2.77 g, 0.114 mol) in anhydrous ethyl ether. The unreacted magnesium was removed under nitrogen and the solution was mixed with anhydrous cadmium chloride (11.18 g, 0.061 mol). The mixture was then refluxed for 1 h. The ethyl ether was removed in vacuo, toluene (125 ml) was added, and refluxing was continued for 0.4 h. After the mixture cooled to room temperature, *m*-methoxyphenylacetyl chloride (21.0 g, 0.114 mol) was added dropwise to the solution. After refluxing for 1 h, the reaction mixture was poured into ice, acidified with a minimum amount of concentrated sulfuric acid, and extracted with toluene (4 × 100 mL). After washing of the organic layer with 10% sodium carbonate (2 × 75 mL) and water, the organic layer was dried and evaporated off. Vacuum distillation of the residue yielded **21** (10.66 g, 47% yield): IR (neat) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.0 (5 H, m), 3.75 (3 H, s, OCH_3), 3.62 (2 H, s, Ar CH_2CO), 2.43 (2 H, m, $COCH_2$), 1.28 (9 H, m). Anal. ($C_9H_9ClO_2$) C, H, Cl.

5-(*m*-Methoxyphenyl)-6-undecanone (17). Triphenylmethane (11.39 g, 0.043 mol) in 75 mL of dry THF was reacted with methyllithium (37.15 g, 0.048 mol) under nitrogen. After the mixture was stirred for 0.5 h, a solution of **21** (10.66 g, 0.049 mol) in 10 mL of dry THF was added dropwise. After the mixture was stirred for 0.5 h, 18.0 g (0.098 mol) of 1-iodobutane in 32 mL of THF was added and the solution refluxed overnight. The reaction mixture was filtered and the solvent evaporated off in vacuo. The residue was flash chromatographed on silica gel with hexane and methylene chloride as eluents, yielding 1.19 g of a pure light yellow oil: IR (neat) 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.0 (4 H, m), 3.75 (3 H, s, OCH_3), 3.51 (1 H, m, Ar CHCO), 2.38 (2 H, m, $COCH_2$), 1.25 (18 H, m). Anal. ($C_{18}H_{28}O_2$) C, H.

5-(*m*-Hydroxyphenyl)-6-undecanone (19). A 0.47-mL (5 mmol) sample of boron tribromide was added dropwise to 280 mg (1 mmol) of compound **17** in 10 mL of methylene chloride at 0 °C under nitrogen. Stirring was continued for 4 h at room temperature. Methanol (5 mL) was added, and after removal of the solvents in vacuo, the residue was taken up in methylene chloride (70 mL). The organic layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent left a viscous oil (200 mg): IR (neat) 3300 (OH), 1705 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 7.0 (4 H, m), 3.50 (1 H, m, Ar CHCO), 2.38 (2 H, m, CH_2CO), 1.24 (18 H, m). Anal. ($C_{17}H_{26}O_2$) C, H.

1-Phenyl-2-heptanol (22). The Grignard reagent from 1-bromopentane (15.1 g, 0.1 mol) and magnesium (2.43 g, 0.1 g mol) in 100 mL of anhydrous ethyl ether was added to freshly distilled phenylacetaldehyde (10.0 g, 0.08 mol) in 20 mL of ethyl ether at 0 °C with stirring. The solution was stirred for 0.5 h, poured into a mixture of 5% HCl and ice, and subsequently extracted with ethyl ether (4 × 125 mL). Vacuum distillation gave 7.88 g (51% yield) of compound **22**: IR (neat) 3380 cm^{-1} (OH); NMR ($CDCl_3$) δ 7.18 (5 H, s), 3.75 (1 H, br s, CHOH), 2.65 (2 H, m, Ar CH_2), 1.35 (11 H, m). Anal. ($C_{13}H_{20}O$) C, H.

1-Phenyl-2-heptanone (23). Pyridinium chlorochromate (6.46 g, 0.03 mol) was added to a solution of compound **22** (4.12 g, 0.02 mol) in 10 mL of methylene chloride. The solution was stirred for 1 h. Celite was added and the mixture was filtered. Evaporation of the solvent followed by vacuum distillation of the residue yielded 2.7 g (72% yield) of product: IR (neat) 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.18 (5 H, br s), 3.59 (2 H, s, Ar CH_2CO), 2.38 (2 H, CH_2CO), 1.21–0.84 (9 H, m). Anal. ($C_{13}H_{18}O$) C, H.

5-Phenyl-6-undecanone (15). From triphenylmethane (2.44 g, 0.01 mol) and potassium metal (0.39 g, 0.01 mol) in 25 mL of anhydrous ethyl ether and 1.92 g (0.01 mol) of compound **23**, compound **15** was obtained as a pale yellow liquid (0.65 g, 26%) after flash chromatography: IR (neat) 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.18 (5 H, s), 3.58 (1 H, Ar CHCO), 2.32 (2 H, m, $COCH_2$), 1.22–0.84 (18 H, m). Anal. ($C_{17}H_{26}O$) C, H.

6-Undecyl-4-hydroxy-2-pyridone (14). A mixture of 6-undecyl-4-hydroxy-2-pyrone (5.32 g, 0.02 mol), concentrated ammonium hydroxide (10 mL), and dioxane (20 mL) was heated to 110 °C for 1 h with stirring. Upon cooling, precipitation of the product ensued. Recrystallization from aqueous ethanol gave **14** (2.25 g) as white needles mp 255–257 °C; NMR (Me_2SO-d_6) δ 5.6 (1 H, d, =CH), 5.4 (1 H, d, =CH), 2.5 (2 H, m, C=CCH_2), 1.3–0.9 (21 H, m). Anal. ($C_{18}H_{31}NO_2$) C, H, N.

Enzyme Inhibition Studies. Human leukocyte elastase was assayed as follows: 10 μL of 1.7 × 10^{-7} M HLE solution in 0.05 M sodium acetate, pH 5.5, 10 μL of dimethyl sulfoxide, and 980 μL of Tris buffer, pH 7.2, were pipetted into a thermostated cuvette. The contents were shaken and allowed to equilibrate for 20 min at 25 °C. Ten microliters of a 3.15 × 10^{-2} M solution of methoxysuccinyl-L-Ala-Ala-Pro-Val-*p*-Nitroanilide in dimethyl sulfoxide was added to the cuvette. The contents were shaken and incubated for 30 s, and the change in absorbance at 410 nm due to *p*-nitroaniline release was monitored for 2 min. The experiment was then repeated in the presence of each inhibitor. 10 μL of a 4.125 × 10^{-4} M inhibitor solution in dimethyl sulfoxide was used. Compounds causing a drastic drop in the hydrolysis rate were assumed to exhibit inhibitory activity. The IC_{50}'s of the active compounds were determined by varying the amount of inhibitor and constructing a percent inhibition vs. [I] plot. Duplicate runs were carried out for each compound. Porcine pancreatic elastase and α-chymotrypsin were assayed as described previously.[8,9]

Acknowledgment. The generous financial support of the National Institutes of Health (NHLBI Grant HL30798-02) is deeply appreciated.

Registry No. **1**, 18742-94-4; **2**, 83499-38-1; **3**, 81017-02-9; **4**, 90632-45-4; **5**, 81017-03-0; **6**, 90632-46-5; **7**, 90632-47-6; **8**, 22073-84-3; **9**, 22073-85-4; **10**, 27424-82-4; **11**, 96649-62-6; **12**, 96649-63-7; **13**, 96649-55-7; **14**, 96649-56-8; **15**, 65899-16-3; **16**, 96649-57-9; **17**, 96649-58-0; **18**, 84736-59-4; **19**, 96649-59-1; **20**, 6834-42-0; **20** (ortho isomer), 28033-63-8; **20** (para isomer), 4693-91-8; **21**, 96649-60-4; **21** (ortho isomer), 96649-61-5; **21** (para isomer), 53917-03-6; **22**, 57243-11-5; **23**, 6683-94-9; *m*-methoxy-

phenylacetic acid, 1798-09-0; *o*-methoxyphenylacetic acid, 93-25-4; *p*-methoxyphenylacetic acid, 104-01-8; 1-bromopentane, 110-53-2; 6-undecyl-4-hydroxy-2-pyrone, 81017-03-0; 4-hydroxy-6-methyl-2-pyrone, 675-10-5; ethyl bromide, 74-96-4; butyl bromide, 109-65-9; pentyl bromide, 110-53-2; heptyl bromide, 629-04-9; undecyl bromide, 693-67-4; (1-butyl) heptyl bromide, 5447-45-0; propionic anhydride, 123-62-6; 6-n-heptyl-4-hydroxy-2-pyrone, 90632-45-4; elastase, 9004-06-2.

Supplementary Material Available: Synthesis and analytical data for compounds **1–13** (4 pages). Ordering information is given on any current masthead page.

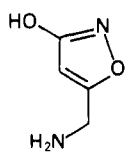
Synthesis and Pharmacological Evaluation of *cis*-2,3,3a,4,5,6,7,7a-Octahydro-3-oxoisoxazolo[5,4-*c*]pyridine: A Structural Analogue of the GABA Agonist THIP

René Nordmann,* Patrick Graff, Richard Maurer, and Beat H. Gähwiler

Preclinical Research, Sandoz Limited, CH 4002 Basel, Switzerland. *Received October 29, 1984*

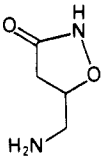
The pharmacological activities of the GABA agonist muscimol (**1**) and its dihydro analogue (**2**) have been shown to be almost identical. The closely related 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol (THIP, **3**), although biologically less active than muscimol, was selected for clinical trials. We report the synthesis of the so far elusive *cis*-2,3,3a,4,5,6,7,7a-octahydro-3-oxoisoxazolo[5,4-*c*]pyridine (*cis*-DH-THIP, *cis*-**4**), which—surprisingly—is devoid of any GABAergic activity.

Muscimol (**1**), a very active and selective GABA receptor agonist, has served as a model compound for a comprehensive series of heterocyclic GABA analogues.[1] Some



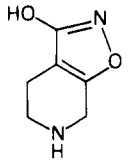
muscimol

1



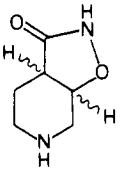
DH-muscimol

2



THIP

3



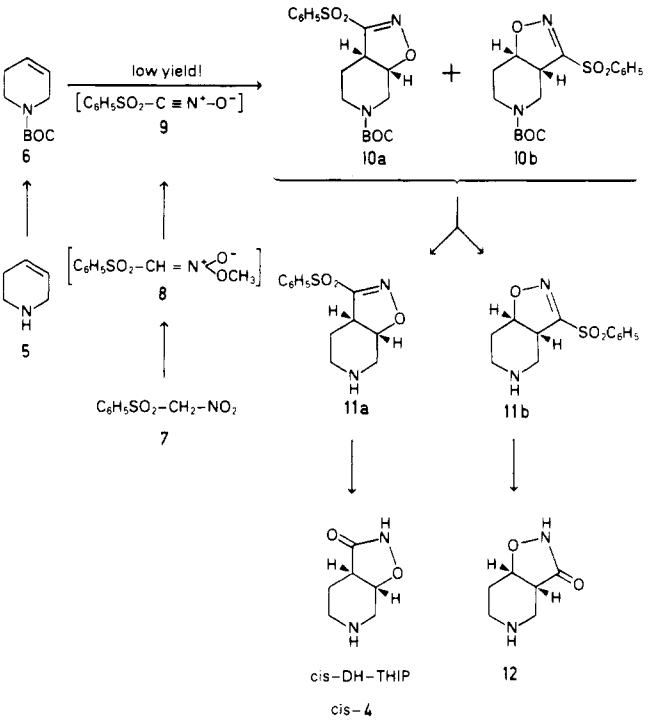
DH-THIP

4

muscimol analogues, including (*R,S*)-4,5-dihydromuscimol (**2**) and 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol (THIP), are potent GABA receptor agonists in vivo and in vitro.[2] The relatively nontoxic compound **3** (THIP), which seems to penetrate the blood–brain barrier was selected for clinical trials.[3]

Previous attempts to synthesize **4**, a dihydro analogue of **3**, have failed.[4] In view of the considerable pharmacological interest in selective GABA receptor agonists, we have decided to develop a synthesis of *cis*-**4** (*cis*-DH-THIP).

Scheme I



We report our successful synthesis of *cis*-2,3,3a,4,5,6,7,7a-octahydro-3-oxoisoxazolo[5,4-*c*]pyridine (*cis*-DH-THIP) and compare its pharmacological activity with that of the two well-characterized GABA agonists **3** (THIP) and muscimol (**1**).

Chemistry. Synthesis of **4** has been approached unsuccessfully[4] in analogy to a reaction sequence developed for the synthesis of **2**[5] and following a general procedure for the preparation of 2-isoxazolin-3-ols. In contrast to

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