Pergamon

*Tetrahedron*, Vol. 53, No. 8, pp. 2775-2784, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00005-7

# The Synthesis of Imidazoline Analogs of the Kainoid Family

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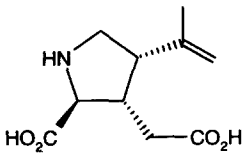
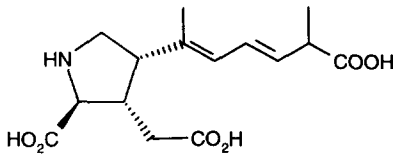
**Abstract**. In an effort to mimic the anthelmintic and insecticidal activties of kainic **1** and domoic **2** acids with compounds of simpler structure and much easier accessibility, the highly functionalised imidazolines **4**, **27**, and **28** were prepared. This involved a synthesis of suitably protected β-aminoglutamic acid derivatives as key intermediates, which were condensed with orthoesters and deprotected to yield the desired compounds.


***Introduction***. The kainoids are a group of natural products with anthelmintic and insecticidal activities. Kainic acid **1** was isolated in 1953 by Takemoto from the algae *Digenea simplex*[1], which had been used as an anthelmintic in Japan. Later in 1959 domoic acid **2** was isolated from a different algae[2], which was also known for its anthelmintic and insecticidal properties[3]. Kainic and domoic acid exert their toxic effect through interaction with the glutamate receptors in the nervous system, and they have become well known as neurophysiological tools[4]. Later the acromelic acids were isolated.[5] They bear heterocyclic substituents at C(4), and are even more potent glutamate agonists than **1** or **2**. Following the total synthesis of these compounds,[6] many analogs were prepared, including the anisyl derivative **3**, which is more potent than the natural kainoids in some nerve preparations[7].

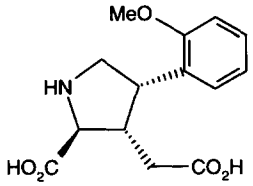
Although many efficient syntheses of these compounds have been described, the processes are too expensive for potential agrochemical usage, and so we attempted to prepare simpler molecules with kainoid like activity. Based on the results and conclusions of many workers, it seems that the the essence of the structure of the kainoids comprises a glutamic acid unit bound in a five-membered ring with an unsaturated substituent at C(4)[6]. In an attempt to incorporate these units in an easily synthesised molecule we chose the imidazoline **4** as target, the similarity of which to the other kainoids can be seen. Here we describe its synthesis in racemic form.



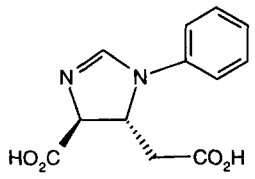

kainic acid **1**




domoic acid **2**



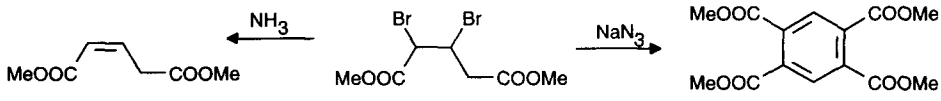

**3**




target **4**

***Results and Discussion.*** Of the various methods of preparing imidazolines,[8] it seemed that the condensation of of the diamine **19** with an appropriate C-1 unit would be most compatible with the substituents in the target **4** (Scheme 4). Thus an efficient synthesis of **19** was required. A number of methods known for the syntheses of simple α,β-diamino acids[9,10] could potentially be applied to the synthesis of **19**.

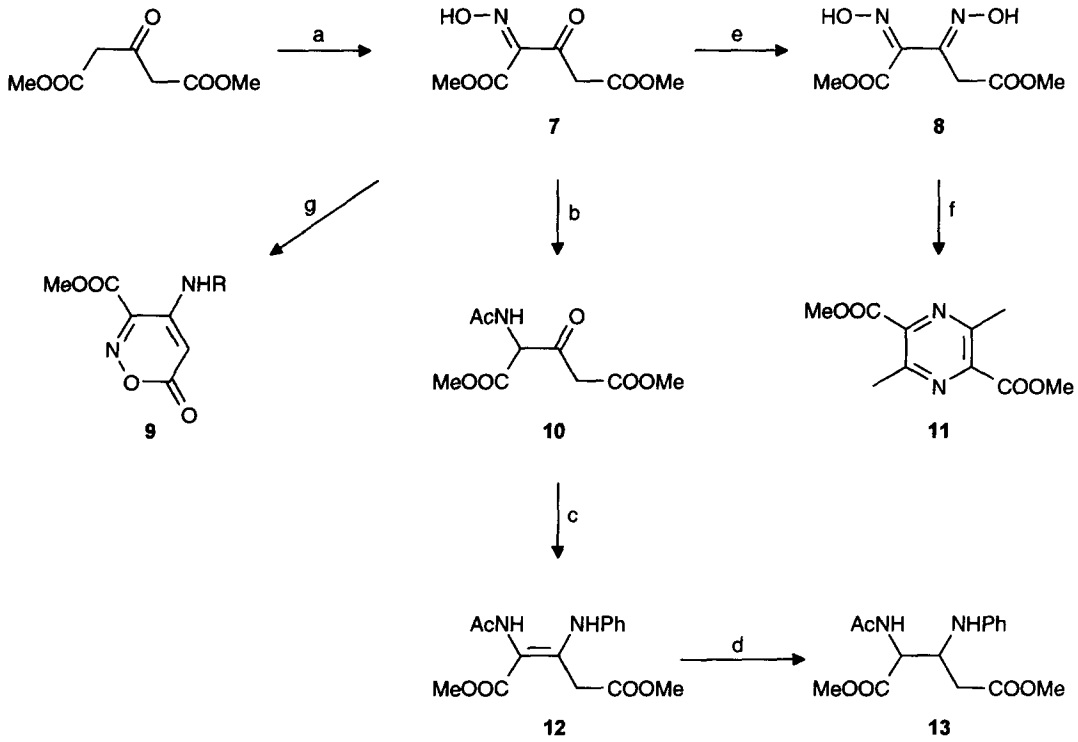
Reaction of **5** with either sodium azide[11] or ammonia[12] did not lead to the desired diamino-compound (Scheme 1), although 2,3-dibromopropanoates react well with both reagents to produce ultimately β-aminoalanine derivatives. Reduction of the bis-oxime **8** (Scheme 2) led to **11**[13] rather than the desired diamino-compound, although again diaminoacids can be prepared by the analogous procedure.[14] Finally an adaptation of the method of Bauer[15] (Scheme 3) led to the desired compound.




**5** **6**

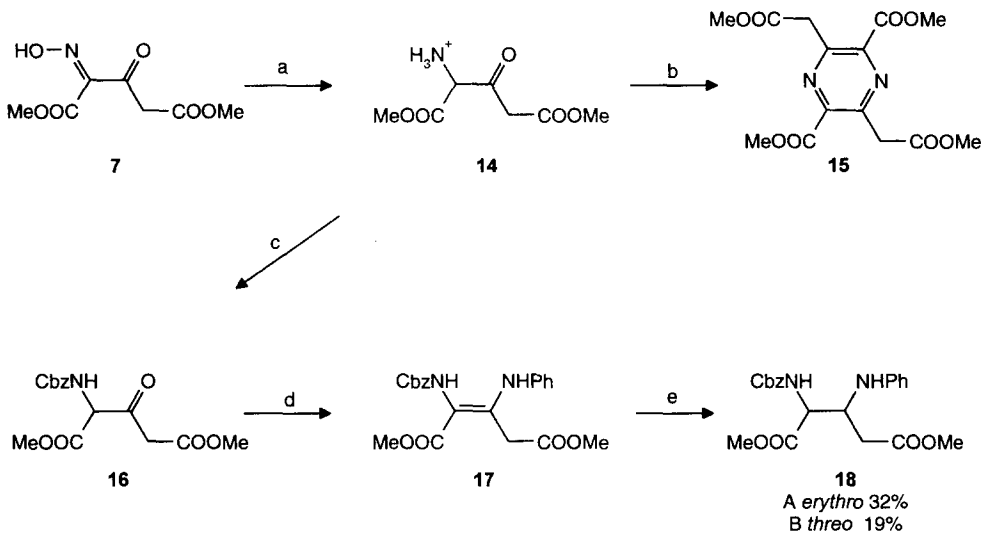
Scheme 1.

The reaction sequence was first studied with an acetamide as amine protecting group, which is easy to prepare, but difficult to remove in the presence of the ester groups. Thus hydrogenation of **7**[16] in the presence of acetic anhydride led to the amide **10** (Scheme 2).[17] Reductive amination was performed in two steps. Enamine formation was straightforward, and subsequent reduction of **12** with cyanoborohydride led to the desired compound **13** as a mixture of diastereomers. An attempted simplification of these steps failed; the conversion first to the enamine followed by reduction of both the enamine and oxime functionalities at the same time was unsuccessful. Ring closure accompanied enamine formation yielding **9**,[18] however, only products of decomposition were isolated from the attempted reduction of this compound. Fortunately, these simplifications were not necessary as the route involving the reductive acetylation of **7** was successful. Therefore the sequence was repeated with the more readily cleavable benzyloxycarbonyl protecting group.



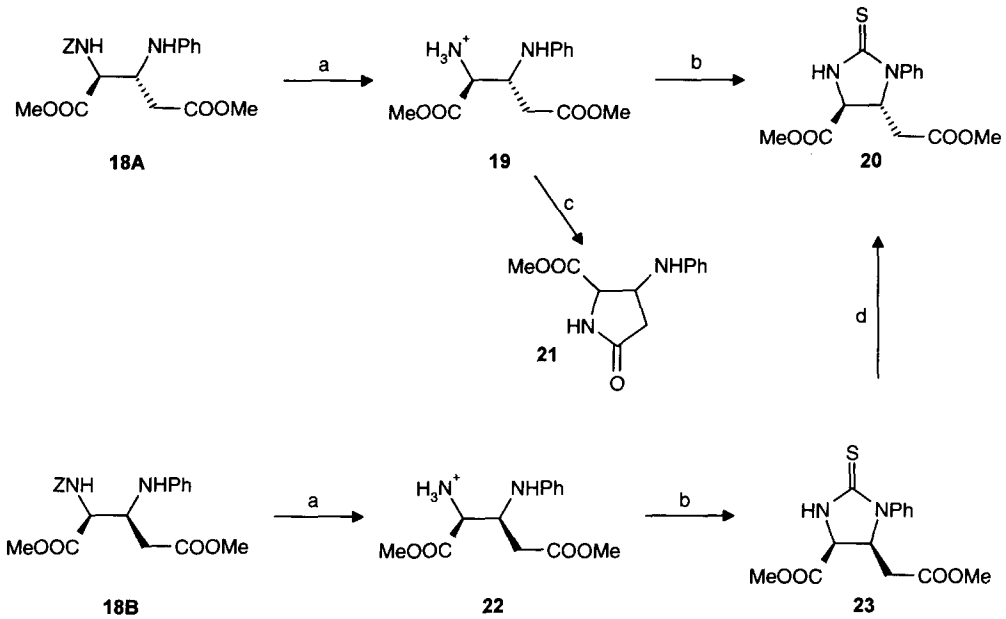

Scheme 2. a. tBuONO, HCl, $Et_2O$ b. $H_2$ 10%, Pd/C, $Ac_2O$ c. $PhNH_2$, benzene d. $NaCNBH_4$, HCl e. $NH_2OH$, MeOH f. $H_2$, Ra-Ni, MeOH g. $RNH_2$, toluene

The conditions used for the introduction of the benzyloxycarbonyl group were important. The amine salt **14** was prepared simply by reduction of **7** in acidic solution.[14] Although **14** is stable in acidic solution, it decomposed slowly giving off $CO_2$ after evaporating the solvent. Neutralisation brought about decomposition of the free base to the pyrazine **15**,[19] so the benzyloxycarbonyl derivative **16** was prepared by first adding BnOCOCl to the acidic solution of **14** and subsequently neutralising with NaOH to pH 6.5. Neutralisation to pH 7 resulted in decomposition. **16** was also unstable to chromatography or distillation, but after solvent extraction of the reaction mixture, crude **16** could be converted further to the enamine **17** using standard conditions in good yield. Finally reduction of **17** with cyanoborohydride led to the desired β-amino-glutamic acid derivative **18** as a mixture of erythro and threo diastereomers. It was possible to convert both diastereomers of **18** to the diastereomerically pure target **4** (Scheme 5), thus avoiding a chromatographic step.

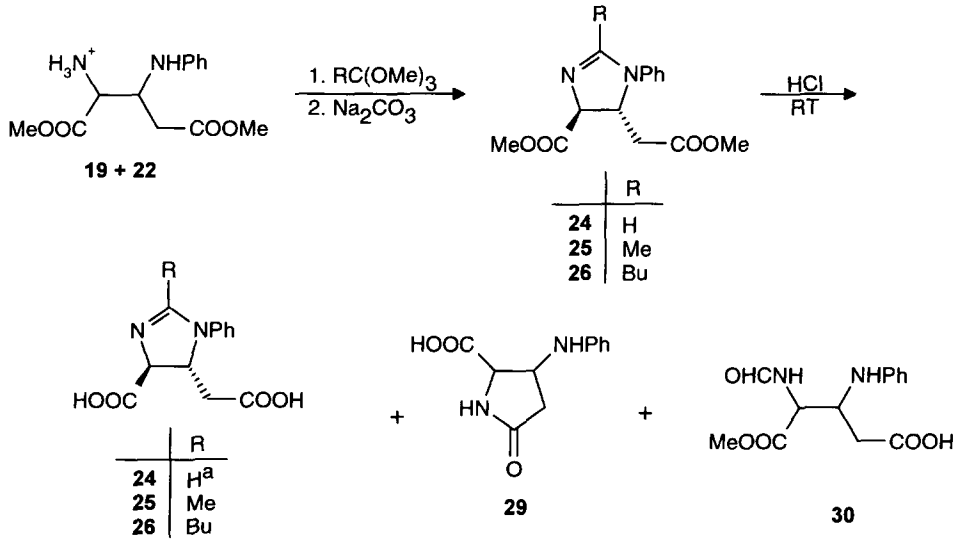



Scheme 3. a. $H_2$, 10% Pd/C, HCl, MeOH b. slow at r.t. c. BnOCOCl, dioxan, NaOH d. $PhNH_2$, benzene e. $NaCNBH_3$, TFA, THF.

The diastereomers of **18** were characterised by conversion to the imidazolidinethiones **20** and **23** (Scheme 4). Hydrogenolysis of each diastereomer of **18** gave **19** and **22** as the hydrochloride salts. The free bases of **19** and **22** were unstable and cyclised readily to the butyrolactam **21**. Therefore thiophosgene was added immediately after neutralisation. Even so, some **21** was formed, but the thioureas **20** and **23** were also isolated in low yield. The key experiment for structure determination was treatment of the cis compound **23** with mild base, which resulted in complete and clean conversion to the trans isomer **20**. This transformation allowed the stereochemistry of the thioureas **20** and **23** and therefore that of the open chain precursors **18 A** and **B** to be determined. It also demonstrated, that the mixture of diastereomers **19** and **22** can be converted to pure trans-substituted products. Consequently the diastereomeric mixture **18 (A+B)** was used for the preparation of the target **4**.




Scheme 4. a. $H_2$, HCl, 5%Pd/C b. $CSCl_2$, $CH_2Cl_2$, $NaHCO_3$, $H_2O$ c. neutralisation. d. $K_2CO_3$ MeOH




Scheme 5. a. As byproducts **29** and **30** were isolated.

The condensation reaction of the diamines **19** and **22** to the imidazoline **24** had to be performed under acidic conditions (Scheme 5). As already mentioned the free bases of **19** and **22** undergo a facile ring closure to form **21**. In fact attempts to use basic conditions involving O-methyl acetimidate[20] or S-methylthioacetimidate[21] as C(1) units resulted only in the formation of **21**. Fortunately however, the reaction with orthoesters requires acidic catalysis,[22] and treatment of the diamines **19** and **22** under these conditions led

to the dihydroimidazoles **24**, **25**, and **26** albeit in moderate yield. Only the trans diastereomers were isolated from these reactions. We assume that the cis-isomers are even more readily isomerised then the thiourea **23**. Finally, after ester hydrolysis, the desired diacids were isolated in good yield.

***Conclusion.*** The cyclic glutamate analogs **4**, **27**, and **28** unfortunately showed no anthelmintic or insecticidal activity in our tests. The glutamic acid subunit in these imidazolines is held by the planar imidazoline ring in a conformation similar to that of the crystal structures of kainic acid **1** and domoic acid **2**.[23] Although this structural similarity seems auspicious, it is quite possible that a conformation of **1** other than that of the crystal structure is necessary, or even that a certain flexibility is required.

However, although our initial goal of mimicing the biological activity of the kainoids was not successful, we have achieved the synthesis of suitably protected β-aminoglutamic acid derivatives and the desired highly functionalised imidazolines.

## EXPERIMENTAL

**2,3-Dibromo-pentanedioic acid dimethyl ester[24] (5).** Bromine (32.5ml, 100.8g, 630mmol) was added to a solution of dimethyl glutaconate (100g, 630mmol) in $CCl_4$ at 35 °C at such a rate that the solution remained at 35 °C (ca 3 hrs). The solvent was evaporated and the crude product distilled (105 °C, 0.06 mm/Hg) to yield 174g of an almost colourless oil. $^1$H NMR (60 MHz, $CDCl_3$) 3.27 (m, 2H-C(4)); 3.66 3.74 (2s, 2MeO); 4.63 (m, H-C(2), H-C(3)). Calc. C:26.44, H:3.17, Br:50.26. Found C:27.2, H:3.2, Br:49.0.

**1,2,4,5 Benzenetetracarboxylic acid tetramethyl ester (6).** A solution of sodium azide (2.9g, 45 mmol) in water (12 ml) was added to a solution of **5** (5g, 15mmol) in ethanol (10ml). The mixture was heated overnight at 100°C and on cooling to rt, diluted with water (100ml) to yield 1.2g (52%) **6** as beige crystals. m.p. 135-137 °C. (Lit[25] 138 °C). $^1$H NMR (60 MHz, $CDCl_3$) 4.00 (s, 4Me); 8.08 (s, aryl). Calc. C:54.2, H:4.55. Found C:54.2, H:4.60.

**4-(4-Methoxycarbonyl-phenylamino)-6-oxo-6H-[1,2] oxazine-3-carboxylic acid methyl ester[18] (9).** A solution of **7**[16] (22g, 108mmol) and 4-aminobenzoic acid methyl ester (19.7g, 130mmol) and a catalytic amount of TsOH were refluxed in toluene with a Dean-Stark apparatus. When the reaction was complete by tlc, the toluene solution was washed with water, dried ($MgSO_4$), evaporated, and the crude product crystallised from $CH_2Cl_2$ and hexane to yield 15.6g (49%) **9** as yellow crystals. m.p. 168-170 °C. $^1$H NMR (60 MHz, $CDCl_3$) 3.90 4.08 (2s, 2MeO); 5.91 (s, H-C(5)); 7.32 8.12 (2d, J=10, Ph); 9.32 (br s, NH). m.s. 304 $(M\text{-}MeOH)^+$ Calc. C:55.3, H:4.0, N:9.2, Found C:55.2, H:4.1, N:9.1

**2,3-Bishydroxyimino-pentanedioic acid dimethyl ester (8).** A solution of **7**[16] (37g, 182mmol) and hydroxylamine hydrochloride (14.5g, 218mmol)in dioxane (150ml), methanol (150ml), and water (2ml) were left at RT for 2 days, then shaken between ether and water. The ether phase was dried and evaporated. The crude material (38g) was chromatographed rapidly twice (50% EtOAc / hexane) to give a product which was triturated with toluene to afford 14g (35%) **8** as beige crystals. m.p. = 105-106 °C. $^1$H NMR (60 MHz, $CDCl_3$+ $D_6$-DMSO) 3.55 (s, 2H-C(4)); 3.60 3.74 (2s, 2MeO); 11.0 11.1 (2s, 2OH). Calc. C:38.90, H:4.6, N:12.96. Found C:39.2, H:4.7, N:12.0

**3,6-Dimethylpyrazine-2,5-dicarboxylic acid dimethyl ester[13] (11).** **8** (10g, 45.8 mmol) in methanol (200ml) was treated with RaNi (10g) and hydrogenated at 180 atmospheres at 35 °C. Uptake of hydrogen stopped after 3.55L (85%). The catalyst was filtered off and the solvent evaporated to yield a mixture of products from which **11**[13] (2g, 19%) were isolated by trituration with iPrOH and filtration. m.p. 133-134 °C

**2-Acetylamino-3-oxo-pentanedioic acid dimethyl ester**[17]**(10).** **7**[16] (30.5g, 150 mmol) in acetic anhydride (153 ml) was treated with 10% Pd/C (3g) and hydrogenated at RT under 3 atmospheres of hydrogen. After ca 30 min. of an exothermic reaction, hydrogen uptake stopped after 6.53 L. The catalyst was filtered off, and the solvent evaporated to yield 31g (91%) of **10**. $^1$H NMR (300 MHz, $CDCl_3$) 2.09 (s, MeCO); 3.75 (s, 2H-C(4)); 3.76 3.84 (2s, 2MeO); 5.42 (d, J=7, H-C(2)); 6.67 (br d, J=7, NH).

**2-Acetylamino-3-phenylamino-pent-2-enedioic acid dimethyl ester (12).** A solution of **10** (6g, 25.8 mmol) and aniline (2.7g, 30 mmol) in benzene (50 ml) were refluxed overnight, the solvent evaporated and the mixture chromatographed (1% MeOH / $CH_2Cl_2$) to yield almost pure material which was triturated with diisopropyl ether to yield 3.2g (42%) of beige crystals. m.p. = 124-127 °C $^1$H NMR (60 MHz, $CDCl_3$) 2.03 (s, MeCO); 3.40 (s, 2H-C(4)); 3.68 3.73 (2s, 2MeO); 6.93 - 7.45 (m, Ph). Calc C: 58.82, H: 5.93, N: 9.15; Found C: 57.7, H: 5.9, N: 9.0

**2-Acetylamino-3-phenylamino-pentanedioic acid dimethyl ester (13).** Methanolic HCl was added with stirring slowly to a solution of **12** (315mg, 1.02 mmol) and $NaCNBH_4$ (64.6mg, 1.02 mmol) and a trace of bromocresol green in methanol (3ml) at 0 °C until the solution stayed yellow. The last additions were made at RT. The solvent was evaporated and the mixture chromatographed (5% MeOH / $CH_2Cl_2$) to yield 240mg (77%) **13** as a mixture of isomers. Calc C:58.43, H:6.54, N:9.09. Found C:59.0, H:6.0, N:9.4. The isomers could be separated by further chromatography (5% MeOH / $CH_2Cl_2$). Isomer A. $^1$H NMR (300 MHz, $CDCl_3$) 2.02 (s, MeCO); 2.57 (dd, J=7 and 16, H-C(4)); 2.65 (dd, J=7,16, H-C(4)); 3.67 3.77 (2s, 2MeO); 4.34 (ddd, J=7,7,5, H-C(3)); 4.35 (br s, NH); 4.84 (dd, J=5,7, H-(C2)); 6.37 (br d, J=7, NH), 6.70 6.74 7.17 (3m, Ph). Isomer B. $^1$H NMR (60 MHz, $CDCl_3$) 2.00 (s, MeCO); 2.58 (br d, J=7, 2H-C(4)); 3.61 3.68 (2s, 2MeO); 4.50 (m, H-C(3)); 4.93 (dd, J=4,7, H-C(4)); 6.75 7.17 (2m, Ph).

**2-Amino-3-oxo-pentanedioic acid dimethyl ester**[14] **(14).** A solution of **7** (213.5g, 525mmol) and HCl (3M in methanol, 743 ml) in methanol (1.3 l) with 10% Pd / C (22g) was hydrogenated at RT. After absorbing 38.1 L (81%) of hydrogen, the reaction stopped. The catalyst was filtered off to yield a solution of **14**. The solution is stable but the product decomposed slowly when evaporated. **15** was isolated form the mixture formed on decomposition of **14.**

**3,6-Bis-methoxycarbonylmethyl-pyrazine-2,5-dicarboxylic acid dimethyl ester (15).** $^1$H NMR (300 MHz, $CDCl_3$) 3.73 (s, 2MeO); 4.00 (s, 2MeO); 4.37 (s, $2CH_2$). Calc. C:49.46, H:4.74 N:8.24 Found C:49.6, H:4.8, N:8.2.

**2-Benzyloxycarbonylamino-3-oxo-pentanedioic acid dimethyl ester (16).** To a solution of freshly evaporated **14** (344g, 1.5mol) in dioxane (1.6 l) at 0 °C was added with stirring benzyl chloroformate (256g, 1.5mol). NaOH (2M, ca 1.2 l) was added with stirring and ice cooling keeping the temperature below 25 °C until the pH reached 6.5 (pH meter). Any further neutralisation or basification lowered the yield. Attempts to add the base and chlorformate at the same time resulted in the formation of **15**. The aqueous phase was washed 3x with ether and the combined organic phase washed with water and dried. The solvent was evaporated and the residue azeotroped twice with toluene to yield 375g (87%) of **16** as a brownish oil. This crude product contains benzyl methyl carbonate which can be distilled off. However, this impurity is innocuous and was usually carried forward to the next step. **16** decomposed on attempted chromatography. $^1$H NMR (60 MHz, $CDCl_3$) 3.57 (s, 2H-C(4)); 2.61 2.67 (2s, 2MeO); 5.00 (s, $CH_2O$); 5.13 (d, J=8, H-C(2)); 5.92 (m, NH); 7.20 (s, Ph).

**2-Benzyloxycarbonylamino-3-phenylamino-pent-2-enedioic acid dimethyl ester (17).** A solution of **16** (2g, 6.2mmol) and aniline (0.72ml, 740mg, 8mmol) in benzene (8ml) was refluxed overnight, and the solvent evaporated. The residue was stirred with ether and the ether phase evaporated and chromatographed (50% EtOAc / hexane) to yield 1.4g (58%) of the product as a yellow oil. $^1$H NMR (60 MHz, $CDCl_3$) 3.39 (s, 2H-C(4)); 3.54 3.66 (2s, 2MeO); 5.10 (s, $CH_2O$); 5.62 (br s, NH); 7.0-7.3 (m, 2Ph). Calc. C:63.31, H:5.57, N:7.03. Found C:63.3, H:5.6, N:7.0.

**2-Benzyloxycarbonylamino-3-phenylamino-pentanedioic acid dimethyl ester (18).** To a solution of **17** (1.1g, 2.7mmol) and TFA (0.3ml, 456mg, 4mmol)in THF (10ml) at 0 °C, $NaCNBH_3$ was added and the reaction mixture allowed to warm to RT. The reaction mixture was shaken with ether and water and the ether evaporated. The crude product (1.2g) was chromatographed (60% EtOAc / hexane) to yield 60mg of isomer A and 600mg of a mixture of A and B. The mixture of A and B was separated by HPLC to yield 260 mg of isomer A (overall 32%) and 190mg of isomer B. **Isomer A.** ***erythro***:- $^1$H NMR (300 MHz, $CDCl_3$) 2.52 (dd, J=7,15, H-C(4)); 2.67 (dd, J=7,15, H-C(4)); 3.62 3.66 (2s, 2MeO); 3.82 (br s, NH); 4.52 (br s, H-C(3)); 4.68 (dd, J=3,7, H-C(2)); 5.14 (s, $CH_2O$); 5.63 (br d, J=7, NH); 6.67 6.74 7.16 (3m, Ph); 7.37 (s, Ph).**Isomer B.** ***threo***:- $^1$H NMR (300 MHz, $CDCl_3$) 2.55 (dd, J=7,15, H-C(4)); 2.62 (dd, J=7,15, H-C(4)); 3.63 3.74 (2s, 2MeO); 4.13 (br s, NH); 4.35 (br s, H-C(3)); 4.67 (dd, J=5,9, H-C(2)); 5.08 (s, $CH_2O$); 5.65 (br d, J=7, NH); 6.69 6.76 7.05-7.42 (3m, 2Ph).

***erythro*-2-Amino-3-phenylamino-pentanedioic acid dimethyl ester hydrochloride (19).** A solution of **18A** (320mg) in methanol (10ml) was treated with methanolic HCl (2.2M, 0.66ml) and 5% Pd/C (65mg) and hydrogenated under normal pressure. After ca 2 hrs 18.4ml of hydrogen had been taken up and the uptake of hydrogen had almost stopped. The catalyst was filtered off and washed with methanol and the filtrate evaporated. The crude material was used for the next reactions.A sample was converted to the free base. 1H NMR (60 MHz, CDCl3) 2.61 (d, J=7, 2H-C(3)); 3.63 (s, 2MeO); 3.71 (m, H-C(2)); 4.32 (M, H-C(3)); 6.4-7-3 (m, Ph). On another occasion, on attempted conversion to the free base, **21** was isolated.

**5-Oxo-3-phenylamino-pyrolidine-2-carboxylic acid methyl ester (21).** m.p. 117-118 °C. $^1$H NMR (300 MHz, $CDCl_3$) 2.47 (dd, J=5,16, H-C(4)); 2.77 (dd, J=8,16, H-C(4)); 3.65 (s, MeO); 4.36 (br d, J=9, NH); 4.64 (m, H-C(2)); H-C(3)); 6.26 (br s, NH); 6.66,6.77,7.19 (3m, Ph). ms. 308 $M^+$.

***threo*-2-Amino-3-phenylamino-pentanedioic acid dimethyl ester hydrochloride (22).** This material was prepared analogously to its *erythro* isomer **19**.

***erythro*-5-Methoxycarbonylmethyl-1-phenyl-2-thioxo-imidazoline-4-carboxylic acid methyl ester (20).** A solution of **19** (100mg, 300μMol) in methanol (2.5ml) and dichloromethane (5ml) was stirred with $NaHCO_3$ (1M). Thiophosgene (22.7 μl, 34mg, 300μMol) was added and the mixture stirred overnight. The mixture was shaken between water and dichloromethane and the organic phase dried and evaporated. The crude product (87mg) was chromatographed (50%EtOAc/hexane) to yield19mg (21%) **20**. m.p. 165-168 °C. $^1$H NMR (250 MHz, $CDCl_3$) 2.70 (d, J=7,$CH_2$-C(5)); 3.60, 3.85 (2s, 2MeO); 4.45 (d, J=5, H-C(4)); 5.01 (dt, J=7,7, H-C(5)); 6.49 (br s, NH); 7.40 (m, Ph). ms. 308 $M^+$

***threo*-5-Methoxycarbonylmethyl-1-phenyl-2-thioxo-imidazoline-4-carboxylic acid methyl ester (23)** This material was prepared analogously to its *erythro* isomer **20**. $^1$H NMR (300 MHz, $CDCl_3$) 2.58 (dd, J=10,18, CH-C(5)); 2.67 (dd, J=5,18, CH-C(5)); 3.57, 3.81 (2s, 2MeO); 4.76 (d, J=10, H-C(4)); 5.08 (ddd, J=5,10,10, H-C(5)); 6.37 (br s, NH); 7.49 (m, Ph). ms. 308 $M^+$. Calc. C:54.53, H:5.23 N:9.08 S:10.40. Found C:53.2, H:5.0, N:8.7 S:10.8.

**Conversion of 23 to 20. 23** (260mg, 844μM) was dissolved in $K_2CO_3$/MeOH (1%, 5ml). After 10 min tlc with 6% acetone / dichloromethane indicated complete and clean conversion to **20**. Evaporation gave 260 mg (100%) crude **20**. NMR spectroscopy showed some impurities.

**5-Methoxycarbonylmethyl-1-phenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid methyl ester (24).** A solution of **19** and **22** (1.25g, 3.7mmol) in methanol (50ml) direct from the hydrogenation step was treated with trimethylorthoformate (1.2ml, 1.2g, 11.4mmol). After 16 h. tlc (70%EtOAc/hexane) showed no reaction so another 5ml (48mmol) trimethylorthoformate was added. Tlc then showed complete reaction so $Na_2CO_3$ (ca 5g) was added and after stirring for 10 min was filtered off. The solvent was evaporated and the crude product chromatographed (80% EtOAc/hexane) to yield 500mg (25%) **24**. mp. 65-67 °C. $^1$H NMR (250 MHz, $CDCl_3$)

2.55 (dd, J=10,16, CH-C(5)); 2.96 (dd, J=4,16, CH-C(5)); 3.88, 3.93 (2s, 2MeO); 4.73 (dd, J=3,6, H-C(4)); 4.94 (ddd, J=4,6,10, H-C(5)); 7.09,7.37 (2m, Ph); 7.48 (d, J=3, H-C(2)). ms. 276 $M^+$. Calc. C:60.86, H:5.84, N:10.14. Found C:60.3, H:5.9, N:10.1

**5-Methoxycarbonylmethyl-2-methyl-1-phenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid methyl ester (25).** Analogously to **24** but chromatographed with 10%MeOH/dichloromethane yielded 24% **25** as an oil. $^1$H NMR (60 MHz, $CDCl_3$) 1.70 (s, Me-C(2)); 2.51 (d, J=7, $CH_2$-C(5)); 3.41, 3.65 (2s, 2MeO), 4.5 (m, H-C(4), H-C(5)); 7.2 (m, Ph).

**5-Methoxycarbonylmethyl-2-butyl-1-phenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid methyl ester (26).** Analogously to **24** but chromatographed with 5%MeOH/dichloromethane yielded crude **26** which was distilled at 70°C in 0.01bar to yield 36% of pure **26**. $^1$H NMR (60 MHz, $CDCl_3$) 0.80, 1.35, 2.05 (3m, Bu); 2.58 (d, J=7, $CH_2$-C(5)); 3.50, 3.76 (2s, 2MeO), 4.53 (m, H-C(4), H-C(5)); 7.3 (m, Ph).

**5-Hydroxycarbonylmethyl-1-phenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid (4). 24** (520mg, 1.88mmol) was dissolved in HCl (2M, 5ml). After 16 h. tlc showed complete reaction so it was neutralised with $NaHCO_3$ to pH 6.8. The solvent was evaporated and the residue chromatographed on reversed phase hplc to afford **4** (350mg, 75%), **29** (56mg, 12%), and **30** (42mg, 7%).

**4** $^1$H NMR (300 MHz, $CD_3OD$) 2.34 (dd, J=8,15, CH-C(5)); 2.49 (dd, J=6,15, CH-C(5)); 4.33 (ddd, J=4,6,8, H-C(5)); 4.56 (dd, J=1,4, H-C(4)); 6.56, 6.82, 7.06 (3m, Ph); 8.14 (d, J=1, H-C(2)). $^{13}$C NMR (90Mhz, $D_6$-DMSO) 177.0, 173.3 (2COOH); 160.3 C(2); 147.9, 128.4, 114.9, 112.8 (Ph); 55.3 C(4); 52.1 C(5); 39.6 (C-COOH).

**5-Oxo-3-phenylamino-pyrolidine-2-carboxylic acid (29).** $^1$H NMR (300 MHz, $CD_3OD$) 1.92 (dd, 7,15, H-C(4)); 2.50 (dd, 7,15, H-C(4)); 3.83 (d, J=7, H-C(2)); 4.05, (dddd, J=5,7,7,7, H-C(3)); 6.15 (d, J=5, NH-C(3)); 6.51, 7.07 (2m, Ph), 7.65 (s, H-N(1)). $^{13}$C NMR (90Mhz, $D_6$-DMSO) 175.2 (COOH), 172.2 C(5); 147.7, 128.9, 115.7, 112.3 (Ph); 60.3 C(2); 50.6 C(3); 37.8 C(4).

**2-Formylamino-3-phenylamino-pentanedioic acid methyl ester (30).** $^1$H NMR (300 MHz, $CD_3OD$) 2.23 (dd, J=10,15, H-C(4)); 2.43 (dd, 5,15, H-C(4)); 3.51 (s,MeO); 3.89 (dd, J=5,7, H-C(2)); 4.23 (m, H-C(3)); 6.04 (d, J=10, NH-C(3)); 6.56, 6.67, 7.07 (3m, Ph); 7.75 (d, J=7, NH-C(2)); 8.03 (s, CHO). $^{13}$C NMR (90Mhz, $D_6$-DMSO) 172.0 C(5); 170.0 C(1); 160.2 CHO; 147.5, 128.3, 115.8, 113.1 Ph; 53.7 C(2); 50.7 C(3); 50.6 MeO; 35.5 C(4).

**5-Hydroxycarbonylmethyl-2-methyl-1-phenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid (27).** Analogous to **4** was isolated 60% **27** from **25**. $^1$H NMR (300 MHz, $CD_3OD$) 2.17 (s, Me); 2.72 (dd, J=6,17, CH-C(5)); 2.82 (dd, J=6,17, CH-C(5)); 4.66 (d, J=7.5, H-C(4)); 4.98 (ddd, J=6,6,7.5, H-C(5)); 7.41, 7.57 (2m, Ph). n.O.e. irradiation of H-C(4), H-C(5), and 2HC-C(5) demonstrated the trans configuration of the C(4)-C(5) substituents.

**5-Hydroxycarbonylmethyl-2-butyl-1-phenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid (28).** Analogous to **4** was isolated 20% **28** from **26**. $^1$H NMR (300 MHz, $CD_3OD$) 0.85 (t, J=7, Bu), 1.34 (tq, J=7,7, Bu); 1.58 (tt, J=7,7, Bu); 2.42 (m, Bu); 2.70 (dd, J=6,17, CH-C(5)); 2.80 (dd, J=6,17, CH-C(5)); 4.58 (d, J=7.5, H-C(4)); 4.86 (ddd, J=6,6,7.5, H-C(5)); 7.42, 7.58 (2m, Ph). NOE irradiation of H-C(4), H-C(5), and 2HC-C(5) demonstrated the trans configuration of the C(4)-C(5) substituents.

## REFERENCES

1. Murakami, S.; Takemoto, T.; Shimizu, Z. *Yakugaku Zasshi*, **1953**, *73*, 1026.
2. Daigo, K. *Yakugaku Zasshi*, **1959**, *79*, 353.

3. Maeda, M.; Kodama, T.; Tanaka, T.; Yoshizumi, H.; Takemoto, T.; Nomoto, K.; Fujita, T. *Chem. Pharm. Bull.* **1986**, *34*, 4892. Maeda, M.; Kodama, T.; Tanaka, T.; Ohfune, Y.; Nomoto, K.; Nishimura, K.; Fujita, T. *J. Pest. Sci*, **1984**, *9*, 27-32. Sakai, M. *Takeda Kenkyusho Nempo*, **1960**, *19*, 37-41. Takemoto, T.; Daigo, K. *Arch. Pharm.* **1960**, *293*, 627-633.
4. McGeer, E. G. et al. "Kainic Acid as a Tool in Neurobiology" Raven Press, N.Y., 1978. Henley, J. M: *Trends in Pharmacological Sciences*, **1994**, *15*, 182-190.
5. Konno, K., Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *J. Am. Chem. Soc.* **1988**, *110*, 4807.
6. Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149-74.
7. Hashimoto, K.; Horikawa, M.; Shirahama, H. *Tetrahedron Lett.* **1990**, *31*, 7047-50.
8. M. Sainsbury, R. S. Theobold in "Rodds Chemistry of Carbon Compounds" Vol 4. Part C, p156-185. Ferm, R. J.; Riebsomer, J. L. *Chem. Rev.* **1954**, *54*, 593.
9. Kollonitsch, J.; Dolouros, G. . *J. Am. Chem. Soc,* **1964**, *86*, 1857-8.
10. Andruszkiewicz, R. *Pol. J. Chem.* **1995**, *69*, 1615-29.
11. Inoue, M. *Bull. Soc. Chem. Jap.* **1961**, *34*, 885.
12. Klebs, E. *Z. Physiol. Chem.* **1894**, *19*, 301. Neuberg, C. *Chem. Zentralblatt II* **1906**, 764. Poduska, K.; Rudiger, J.; Sorm, F. *Coll, Cz. Chem. Comm.* **1955**, *20*, 1174. Moureu, H.; Chovin, P.; Petit, L. *Bull. Soc. Chim. Fr.* **1955**, 1573-83.
13. Iida, H.; Hayashida, K.; Yamada, M.; Takehashi, K.; Yamada K. *Syn. Comm.* **1973**, *3*, 225-230. Atkins, H.; Reeve, E.W. *J. Amer. Chem. Soc.* **1938**, *60*, 1328.
14. du Vignaud, V.; Melville, D. B. *J. Biol. Chem.* **1942**, 146, 475.
15. Bauer, B. A. (Ethyl Corp.) USP 4,593,118. Spanish Patent E. S. 549,891 (CA 108:37491k)
16. Pechmann, H. *Ber. Dtsch Chem. Ges.* **1891**, *24*, 857-67. Harington, C. R.; Randall, S. S. *Biochem. J.* **1931**, *25*, 1917-30
17. Leanza, W. J.; Pfister, K. *J. Biol. Chem.* **1953**, *201*, 377
18. The 4-methoxy derivative of **9** is known. Birkofer, L.; Feldmann, H. *Annalen der Chemie* **1964**, *677*, 150-153.
19. The dihydro derivative of **15** was isolated from a similar decomposition mixture. Aberhalden, E and Murke, H. *Z. Physiolog. Chem.* **1937**, *247*, 231
20. Yonetani, K.; Hirotsu, Y.; Shiba, T.; Bull. *Chem. Soc. Jap.* **1975**, *48*, 3302. Jones, R. C. F.; Ward, G. J. *Tet. Lett.* **1988**, *29*, 3853.
21. Gilbert, I. H.; Rees, D. C.; Crockett, A. K.; Jones, R.C.F. *Tetrahedron* **1995**, *51*, 6315-36.
22. Martin, P. K.; Mathews, H. R.; Rapoport, H.; Thygarajan, G. *J. Org. Chem.* **1968**, *33*, 3758-61. Levene P. A.; Schormüller A. *J. Biol. Chem.* **1934**, *106*, 595-602.
23. Nomoto, K.; Takemoto, T.; Maeda, M.; In, Y.; Doi, M.; Inoue, M.; Ishida, T. *Bioch. Biop. Res. Comm.* **1992**, *187*, 325-331.
24. This compound was prepared analogously to the ethyl ester. Feist, F. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 135-8.
25. A. Baeyer *Ann. Chem. Pharm.* **1873**, *166*, 325-350.


(*Received in Germany* 15 *November* 1996; *accepted* 29 *December* 1996)