0.01 Torr (bulb-to-bulb) 543 mg of **7** (77%) as colourless oil. IR (neat): 3060*w*, 3030*w*, 2920*m*, 2860*m*, 1670*w*, 1500*m*, 1455*m*, 1430*m*, 1340*s*, 1250*m*, 1170*s*, 1090*s*, 1035(sh), 1020*s*, 920*s*, 880*s*, 730*s*, 690*s*. ^{1}H-NMR ($CDCl_3$): 2.65 (*m*, 2 H); 4.45 (*m*, 2 H); 4.50 (*d*, *J* = 11 Hz, 1 H); 4.75 (*d*, 1 H); 5.00 (*m*, 2 H); 5.30 (*m*, 1 H); 7.38 (*m*, 5 H). MS (*m/e*): 190 (1, M^+), 144 (1), 129 (5), 99 (17), 92 (34), 91 (100), 83 (22), 65 (11), 55 (17). Anal. calc. for $C_{12}H_{14}O_2$: C 75.76, H 7.42; found: C 75.55, H 7.60.

2,2-Dimethoxy-3-methylideneoxolane (**12**)

As described above, **11** (374 mg, 1.68 mmol) was reduced in presence of Zn (1.75 g), NH_4Cl (300 mg) and hydroxycobalamin hydrochloride (70 mg, 0.05 mmol) in DMF (25 ml) at r.t. for 5 h. Product after dist. at 60°/20 Torr (bulb-to-bulb) 25 mg of **12** (13%, purity according GC/GC-MS 54%). ^{1}H-NMR ($CDCl_3$): 2.72 (*dt*, *J* = 7, 2 Hz, 2 H); 3.33 (*s*, 6 H); 3.97 (*t*, 2 H); 5.24 (*m*, 2 H). GC-MS (sample with ret. time of **12**): (*m/e*): 143 (1, M^+), 129 (*s*), 113 (100), 91 (9), 81 (55), 69 (11), 59 (55), 55 (22). Compounds **13** and **14** have been detected qualitatively by MS.

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Herbstversammlung Bern 19. Oktober 1990 Sektion für Medizinische Chemie

Chimia 45 (1991) 88–89

Structure-Activity Studies for Potassium-Channel Opening in Pinacidil-Type Cyanoguanidines and Nitroethenediamines

Paul W. Manley* and **Ulrich Quast**

Pinacidil (*rac*-**1**; *N*-cyano-*N'*-(4-pyridinyl)-*N''*-(1,2,2-trimethylpropyl)guanidine) is a vasorelaxant drug [1] which acts primarily through the opening of membrane K channels in vascular smooth-muscle cells [2]. As part of a structure-activity study aimed towards the elucidation of the pharmacophore responsible for K-channel opening, the enantiomers of pinacidil and the bioisosteric nitroethenediamines [3] were prepared and evaluated pharmacologically.

The enantioselective syntheses of the compounds were achieved as follows: pinacolone was reacted with the individual (+)-(*R*)- and (–)-(*S*)-1-phenylethylamines to afford the corresponding chiral (*E*)-imines (*Scheme 1*). Reduction of the imines with $BH_3 \cdot THF$ resulted in addition of H_2 to the less hindered face of the azomethine to give the individual (*R,R*)- and (*S,S*)-benzylamines, which, on hydrogenolysis (10% Pd/C, H_2), afforded the (*R*)- and (*S*)-1,2,2-trimethylpropylamines having high enantiomeric purity. These, on addition to 4-pyridyl isothiocyanate, followed by elimination of H_2S from the resulting thioureas using dicyclohexylcarbodiimide and $EtN(i\text{-}Pr)_2$ gave the diimides, which were reacted *in situ* with cyanamide to give the (*R*)- and (*S*)-enantiomers of pinacidil in high overall yield, having $[\alpha]_D^{20} = -148$ and $[\alpha]_D^{20} = +144$ (*c* = 1.00; EtOH) and ee > 99.5% by NMR. (These values compare favourably with those of $[\alpha]_D^{20} = -135$ and +135 in the literature[4]).

The corresponding nitroethenediamine analogues (**3** and **4**; *Scheme 2*) were prepared *via* the consecutive addition of the required pyridineamine followed by the (*R*)- or (*S*)-1,2,2-trimethylpropylamines to $(Me_2S)_2CHNO_2$ [5], having high enantiomeric purity and existing exclusively in the *E*-configuration as shown by NOE studies.

Biological activity was quantified *in vitro* by simultaneous measurements of inhi-

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0.01 Torr (bulb-to-bulb) 543 mg of **7** (77%) as colourless oil. IR (neat): 3060*w*, 3030*w*, 2920*m*, 2860*m*, 1670*w*, 1500*m*, 1455*m*, 1430*m*, 1340*s*, 1250*m*, 1170*s*, 1090*s*, 1035(sh), 1020*s*, 920*s*, 880*s*, 730*s*, 690*s*. ^{1}H-NMR ($CDCl_3$): 2.65 (*m*, 2 H); 4.45 (*m*, 2 H); 4.50 (*d*, *J* = 11 Hz, 1 H); 4.75 (*d*, 1 H); 5.00 (*m*, 2 H); 5.30 (*m*, 1 H); 7.38 (*m*, 5 H). MS (*m/e*): 190 (1, M^+), 144 (1), 129 (5), 99 (17), 92 (34), 91 (100), 83 (22), 65 (11), 55 (17). Anal. calc. for $C_{12}H_{14}O_2$: C 75.76, H 7.42; found: C 75.55, H 7.60.

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Biological activity was quantified *in vitro* by simultaneous measurements of inhi-

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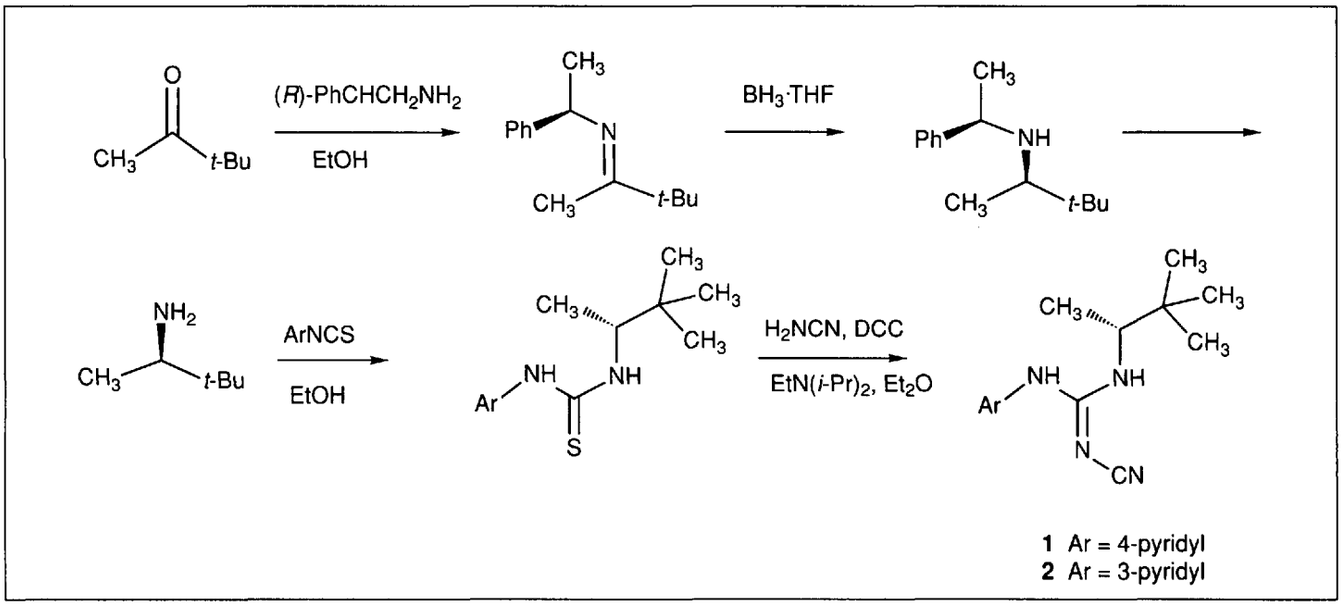
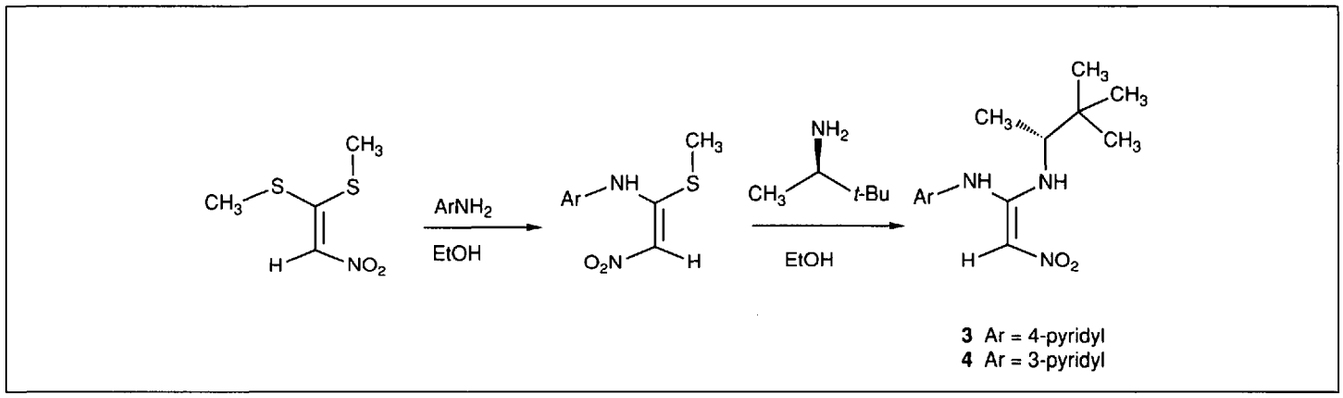
Scheme 1



Scheme 2



bition of spontaneous mechanical activity (pIC_{50}) and stimulation of ^{86}Rb-efflux (pEC_{15}) in rat portal veins [6], and revealed that K-channel opening activity was stereoselective with (*R*)-pinacidil (pIC_{50} = 7.6) being 12 times more potent than (*S*)-pinacidil (pIC_{50} = 6.1). Similar stereoselectivity was found for the 3-pyridyl analogues of pinacidil (**2**). Paradoxically, however, with the nitroethenediamines, as illustrated for the 3-pyridyl analogue **4**, the stereoselectivity for K-channel opening was reversed, with the (*S*)-enantiomer (pIC_{50} = 8.0) being 100-fold more active than its corresponding (*R*)-enantiomer (pIC_{50} = 6.0).

(Abstract by the authors)

Received: November 30, 1990

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Chimia 45 (1991) 89–90

The Search for Peptidoleukotriene Antagonists

Andreas von Sprecher*, Alfred Sallmann, Andreas Beck, Werner Breitenstein, Hansruedi Wiestner, Sabine Kimmel, Wayne H. Anderson, Gary P. Anderson, Natarajan Subramanian, and **Michael A. Bray**

The peptidoleukotrienes LTC_4, LTD_4, and LTE_4 are thought to play a major role in allergic asthma, due to their potent bronchoconstrictor and inflammatory properties. The first leukotriene (LT) antagonist, *FPL55712*, was discovered in 1973 six years before the structures of the LT's were defined by *Samuelsson* and *Corey*. Initial chemical approaches to the discovery of new LT antagonists were based mainly on the structure of *FPL55712* and, after 1980, on the structure of LTD_4. *LY171883, L-648051, Ro23-3544, CGP35949D*, and *YM-16638* are examples of *FPL55712* analogs that are or were in clinical development. However, the clinical data reported so far are not encouraging. These compounds, as well as the first LT analogs, can be considered to be 'first generation' antagonists showing antagonist potency in the range of *FPL55712*. Recently 'second generation' antagonists with greatly enhanced potency have been

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