A solution of 1.87 g (2.03 mmol) of the prepared 11 in dry dimethyl sulfoxide (10 mL) was treated with 2.32 g (20.7 mmol) of potassium *tert*-butoxide. After the dark solution was stirred for 8 h at 50 °C, the reaction mixture was cooled to room temperature and water (40 mL) was added dropwise. The mixture was extracted with hexane (5 × 20 mL). The organic extract was dried over anhydrous magnesium sulfate and then evaporated in vacuo. The residue was chromatographed over silica gel using hexane as eluent to afford 0.26 g (43% from **10**) of 1 as colorless prisms (ether): mp 211–213 °C dec; M^+ = 234.1400 (calc 234.1409); IR (KBr) 3059, 3042, 2928, 2880, 1618, 902, 768, 692 cm^{-1}; UV (cyclohexane) λ_{max} = 243 nm (log ϵ = 4.41), 212 nm (shoulder, log ϵ = 4.08); ^1H NMR ($CDCl_3$) δ 2.33 (s, 2 H), 3.18 (dd, 4 H, J = 4.5, 3.3 Hz), 4.78 (s, 4 H), 5.12 (s, 4 H), 5.84 (dd, 4 H, J = 4.6, 3.2 Hz); ^{13}C NMR ($CDCl_3$) δ 42.57 (d), 47.22 (d), 102.4 (t), 130.6 (d), 147.4 (s). Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.06; H, 7.79.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support under Grant NSC78-0208-M029-02.

Dichloromethane as Reactant in Synthesis: An Expedient Transformation of Prolinamide to a Novel Pyrrolo[1,2-*c*]imidazolone

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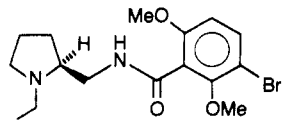
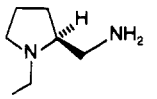
In the course of our work to achieve an efficient production method for the neuroleptic drug remoxipride (**1**),[2,3] we have been developing a new synthetic route for (*S*)-2-(aminomethyl)-1-ethylpyrrolidine (**2**), a crucial building block for **1** and for other pharmacologically interesting compounds.[4] Our favored synthesis[5] of **2** starts from



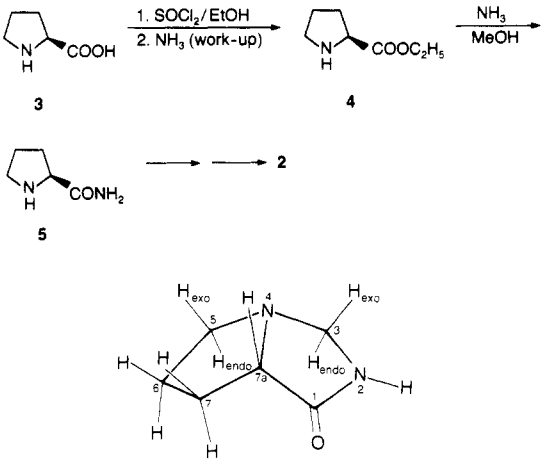
1



2

(*S*)-proline (**3**)[6] and proceeds in a virtually stereoconservative[7] fashion according to Scheme I. On certain occasions, especially when running large-scale experiments (e.g. in the pilot plant), we noted the formation of 3–4% (GC) of an impurity in the transformation of ester **4** to amide **5**. We now present the structure elucidation of the by-product as **6** and a mechanistic proposal for its formation.

Scheme I



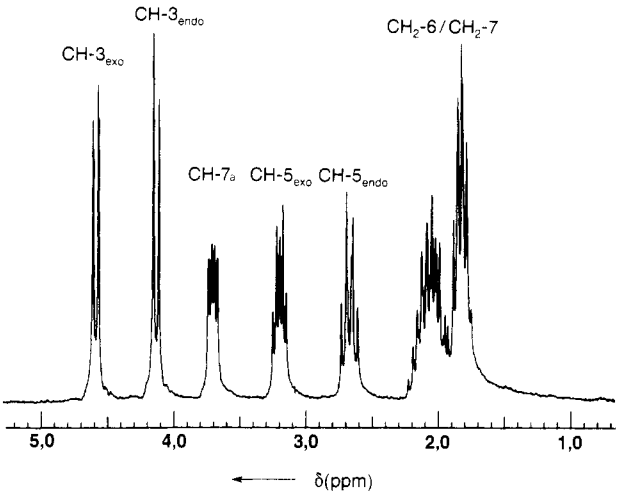


Figure 1. Right-hand part of ^1H NMR spectrum (200 MHz, $CDCl_3$) of **6**, with the indicated assignment of the signals.

Results and Discussion

To determine the source of the unknown impurity, we carefully reexamined the first two steps of the synthesis indicated in Scheme I. Thus, (*S*)-proline ethyl ester (**4**) is synthesized by following a standard procedure[8] from (*S*)-proline via the acid chloride. The subsequent amination is conducted under rather forced conditions using a large excess of NH_3 (10–15 equiv) in methanol at 40 °C (3 atm), which transforms the major part of **4** to its methyl ester[9] prior to being converted to amide **5**.

Comparison of our laboratory experience from these steps with the observed actual large-scale performance indicated that residual amounts of the dichloromethane used for extraction purposes during workup in the esterification step could be responsible for the impurity formation. Supporting evidence for this assumption was obtained when it was found that ordinary aminations of

(1) Present address: Astra Pain Control AB, Research & Development, Preclinical Research, S-151 85 Södertälje.

(2) Under clinical development by Astra Research Centre AB, S-151 85 Södertälje, Sweden. Remoxipride is the active principle in pharmaceutical preparations named Roxiam.

(3) See, e.g.: (a) Florvall, L.; Ögren, S.-O. *J. Med. Chem.* **1982**, *25*, 1280–86. (b) McCreadie, R. G.; Todd, N.; Livingstone, M.; Ecclestone, D.; Watt, J. A. G.; Tait, D.; Crocket, G.; Mitchell, M. G.; Huitfeldt, B. *Acta Psychiatr. Scand.* **1988**, *78*, 49–56.

(4) Högberg, T.; Rämsby, S.; Ögren, S.-O.; Norinder, U. *Acta Pharm. Suec.* **1987**, *24*, 289–328 and references cited therein.

(5) (a) Federsel, H.-J.; Högberg, T.; Rämsby, S.; Ström, P. Swedish Patent Application 8 602 339-7, 1986. (b) Högberg, T.; Rämsby, S.; Ström, P. *Acta Chem. Scand.* **1989**, *43*, 660–64.

(6) Natural enantiomer (i.e. L configuration).

(7) Starting with (*S*)-proline of commercial quality (>99% ee; GC after N-derivatization with (*R*)-α-(methoxyphenyl)acetyl chloride followed by transformation of the carboxylic group to the methyl ester using diazomethane), **2** is obtained with an optical purity of ca. 95% ee (GC after NH_2 derivatization with the previously mentioned acid chloride).

(8) Deimer, K.-H. In *Methoden der organischen Chemie* (*Houben-Weyl*) 4th ed.; Georg Thieme Verlag: Stuttgart, 1974; Vol XV/1, p 315 ff.

(9) A kinetic study on the amination of (*S*)-*N*-ethylproline ethyl ester has been reported: Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033–36.

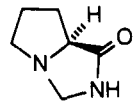
0022-3263/90/1955-2254$02.50/0

4 conducted in the presence of increasing amounts of dichloromethane were paralleled by a corresponding increase of the unknown (using ca. 11 equiv of CH_2Cl_2 afforded a GC conversion of 85%). When dichloromethane was instead allowed to react with authentic prolinamide (**5**) under conditions rather similar to the ones indicated above (i.e. 9 equiv of CH_2Cl_2/7 equiv of NH_3 in MeOH at ca. 40 °C (3 atm)), the kinetics and the conversion observed (52% GC after 2 days) were practically identical with those in the runs where ester **4** was used as the starting material. However, merely refluxing **5** in CH_2Cl_2 (in the absence of NH_3) did generate only very minor amounts (2–3% after 2 days) of the unknown.

Thus, starting with **4**, we were able to perform an efficient conversion to the unknown, and after purification a material was obtained which could be used for a complete structural elucidation. Mass spectral analysis using both electron impact and chemical ionization techniques showed a molecular ion at m/z 126. Furthermore, the presence of a pyrrolidine nucleus was strongly indicated by observing the base peak at m/z 70. The ^{13}C NMR spectrum clearly revealed the presence of six carbon atoms, one in the carbonyl area (δ 179 ppm) and five in the aliphatic region (δ 25–66 ppm).

In the ^1H NMR spectrum (see Figure 1), seven signals showing varying complexity with regard to the individual peak multiplicities are displayed in the region between δ 1.6 and 4.7 ppm. The intensity ratios suggest that each of the five signals appearing to the left in the spectrum corresponds to a single proton, whereas the remaining peaks (δ 2.1 and 1.8 ppm, respectively) represent two protons each. In addition, a broad singlet representing one proton is found downfield at δ 7.8 ppm. Taking into account that the molecule contains only five aliphatic carbon atoms (^{13}C NMR), these observations strongly indicate the presence of nonequivalent, geminal protons.

We thus conclude that the impurity formed actually is (*S*)-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**6**), which, to the best of our knowledge, has not previously been reported in the literature.

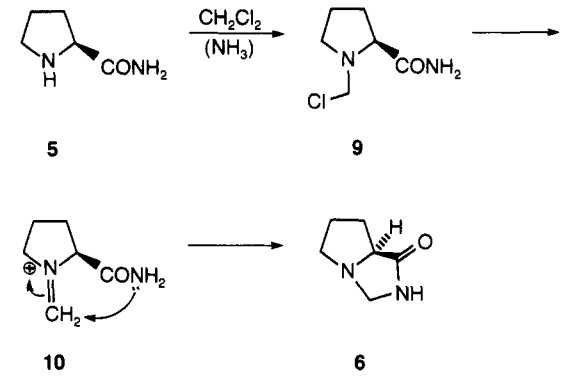


6

The assignment of the ^1H NMR signals has been indicated in Figure 1. It is particularly interesting to note the strong upfield shifts (ca. 0.5 ppm) of the C-3 and C-5 endo protons (see the stereostructure of **6** given in Figure 1 for the numbering), respectively, which clearly can be attributed to the shielding effect that they experience due to their constrained geometric arrangement.[10]

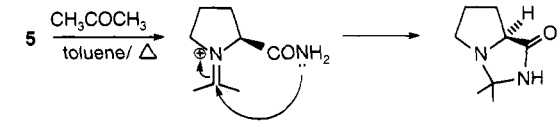
The use of dichloromethane as solvent for either reaction or extraction purposes is very common. Throughout the years, several reports have appeared in the literature dealing with dichloromethane-induced transformations, preferably alkylations of amines, which (in the majority of cases) have been considered as undesired side reactions. Particular attention has been paid to the fact that these reactions can take place under rather mild conditions (e.g.

Scheme II



5 **9** **10** **6**

Scheme III



11 **12**

for pyrrolidine, Nevstad and Songstad[11] have found that the half-life τ = 10 h at 25 °C).

Some years ago, Mills[12] et al. presented a general overview of the reaction of amines with dichloromethane. Regarding the synthetic potential of these reactions, fairly acceptable yields of aminals (species where two amine residues are linked together via a methylene group) were obtained from secondary amines under basic conditions. In one of the reported cases where a bis-amino compound (i.e. *N*-methylethylenediamine) was used, the aminal formation proceeds in an *intramolecular* fashion affording a cyclic product.

Recently, the Mills[13] group presented further convincing evidence (obtained from NMR experiments) that pyrrolidine in the presence of dichloromethane undergoes an N-alkylation to 1-(chloromethyl)pyrrolidine (**7**). This species is, however, rapidly converted to the transient iminium intermediate **8**, which in turn undergoes a fast reaction with a suitable nucleophile present in the system (e.g. pyrrolidine).

7 **8**

By analogy with these findings, we propose the reaction sequence shown in Scheme II as being responsible for the formation of **6**. It is rather plausible that the penultimate intermediate preceding the actual ring closure is the strongly electrophilic iminium compound **10** (formed from the chloromethylpyrrolidine **9**), which cyclizes in an intramolecular fashion, affording an energetically favored 5-membered ring instead of being attacked by an external nucleophile. Likewise, in another approach to bicyclic imidazolidinones, an iminium species has been postulated

(10) Recently, Maryanoff and co-workers have reported a similar upfield shift (i.e. ca. 0.5–1.0 ppm) for endo vs exo protons in various bicyclic systems featuring a nitrogen atom at the bridgehead position (e.g. pyrrolo[2,1-*a*]isoquinolines); Maryanoff, B. E.; McComsey, D. F.; Inners, R. R.; Mutter, M. S.; Wooden, G. P.; Mayo, S. L.; Olofson, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 2487–96.

(11) Nevstad, G. O.; Songstad, J. *Acta Chem. Scand., Ser. B* **1984**, *38*, 469–77.

(12) Mills, J. E.; Maryanoff, C. A.; Cosgrove, R. M.; Scott, L.; McComsey, D. F. *Org. Prep. Proc. Int.* **1984**, *16*, 97–114 and references cited therein.

(13) Mills, J. E.; Maryanoff, C. A.; McComsey, D. F.; Stanzione, R. C.; Scott, L. *J. Org. Chem.* **1987**, *52*, 1857–59.

to undergo cyclization via an intramolecular attack of an amido group.[14] A further support for the mechanism was obtained from the observation that prolinamide (**5**) undergoes a facile conversion to the known dimethylpyrroloimidazolone **12** in the presence of acetone,[15] according to the proposed sequence in Scheme III.

In this case, the obvious reaction intermediate (i.e. acetone adduct **11**) is a direct analogue to **10**, postulated to be the reactive species generating the novel pyrroloimidazolone **6**. Similar condensations (i.e. between acetone and amino/amido functional groups within the same molecule) are rather well established in the field of penicillin chemistry.[16]

Conclusions

This investigation has clearly demonstrated that reacting (*S*)-prolinamide (generated in situ from (*S*)-proline ethyl ester and ammonia) with dichloromethane affords the novel, chiral pyrroloimidazolone **6**. Further explorative work will show if this reaction can be found synthetically useful for the conversion of e.g. easily accessible α-amino acids to a range of substituted 1,3-imidazol-4-ones.

Experimental Section

All utilized chemicals were of reagent grade and were not submitted to any particular treatment (i.e. drying, purification) prior to use. Melting points were determined in capillary tubes on a Büchi SMP 20 melting point apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer Model 681 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX 90 Q (operating at 90 and 22.50 MHz, respectively) or on a JEOL FX 200 (operating at 200 and 50.10 MHz, respectively). Chemical shifts are reported in ppm on the δ scale relative to tetramethylsilane (Me_4Si). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet); br is used as abbreviation for broadened. Mass spectra (electron impact, ionizing voltage 70 eV) were obtained on a Hewlett-Packard Model 5970 A mass-selective detector, equipped with a Hewlett-Packard MS Chem Station, and the chemical ionization (CI) spectra were recorded on a LKB 2091 spectrometer using methane as the ionizing gas. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The optical purity of (*S*)-proline ethyl ester (**4**) was determined on GC after derivatization (ultrasonic bath, room temperature/5 min) with (*R*)-α-(methoxyphenyl)acetyl chloride (prepared from (*R*)-α-(methoxyphenyl)acetic acid; Fluka AG) in CH_2Cl_2/i-Pr_2EtN, using a fused silica capillary column (30 m × 0.32 mm) coated with 1.0 μm of cross-linked phenylcyanopropylmethylsilicone (J&W DB 1701 30W) at 240 °C isothermal oven temperature and a flame-ionization detector. Microanalyses were performed by Mikro Kemi AB, S-750 19 Uppsala, Sweden.

(*S*)-Proline Ethyl Ester (4). (*S*)-Proline (50.0 g, 0.43 mol) was suspended in ethanol (400 mL) and heated to 60 °C. Thionyl chloride (92.1 g, 0.77 mol) was added in one portion, and the resulting solution was allowed to react for 4 h. Excess thionyl chloride and ethanol were evaporated and followed by the addition of dichloromethane (250 mL), water (50 mL), and concentrated ammonia (75 mL). The organic phase was separated off and concentrated in vacuo to afford 63.6 g (97%) of a yellowish oil with a GC purity of ca. 95%: optical purity > 99.8% ee (GC); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.28 (t, 3 H, ester CH_3), 1.74–2.13 (m, 4 H, pyrrolidine CH_2-3 and CH_2-4), 2.88–3.05 (m, 2 H, pyrrolidine CH_2-5), 3.66–3.74 (m, 1 H, pyrrolidine CH-2), 4.19 (q, 2 H, ester CH_2); mass spectrum (EI 70 eV), *m/z* (relative intensity) 143 (M^+, 0.9), 71 (4.9), 70 ($M^+ - COOC_2H_5$, 100), 68 (8.9), 43 (14.2), 41 (15.0).

(*S*)-Hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (6). (*S*)-Proline ethyl ester (**4**) (31.0 g, 0.21 mol) was dissolved in dichloromethane (150 mL, ca. 2.34 mol) and placed in a stainless steel reactor. Gaseous ammonia (55.0 g, 3.24 mol) dissolved in methanol (150 mL) was added to the reactor, which was then sealed. The reaction mixture was stirred at 50 °C (3.5 bar) for 2 days, after which time the solution was cooled and the precipitated salts were filtered off. Removal of the solvents was performed on a rotary evaporator under reduced pressure to give 33.6 g of a crude, yellowish oil. A portion (15.0 g) of this oil was submitted to a chromatographic purification on a silica gel column (500 g) using methanol/ethanol (10:1) as eluant. The fractions containing the desired product (checked on GC) were combined and concentrated in vacuo to afford 7.0 g of a yellow oil, which subsequently was distilled to give 2.2 g (18%) of product **6** (GC purity >99%): bp 110 °C (0.05 mmHg); mp 95–103 °C; $[\alpha]^{20}_D$ −77.2° (*c* 1, MeOH); IR (KBr) 1690 cm^{-1} (amide C=O); ^{1}H NMR (200 MHz,$CDCl_3$) δ 1.72–2.23 (m, 4 H, CH_2-6, CH_2-7), 2.57–2.74 (m, 1 H, CH-5$_{endo}$), 3.14–3.27 (m, 1 H, CH-5$_{exo}$), 3.62–3.77 (m, 1 H, CH-7a), 4.14 (d, 1 H, CH-3$_{endo}$), 4.59 (d, 1 H, CH-3$_{exo}$), 7.79 (br s, 1 H, NH-2); ^{13}C NMR (50.10 MHz, $CDCl_3$) δ 25.4 and 27.5 (C-6 and C-7), 56.0 (C-5), 64.3 (C-7a), 66.1 (C-3), 179.4 (C-1); mass spectrum (EI 70 eV), *m/z* (relative intensity) 126 (M^+, 39.8), 98 ($M^+ - 28$, 33.5), 83 ($M^+ - CONH$, 78.4), 70 ($M^+ - CHNHCO$, 100), 55 (C_4H_7, 55.6), 41 (C_3H_5, 48.8). Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21; O, 12.68. Found: C, 57.1; H, 7.85; N, 21.95; O, 13.1.

Acknowledgment. We thank Egil Forsberg and Britt-Marie Gawell of our Process Development Laboratory for skillful analytical assistance, mainly with GC and mass spectrometry. The initial recordings of NMR spectra performed by Dr. Ulla Jacobsson at the Department of Organic Chemistry, Royal Institute of Technology, Stockholm, are gratefully acknowledged. We are obliged to Dr. Kurt L. Loening, Chemical Abstracts Service, Columbus, OH, for the advice concerning the proper nomenclature of **6**.

Registry No. **3**, 147-85-3; **4**, 5817-26-5; **6**, 125643-09-6; CH_2Cl_2, 75-09-2.

(14) Kukla, M. J.; Breslin, H. J. *J. Org. Chem.* **1987**, *52*, 5046–48.
(15) Poloński, T. *Tetrahedron* **1985**, *41*, 611–16.
(16) See, e.g.: Panetta, C. A.; Pesh-Imam, M. *J. Org. Chem.* **1972**, *37*, 302–04.

Chemical Modification of Paraherquamide. 2. Replacement of the C-14 Methyl Group[1]

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Paraherquamide (**1**) is a toxic metabolite of *Penicillium paraherquei* that was reported several years ago by Yamazaki et al.[2,3] It is structurally related to the marcfortines that were isolated from *P. roqueforti* by Polonsky et al.[4] The unusual structures of these oxindole alkaloids have recently begun to attract the attention of synthetic

(1) For part 1, see: Blizzard, T. A.; Marino, G.; Mrozik, H.; Fisher, M. H.; Hoogsteen, K.; Springer, J. P. *J. Org. Chem.* **1989**, *54*, 2657.
(2) (a) Yamazaki, M.; Okuyama, E.; Kobayashi, M.; Inoue, H. *Tetrahedron Lett.* **1981**, *22*, 135. (b) Yamazaki, M.; Fujimoto, H.; Okuyama, E.; Ohta, Y. *Maikotokishin (Tokyo)* **1980**, *10*, 27; *Chem. Abstr.* **1981**, *95*, 19321p.
(3) The *Chemical Abstracts* name for paraherquamide is spiro[4*H*,8*H*-[1,4]dioxepino[2,3-*g*]indole-8,7′(8′*H*)-[5*H*,6*H*-5a,9a](iminomethano)[1*H*]cyclopent[*f*]indolizine]-9,10′(10*H*)-dione, 2′,3′,8′a,9′-tetrahydro-1′-hydroxy-1′,4,4,8′,8′,11′-hexamethyl-, (1′α,5′aβ,7′β,8′aβ,9′aβ)-(−). In the interest of brevity and clarity we have used trivial names based on paraherquamide rather than *Chemical Abstracts* names throughout this paper.
(4) (a) Polonsky, J.; Merrien, M. A.; Prange, T.; Pascard, C.; Moreau, S. *J. Chem. Soc., Chem. Commun.* **1980**, 601. (b) Prange, T.; Billion, M. A.; Vuilhorgne, M.; Pascard, C.; Polonsky, J.; Moreau, S. *Tetrahedron Lett.* **1981**, *22*, 1977.

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