Pergamon

Tetrahedron, Vol. 53, No. 23, pp. 7917-7928, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00464-X

Resolution of 4-Cyano-4-(4-nitrophenyl)hexanoic Acid: Synthesis of (*R*) and (*S*)-3-(4-Aminophenyl)-3-ethylpiperidine-2,6-dione (Aminoglutethimide[1])

Osman Achmatowicz*, Iwona Malinowska, Barbara Szechner

Pharmaceutical Research Institute, 8 Rydygiera Str., 01-793 Warszawa, Poland;

Jan K. Maurin

Institute of Atomic Energy, 05-400 Otwock-Świerk, Poland

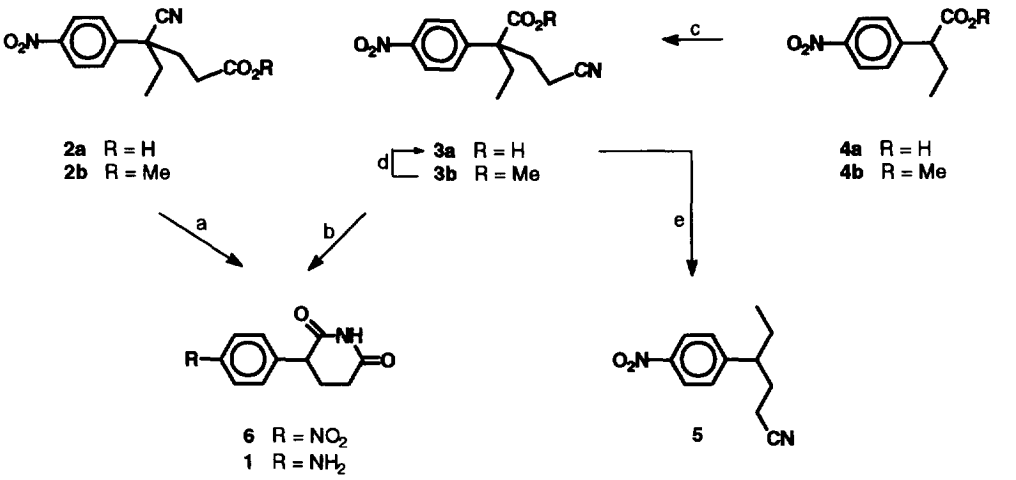
Abstract: Using (*R*)- or (*S*)-1-phenylethylamine as a resolving agent, (*R*)- and (*S*)-4-cyano-4-(4-nitrophenyl)hexanoic acids have been isolated. Cyclization of each enantiomer, followed by reduction of the nitro group, afforded (*R*)- and (*S*)-aminoglutethimide of high (>99% *ee*) enantiomeric purity, respectively. The absolute configuration of (*R*)-(+)-3-(4-nitrophenyl)-3-ethylpiperidine-2,6-dione was solved by X-ray single crystal analysis thus establishing the (*R*)-configuration of the dextrorotatory aminoglutethimide. Attempted resolution of the other precursor of aminoglutethimide, 4-cyano-2-ethyl-(4-nitrophenyl)butanoic acid with (*S*)-1-phenylethylamine led to the formation of the double salt. Its crystal structure was elucidated by X-ray crystallographic analysis. © 1997 Elsevier Science Ltd.

rac-3-(4-Aminophenyl)-3-ethylpiperidine-2,6-dione (**1**) with international non-proprietary name aminoglutethimide[1] blocks several steroid biosynthetic steps by a reversible competitive inhibition of $P450_{arom}$[2]. This property of **1** has been used in the clinic for treating women with cases of brest cancer to decrease plasma estrogen level thus removing the stimulus to tumor growth[3]. Because aminoglutethimide (**1**) exhibits stereospecificity to the target enzyme its anti-steroidogenic effects are mostly attributable to the dextrorotatory enantiomer[4] whereas both (*R*) and (*S*) enantiomers possess undesirable neuropharmacogical acivity. It may be anticipated that (*R*)-(+)-aminoglutethimide would be a safer drug and consequently a method of its enantioselective synthesis is desirable.

Both enantiomers of aminoglutethimide (**1**) have been obtained before by rather tedious resolution of the racemate *via* diastereoisomeric salts with D and L-tartaric acid, respectively[5]. In our approach we have turned our attention to acids **2a** and **3a** as potential chiral substrates for the (*R*)- and (*S*)-**1** synthesis. Acid catalyzed cyclization of ester **2b** is an established procedure in the synthesis[6] of aminoglutethimide (**1**) (Scheme 1). Acid

2a appeared to be particularly suitable for the resolution of its diastereoisomeric salts because of the immediate vicinity of the carboxyl group to the chiral center.

Scheme 1



a. H_2SO_4 - AcOH, 95°C, 2h; b. PPA, 180°C, 2h; c. CH_2=CHCN, K_2CO_3, TEBA, CH_2Cl_2/reflux, 1.5h; d. 3% KOH, THF-MeOH-H_2O, 2h, r.t.; e. NEt_3, 80°C, 0.5 h.

RESULTS AND DISCUSSION

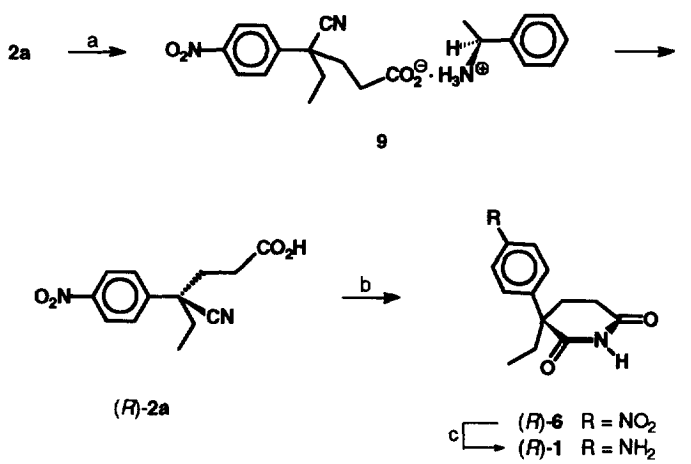
4-Cyano-2-ethyl-2-(4-nitrophenyl)butanoic acid (**3a**).

Michael addition of ester **4b** to acrylonitrile and subsequent hydrolysis of of the product **3b** afforded acid **3a**. Treatment of cyanoester **3b** with polyphosphoric acid gave nitro compound **6** in high yield (Scheme 1). It should be however mentioned that cyclization of **3b** required more forcing conditions than in case of **2b**[6], presumably because the intramolecular attack of immonium cation on the methoxycarbonyl group in **3b** is sterically hindered. Attempted resolution of acid **3a** by fractional crystallization of diastereoisomeric salts with (*S*)-(1-phenyl)ethylamine [(*S*)-7] failed due to the formation of the double salt[7] **8**, as shown by X-ray crystallography (*vide infra*). Other amines have not been examined as resolving agents because acid **3a** turned out to be unstable in basic conditions. We noticed some decarboxylation of **3a** during hydrolysis of **3b** (5% NaOH in aqeous methanol, <60°C) and drying its (S)-phenylethylammonium salt **8** (≤60°C). Heating of **3a** with equimolar amount of triethylamine at 80°C for 30 minutes resulted in complete decarboxylation yielding quantitatively (4-nitrophenyl)hexanonitrile (**5**) (Scheme 1).

Synthesis of (R)- and (S)-Aminoglutethimide [(*R*)-**1** and (*S*)-**1**]

The first stage involved separation of the (*R*) and (*S*) forms of the acid **2a** as their salts of (*R*)- or (*S*)-1-phenylethylamine. The acid **2a** was prepared by hydrolysis of ester **2b**[6]. Three crystallizations from water of its salt **9**, after liberation of the acid in the usual manner, afforded (*R*)-**2a**, $[\alpha]_D$ -22.3° and (*S*)-**2a**, $[\alpha]_D$ +23.2°, respectively (Scheme 2[8]). Enantiomeric acids unlike crystalline racemic compound **2a** are thick yellow oils which in our hands failed to crystallize. Acids (*R*)-**2a** and (*S*)-**2a** heated with acetic anhydride - sulfuric acid mixture for 2 h at 95° afforded nitroglutethimide (*R*)-**6** and (*S*)-**6**, respectively, of high (>98% *ee*) enantiomeric purity in an excellent yield. One recrystallization of compounds (*R*)-**6** and (*S*)-**6** from methanol raised their *ee* above 99%. Hydrogenation of (*R*)-**6** and (*S*)-**6** in the presence of Raney Ni yielded quantitatively (*R*)-aminoglutethimide [(*R*)-**1**], $[\alpha]_D$ +163° and (*S*)-aminoglutethimide [(*S*)-**1**, $[\alpha]_D$ -163°, respectively, as colorless solids of enantiomeric purity above 99% according to chiral HPLC.

Scheme 2



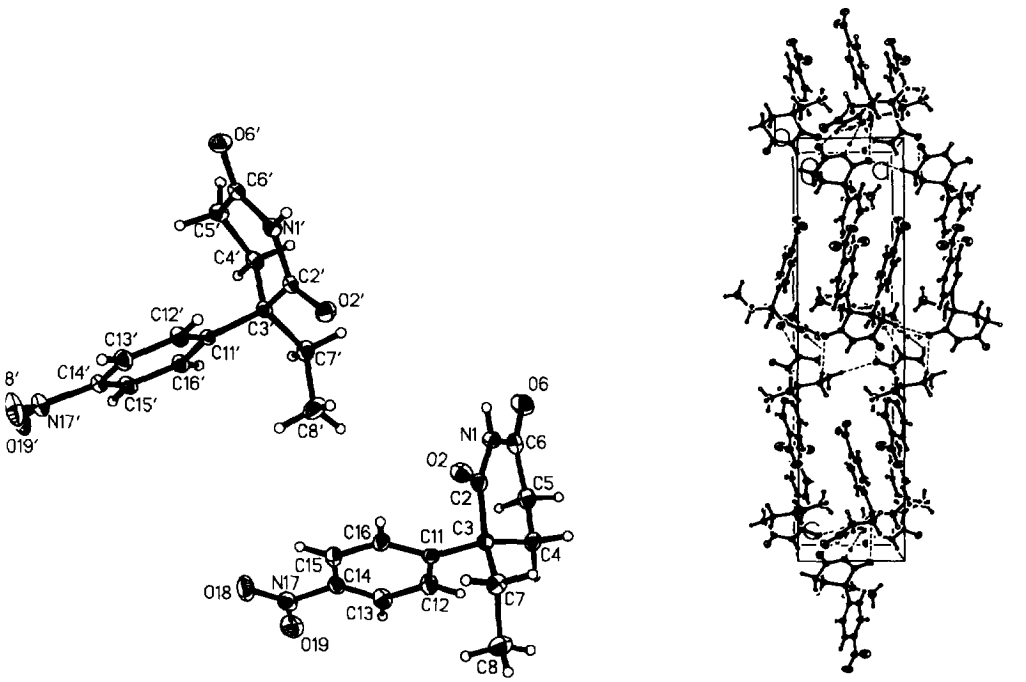
a.(*R*)-**7**, MeCN; b.H_2SO_4-AcOH/95°C, 2h; c. H_2 - 10% Pd-C.

The absolute configuration of (*R*)-**1** and (*S*)-**1** has been determined by their transformation into (*R*)- and (*S*)- enantiomers, respectively, of 3-ethyl-3-phenylpiperidine-2,6-dione[5]. The absolute configuration of the latter has been in turn based on the CD curves in comparison with a compound of known absolute configuration, (*S*)-(-)-2-ethyl-2-phenylsuccinimide[9]. To obtain an independent and unequivocal proof of the dextrarotatory aminoglutethimide configuration, as well as of acid (*R*)-(-)-**2a** and (*S*)-(+)-**2a**, the X-ray crystallographic analysis of ((*R*)-(+)-**6** was carried out.

Crystal and molecular structure of 3-ethyl-3-(4-nitrophenyl)piperidine-2,6-dione [(*R*)-**6**]

The molecular geometry and the atomic numbering of the two independent molecules of (*R*)-**6** present in the asymmetric part of the unit cell are given in Fig. 1A. Packing of the molecules in the unit cell as well as hydrogen bonds occuring in the crystal lattice are shown in Fig.1B. Two independent molecules of (*R*)-**6** have appreciably different conformations. In both molecules imide rings occur in a sofa conformation with atoms N1, C2 and C6 (or N1', C2', C6') in plane and atom C4 (or C4') out of plane. However they depart from the ideal form to a different degree. This is evident from torsion angles (Table 1) and asymmetry parameters[10] calculated for structures in Fig. 1A. The values for „non-primed": ΔC_s^1 =5.41°, ΔC_2^{34} = 11.1° and „primed": ΔC_s^1 = 8.22°, ΔC_2^{34} = 13.10° indicate that the latter is distorted to a larger extend towards a half-chair form. In both structures (Fig. 1A) the nitro group is nearly coplanar with the phenyl ring (the dihedral angles are 3.7(3)° and 7.4(3)°, respectively) and the aryl substituent occupies the axial position. On the other hand the rotation of phenyl ring relatively to the imide moiety is different in both structures as can be seen from the comparison of

Fig. 1. The ORTEP drawings of molecule of (*R*)-**6** with the numbering scheme (A) and of the unit cell of (*R*)-**6** (B).



A B

torsional angles values: 23.2° (C4-C3-C11-C12) and 65° (C4'-C3'-C11'-C12'), respectively. The detailed conformation of the non-planar fragments of the molecules could be perceived from the selected torsion angles collected in Table 1.

Table 1. Selected torsion angles in the solid state structures of (*R*)-**6** molecules shown in Fig. 1

C4-C3-C11-C12	23.2	C4'-C3'-C11'-C12'	-112.6
C4-C3-C11-C16	-160.1	C4'-C3'-C11'-C16'	65.0
C4-C3-C7-C8	-65.3	C4'-C3'-C7'-C8'	-169.6
C6-N1-C2-C3	-9.8	C6'-N1'-C2'-C3'	-4.6
N1-C2-C3-C4	33.9	N1'-C2'-C3'-C4'	33.5
C2-C3-C4-C5	-53.3	C2'-C3'-C4'-C5'	-55.1
C3-C4-C5-C6	49.6	C3'-C4'-C5'-C6'	48.0
C4-C5-C6-N1	-22.8	C4'-C5'-C6'-N1'	-17.5
C5-C6-N1-C2	3.1	C5'-C6'-N1'-C2'	-4.6
C2-C3-C11-C16	-41.3	C2'-C3'-C11'-C16'	-176.8
C2-C3-C11-C12	142.1	C2'-C3'-C11'-C12'	5.6

The crystal structure of (*R*)-**6** is held together by a series of N-H····O and C-H·····O hydrogen bonds clearly visible in the unit cell content (Fig. 1B). Their geometries are listed in Table 2. The planar fragments of the two independent molecules, which are hydrogen bonded to each other *via* N-H····O bonds, make a dihedral angle of 60.0(1)°.

The crystal structure of (R)-**6** is composed of dimers resultant from intermolecular hydrogen bonding between imide and carbonyl group and resembles somewhat the centrosymmetric structure of *rac*-aminoglutethimide (**1**)[11] and other substituted glutarimides[12]. The dimers are hydrogen bonded to each other by much weaker contacts, *i.e.* $NH_{amino}\cdots O_{C=O}$ in the amino analogue[9] and $CH\cdots O_{C=O}$ in the present structure.

Table 2. Hydrogen Bonds Geometries for (*R*)-**6**.

	Distances (Å)			Angle (°)
D-H····A	D····A	D-H	H····A	D-H····A
N(1)-H(1)····O(6')#1	2.934(3)	0.87(4)	2.072(42)	170(3)
N(1')-H(1')····O(2)#2	2.906(3)	0.91(3)	2.006(33)	173(3)
C(4')-H(4A')····O(2')#2	3.330(3)	0.97	2.526(3)	140.20(8)
C(5')-H(5A')····O(2')#3	3.530(3)	0.97	2.565(3)	173.30(8)
C(5)-H(5A)····O(6')#4	3.370(4)	0.97	2.589(4)	137.68(8)
C(4)-H(4A)····O(6)#5	3.509(4)	0.97	2.739(4)	136.82(8)

Symmetry transformations used to obtain equivalent atoms:
#1 0.5+x, 0.5-y, -z #2 x-0.5, 0.5-y, -z #3 x-1, y, z #4 1+x, 1+y, z #5 0.5+x, 1.5-y, -z

Most importantly, by establishing the (*R*) configuration for the dextrorotatory nitro compound (*R*)-**6** (*cf.* Fig. 1A), it was possible to confirm the proposed configuration of (*R*)-(+) and (*S*)-(-)-aminoglutethimide (**1**) as well as of the acids (*R*)-(-) and (*S*)-(+)-**2a**, obtained by resolution.

Crystal and molecular structure of (S)-(1-phenyl)ethylammonium (R,S)-4-cyano-2-ethyl-2-(4-nitrophenyl)-hexanoate double salt (**8**)

The unit cell of the double salt **8** is composed of 4 molecules of protonated base (*S*)-**7** and 4 anions of acid **1a** (two of each enantiomer) and 2 molecules of water, typical of a 1:1 double salt[7]. Although the intensity statistics pointed to a non-centrosymmetric space group, the unit cell content resembles the centrosymmetric case with one base and one acid molecule in the asymmetric part of the unit cell with the coordinate system shifted by the vector [0.25,0,0.025] and $P2_1/n$ symmetry. The similarity of both structures depend not only on the number of molecules in the unit cell, but also on the enantiomeric content of the crystal. As far as all amine molecules are (*S*)-enantiomers, the unit cell contains racemate of the acid [two (*R*) and two (*S*) enantiomer molecules]. Moreover the geometry of protonated amino group resembles methyl group, and this makes similar (*S*) and (*R*)-enantiomers of the amine. The difference between the $P2_1$ and $P2_1/n$ parts of the unit cell is the content of water - the asymmetric section containing only one water molecule.

Fig. 2. The ORTEP drawing of the part of the unit cell of **8** with hydrogen bonds shown as dashed lines (A) and of molecules (*R*)-**7** - „B" and (*R*)-**3a** - „C" with the numbering scheme (B).

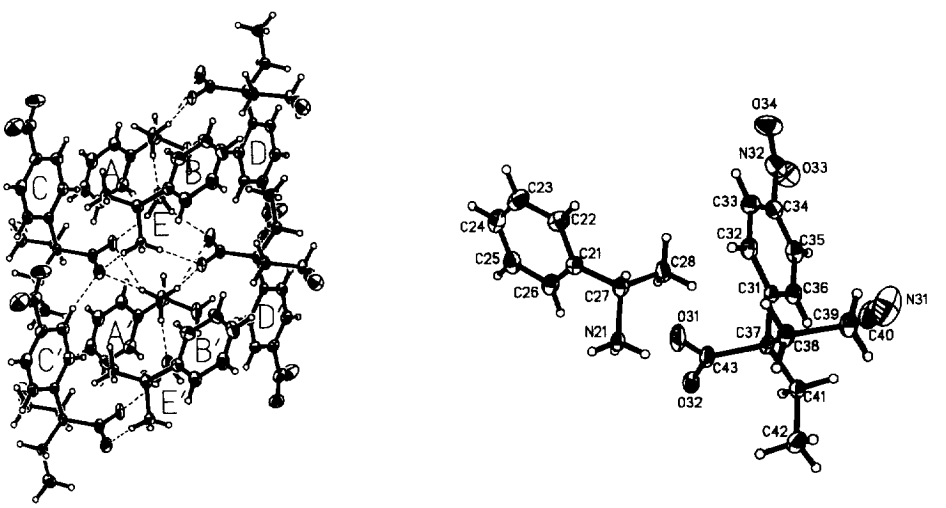


Fig. 2A shows a view of a part of the crystal lattice displaying all types of hydrogen bonds indicated as dashed lines. For clarity, all molecules are denoted with capital letters: A and B [(*S*)-7], C [(*R*)-**2a**], D [(*S*)-**2a**] and E (H_2O). The primed letters correspond to the symmetry related molecules. The geometries of hydrogen bonds are listed in Table 3. The ORTEP drawing with the numbering scheme of molecules „B" [(*S*)-7] and „C" [(*R*)-**2a**] is shown in Fig.2B.

Table 3. Hydrogen Bonds Geometries for Double Salt **8**.

D-H···A	D···A	H···A	D-H	angle D-H···A
O(2)-H(2B)···O(31)	2.784(5)	1.871(16)	0.979(5)	154(3)
O(2)-H(2A)···O(52)	2.901(6)	1.985(25)	0.979(5)	155(5)
N(11)-H(11A)···O(51)#1	3.031(5)	2.221(5)	0.890	151.2(1)
N(11)-H(11A)···O(52)#1	3.298(8)	2.524(8)	0.890	145.8(1)
N(11)-H(11B)···O(2)#2	2.991(6)	2.129(6)	0.890	162.8(1)
N(11)-H(11C)···O(32)#1	2.983(5)	2.102(5)	0.890	170.5(1)
N(11)-H(11C)···O(31)#1	3.169(6)	2.500(6)	0.890	132.4(1)
N(21)-H(21C)···O(51)	2.691(4)	1.850(4)	0.890	156.9(1)
N(21)-H(21A)···O(32)	2.763(4)	1.939(4)	0.890	153.4(1)
N(21)-H(21B)···N(51)#3	3.054(5)	2.129(5)	0.890	156.0(1)
C(33)-H(33)···O(32)#4	3.343(6)	2.497(6)	0.930	151.5(1)

Symmetry transformations used to generate equivalent atoms:
#1 1-x, y-0.5, 1-z #2 -x, y-0.5, 1-z #3 1-x, 0.5+y, -z #4 -1+x, y, z

The amine „A" forms slightly longer bifurcated hydrogen bonds with both molecules of the acid comparing to those formed by molecule „B". The third hydrogen atom of the ammonium group of molecule „A" is involved in a hydrogen bond with a water molecule, whereas for molecule „B" it is hydrogen-bonded to the nitrile group of „D" molecule. The amino group of „A" molecule and the carbonyl group of „D" molecule are partly disordered (for clarity only one orientation of either disordered group is shown). The geometries of the two amino molecules are similar, the rotation of the aminoethyl substituent relatively to the phenyl ring differ by ca. 15°. Also the geometries of both enantiomeric acid **2a** anions are very similar. The planar phenyl rings make dihedral angles with the nitro group of 16.0(7)° and 19.8(6)°, for molecules „C" and „D", respectively. The carboxylate group is nearly perpendicular to the ring; the dihedral angles 81.2(3)° and 84.2(2)° for molecules „C" and „D", respectively. The disorder of the amino group of the molecule „A" with occupation factor 0.89 for main orientation was realized by the small shift of N-atom. Also one oxygen atom of the carboxylate group of molecule „D" has two different positions with occupation factor of 0.81 for the main one. The other significant structural feature of the structures, which should be mentioned, concerns the elongation of the carbon-carbon sp^3-sp^2 bond involving the quaternary carbon atom of (*R*)-**3a** and (*S*)-**3a** in the double salt **8**, as well as in (*R*)-**6**. The bond lenghts (see Table 4) are higher that the values (ca. 1.50 Å) usually possessed by

sp^3-sp^2 carbon-carbon single bond. The elongation of the of the Csp^3 - Csp^2 bond observed in our cases is attributrd to steric crowding of the quaternary tetrahedral carbon atom. The other bond distances and angles agree with the literature data.

Table 4. Bond lengths (Å) of the Csp^3-Csp^2 in (*R*)-**3a**, (*S*)-**3a** and (*R*)-**6**

Molecule	Bond[a]	Length (Å)
(*R*)-**3a**	C31-C37	1.532(5)
(*S*)-**3a**	C51-C57	1.531(5)
(*R*)-**6**	C3-C11	1.543(3)
(*R*)-**6**	C3'-C11'	1.536(3)

[a]Atom numbering as in Fig. 2B [(*R*)-**3a**] and Fig.1A [(*R*)-**6**]

EXPERIMENTAL

Melting points were determined on a Büchi 535 apparatus in capillary tubes and are uncorrected. IR spectra were measured with a Nicolet FT-IR Impact 410 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 2000 spectrometer using TMS as internal reference. High resolution mass spectra (HRMS) were obtained on AMD 604 spectrometer. HPLC was carried out on Shimadzu LC-6A equipped with Chiracel OJ, 0.46x25 cm column. All reactions and separations were monitored in TLC using silica gel 60 F_{254} aluminum precoated plates. Silica gel 60 (Merck, 230-430 mesh) was used for column chromatography.

X-Ray structure determination of (R)-6 and double salt **8**.

Compounds (*R*)-**6** and **8** were crystallized from methanol and water, respectively. Columnar and platy crystals of **8** and (*R*)-**6**, respectively, were mounted on KUMA KM-4 K-axis single crystal diffractometer. Graphite monochromatized CuKα radiation was used to collect the data. Unit cell parameters were obtained by the least-squares treatment of 25 reflections with $18.7 \leq 2\theta \leq 24.8°$ [(*R*)-**6**] and $40 \leq 2\theta \leq 44°$ (**8**). Data were corrected for Lorenz-polarization factors but not for absorption. Structures were solved using direct methods from SHELXS-86[13] program and then refined basing on F^2 by application of SHELXL-93 program[14]. Almost all heavy atoms were found on the E-map; the remaining atoms were located during subsequent Δρ syntheses. The hydrogen atoms were included during refinement in their calculated positions, and their isotropic displacement parameters were taken as 1.2 times larger (1.5 for methyl and amino group hydrogens) than the equivalent thermal parameters of the respective carbon atoms. The absolute configuration of (*R*)-**6** was verified on the basis of the calculated Flack parameter[15]. The data collection and the refinement details are collected in Table 5.

Table 5. Data Collection and Processing Parameters of Compounds (*R*)-**6** and **8**[16]

	(*R*)-**6**	**8**
Empirical formula	$C_{13}H_{14}N_2O_4$	$C_{21}H_{26}N_3O_{4.5}$
Formula weight	262.26	392.45
Temperature	293(2) K	293(2) K
Wavelength	1.54178 Å	1.54178 Å
Crystal system	Orthorombic	Monoclinic
Space group	$P2_12_12_1$	$P\ 2_1$
Unit cell dimensions	a = 7.1710(10) Å b = 12.5080(10) Å c = 28.334(3) Å	a = 7.200(3) Å b = 13.998(3) Å c = 20.724(4) Å β = 97.17(3)°
Volume	2541.4(5) $Å^3$	2072.3(11) $Å^3$
Z	8	4
Density (calculated)	1.371 Mg/m^3	1.258 Mg/m^3
Absorption coefficient	0.862 mm^{-1}	0.732 mm^{-1}
F(000)	1104	836
Crystal size	0.4 x 0.3 x 0.15 mm	0.5 x 0.4 x 0.35 mm
θ range for data collection	3.12 to 80.20°	2.15 to 70.16°
Index range	$-6\le h\le 9$, $-11\le k\le 14$, $-26\le l\le 36$	$-8\le h\le 6$, $-11\le k\le 17$, $-25\le l\le 25$
Reflections collected	4103	4260
Independent reflections	3617 [R(int) = 0.0224]	3897[R(int) = 0.0520]
Absorption correction	Not applied	Not applied
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data (restraines) parameters	3617 / 0 / 351	3897 / 58 / 524
Goodness-of-fit on F^2	0.993	1.013
Final R indices [$I>2\sigma(I)$]	R = 0.0372, $wR(F^2)$ = 0.0973	R = 0.0522, $wR(F^2)$ = 0.1465
R indices (all data)	R = 0.0595, $wR(F^2)$ = 0.1069	R = 0.0694, $wR(F^2)$ = 0.1581
Absoloute structure parameter	0.0(3)	0.4(4)
Extinction coefficient		0.0037(5)
$\Delta\rho_{max}$ and $\Delta\rho_{min}$	0.142 and -0.180 e.$Å^3$	0.318 and -0.179 e·$Å^{-3}$

Methyl 4-cyano-4-(4-nitrophenyl)hexanoate (2b)

Powdered potassium carbonate (87 g, 0.63 mol) and TEBA (3.2 g) were added to a solution of 2-(4-nitrophenyl)butanonitrile (120 g, 0.63 mol) in toluene (750 mL). The mixture was warmed to 45°C and methyl acrylate (58.7 g, 0.68 mol) was added with stirring over 0.5 h. The temperature was mainatined at 45°C and stirring was continued for 2 h. The potassium carbonate was filtered off, extracted with toluene (100 mL), and the combined organic solutions washed with water (4x100 mL) and dried ($MgSO_4$). The volatiles were removed in vacuo and the residue distilled yielding 166 g (96%) of ester **2b**[6], b.p. 136-142°C/0.6 Torr.

***rac*-4-Cyano-4-(4-nitrophenyl)hexanoic acid (2a)**

Sodium hydroxide (12.0 g, 0.3 mol) dissolved in water (120 mL) was added with stirring to a solution of ester **2b** (55.3 g, 0.2 mol) in methanol (250 mL). The temperature was maintained <30°C and the stirring continued for 4 h. After most of the methanol was evaporated under reduced pressure the reaction mixture was diluted with water (100 mL) and washed with dichloromethane (2x50 mL). The aqueous solution was brought to pH 3 with conc. hydrochloric acid, chilled on the ice-water bath, deposited solid filtered off and recrystallized from aqueous methanol to give 49.0 g (89%) of **1a**, m.p. 122-124°C. IR ($CHCl_3$) ν_{max}: 3200-2700, 2242, 1715, 1608, 1528, 1349, 855 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.31-8.24 (m, 2H, aromatic);

7.65-7.58 (m, 2H, aromatic); 2.65-1.93 (m, 6H, -$[CH_2]_3$-); 0.95 (t, J = 7.4 Hz, 3H, CH_3). Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68%. Found: C, 59.53; H, 5.30; N, 10.49%.

Methyl 2-(4-nitrophenyl)butanoate (4b)

Thionyl chloride (24 mL) was added with stirring to a solution of acid **4a**[17] (138 g, 0.659 mol) in methanol (750 mL) chilled to <10°C and the mixture left at r.t. overnight. Methanol was removed in vacuo, residue dissolved in dichloromethane (300 mL) and washed successively with sat. sodium hydrogen carbonate (150 mL), water (150 mL), dried ($MgSO_4$) and evaporated. Distillation of the residue afforded 141.5 g (96%) of ester **5b**, b.p. 125-130°C/0.6 Torr. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.21-8.14 (m, 2H, aromatic); 7.51-7.44 (m, 2H, aromatic); 3.68 (s, 3H, OCH_3); 3.58 (t, $J_{2,3}$ = 7.7 Hz, 1H, H-2); 2.13 (dquint, $J_{3,3'}$ = 14.6 Hz, 1H, H-3), 1.81 (dquint, 1H, H-3'); 0.83 (t, $J_{3,4}$ = 7.4 Hz, 3H, CH_3).

Methyl 4-cyano-2-ethyl-2-(4-nitrophenyl)butanoate (3b)

To a solution of ester **4b** (150 g, 0.63 mol) in acetonitrile (750 mL) chilled to 10°C was added powdered potassium hydroxide (20 g, 0.36 mol) and the acrylonitrile (60 mL, 0.90 mol) was added dropwise over 15 min maintaining temperature <15°C. After stirring the mixture for 15 min the excess acrylonitrile was evaporated and to the residue was added dichloromethane (700 mL) and water (500 mL). The organic layer was separated and washed with water (4x100 mL), dried ($MgSO_4$) and evaporated. The solid residue was recrystallized from ethanol to yield 136.5 g (75%) of ester **3b**, m.p. 88-90°C. IR ($CHCl_3$) ν_{max}: 2253, 1733, 1607, 1529, 1352, 855 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.29-8.22 (m, 2H, aromatic); 7.47-7.40 (m, 2H, aromatic); 3.75 (s, 3H, OCH_3); 2.65-1.85 (m, 6H, -$[CH_2]_3$-); 0.93 (t, J = 7.4 Hz, 3H, CH_3). Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.79; N, 10.14%. Found: C, 60.82; H, 5.99; N, 10.07%.

4-Cyano-2-ethyl-2-(4-nitrophenyl)butanoic acid (3a)

To a solution of ester **3b** (19.6 g, 0.07 mol) was added potassium hydroxide (7.85 g, 0.14 mol) dissolved in water (24 mL), methanol (70 mL) and the homogenous mixture was left for 48 h. The solvents were evaporated under reduced pressure, the residue diluted with water (200 mL) and washed with dichloromethane (2x50 mL). TLC showed taht the dichloromethane extracts contained nitrile **6**. The aqueous layer was decolorized with active carbon, brought to pH 3 with conc. hydrochloric acid and extracted with dichloromethane (3x50 mL). Organic layer was washed with water (50 mL), dried ($MgSO_4$) and evaporated to yield 16.5 g (88%) of acid **2a**, m.p. 143-144°C. IR ($CHCl_3$) ν_{max}: 3497-2600, 2253, 1709, 1607, 1525, 1351, 855 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.28-8.21 (m, 2H, aromatic); 7.53-7.46 (m, 2H, aromatic), 2.57-2.03 (m, 6H, -$[CH_2]_3$-); 0.91 (t, J = 7.4 Hz, 3H, CH_3). Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.34; N, 10.68%. Found: C, 59.85; H, 5.45; N, 10.27%.

4-(4-Nitrophenyl)hexanonitrile (5)

Acid **3a** (1.0 g, 3.8 mmol) and triethylamine (0.04 g, 3.8 mmol) were heated at 90°C untill the evolution of CO_2 ceased (15 min). The reaction mixture was dissolved in dichloromethane (50 mL), washed with water (2x10 mL), dried ($MgSO_4$) and evaporated. Bulb-to-bulb distillation of the residue afforded 0.80 g (96%) of nitrile **5**, b.p. 225° (air-bath)/0.6 Torr. IR ($CHCl_3$) ν_{max}: 2248, 1607, 1527, 1349, 857 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.25-8.18 (m, 2H, aromatic); 7.39-7.32 (m, 2H, aromatic); 2.85-2.70 (m, 1H, H-4); 2.36-1.54 (m, 6H, -$[CH_2]_3$-); 0.81 (t, $J_{5,6}$ = 7.4 Hz, 3H, CH_3). Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84%. Found: C, 65.78; H, 6.59; N, 12.86%.

***rac*-3-Ethyl-3-(4-nitrophenyl)piperidine-2,6-dione (6)**

Polyphosphoric acid (0.80 g) was added to ester **3b** (0.10 g, 0.38 mmol) and the mixture was heated to 180° C for 0.5 h. To the coold reaction mixture ice (10 g) was added and after 1 h the precipitate was filtered off, washed with water and dried. Recrystallization from methanol gave 0.078 g (82%) of imide **6**, m.p. 140-142° C (lit.[6] m.p. 137-139° C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.28-8.20 (m, 2H, aromatic); 8.02 (bs, 1H, NH); 7.53-7.46 (m, 2H, aromatic); 2.68 (ddd, $J_{5,5'}$ = 15.0, $J_{4,5}$ = 12.3, $J_{4',5}$ = 7.9 Hz, 1H, H-5); 2.47-2.28 (m, 3H, H-4, H-4', H-5'); 2.12 and 1.97 (2xdq, J_d = 14.3, J_q = 7.4 Hz, 2x1H, -CH_2-); 0.90 (t, 3H, CH_3).

(*S*)-1-Phenylethylammonium *rac*-4-cyano-2-ethyl-2-(4-nitrophenyl)butanoate (8)

To a stirred suspension of acid **3a** (40 g, 0.15 mol) in water (400 mL), warmed to 60°C, was added (*S*)-1-phenylethylamine [(*S*)-7] (18.2 g, 0.15 mol) and the mixture was stirred till the homogenous solution was obtained, decolorized with active carbon, filtered and left at room temperature. Deposited crystals were separated and recrystallized from water to give 30.5 g of salt **8**, m.p. 97-99°C, $[\alpha]_D$ -2.3° (c1, MeOH). IR ($CHCl_3$) ν_{max}: 2251, 1597, 1523, 1372, 1350, 856 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.13-8.06 (m, 2H, aromatic); 7.54-7.46 (m, 2H, aromatic); 7.29 (bs, 5H, C_6H_5); 4.36 (q, J = 7.0 Hz, 1H, CH-N); 2.26-1.70 (m, 6H, -$[CH_2]_3$-]; 1.47 (d, 3H, CH_3); 0.68 (t, J = 7.3 Hz, 3H, CH_3). Anal. Calcd. for $C_{21}H_{25}N_3O_4 \cdot ½H_2O$: C, 64.25; H, 6.68; N, 10.71%. Found: C, 63.98; H, 6.91; N, 10.45%.

(*R*)-1-Phenylethylammonium (*R*)-4-cyano-4-(4-nitrophenyl)hexanoate [(*R,R*)-9]

A solution of acid **2a** (41.6 g, 0.16 mol) and (*R*)-1-phenylethylamine [(*R*)-7] (19.3 g, 0.16 mol) in acetonitrile was heated to 70°C and left to crystallize. The solid was filtered off and recrystallized three times from water (1:10) to give 11.0 g (36%) of salt (*R,R*)-**9**, m.p. 152-155°C, $[\alpha]_D$ -9.6° (c 1, MeOH). ^1H NMR (200 MHz, $CDCl_3$): δ 8.25-8.18 (m, 2H, aromatic); 7.53-7.46 (m, 2H, aromatic); 7.28 (bs, 5H, C_6H_5); 4.14 (q, J = 6.8 Hz, 1H, >CH-N); 2.20-1.65 (m, 6H, -$[CH_2]_3$-). Anal. Calcd. for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96%. Found: C, 65.70; H, 6.66; N, 10.95%.

(*S*)-1-Phenylethylammonium (*S*)-4-cyano-4-(4-nitrophenyl)hexanoate [(*S,S*)-9]

Prepared according to the procedure described above, but using (*S*)-1-phenylethylamine [(*S*)-7], the salt (*S,S*)-**9** had m.p. 152-154°C, $[\alpha]_D$ +9.4° (c 1, MeOH). ^1H NMR spectrum identical with one of (*R,R*)-**9**. Anal. Calcd. for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96%. Found: C, 65.54; H, 6.51; N, 10.88%.

(*R*)-(-)-4-Cyano-4-(4-nitrophenyl)hexanoic acid [(*R*)-2a]

A suspension of salt (*R,R*)-**9**, $[\alpha]_D$ -9.6°, (11.0 g, 28.7 mmol) in water (100 mL) was brought to pH~9 with sodium bicarbonate and washed with dichloromethane (3x20 mL) to recover (*R*)-**7**. The water layer was acidified with conc. hydrochloric acid to pH 4 and extracted with dichloromethane (200 mL). The organic solution was washed with water (50 mL), dried ($MgSO_4$) and evaporated to yield 7.0 g (93%) of acid (*R*)-**2a** as yellowish viscous oil, $[\alpha]_D$ -22.3° (c 1, MeOH).

(*S*)-(+)-4-Cyano-4-(4-nitrophenyl)hexanoic acid [(*S*)-2a]

Prepared according to the procedure described above, but using salt (*S,S*)-**9**, $[\alpha]_D$ +9.4°, acid (*S*)-**2a** had $[\alpha]_D$ +23.2°.

(*R*)-(+)-3-Ethyl-3-(4-nitrophenyl)piperidine-2,6-dione [(*R*)-6]

To a warm (~70°C) solution of acid (*R*)-**2a** (7.0 g) in acetic acid (5.7 mL) was added conc. sulfuric acid (1.1 mL) and the mixture was heated to 95°C for 2 h. The reaction mixture was cooled and poured onto ice (50 g) and after 1 h the precipitate was filtered off, washed with water and dried to give 6.4 g (91.5%) of (*R*)-**6**, *ee* 97.5% (HPLC). Recrystallization from methanol gave 5.6 g (80%) of product (*R*)-**6**, m.p. 137-139°, $[\alpha]_D$ +129.3° (c 1, MeOH), *ee* >99% (HPLC). ^1H NMR spectrum identical with one of racemic imide **6**. IR ($CHCl_3$) ν_{max} 3364, 1708, 1606, 1525, 1351, 1185, 855 cm^{-1}.

(*S*)-(-)-3-Ethyl-3-(4-nitrophenyl)piperidine-2,6-dione [(*S*)-6]

Cyclization of acid (S)-**2a** according to the above procedure gave 80% of imide (*S*)-**6**, m.p. 137-139°, $[\alpha]_D$ -129.0° (c 1, MeOH). ^1H NMR and IR spectra identical with those of enantiomer (*R*)-**6**.

(*R*)-(+)-3-Ethyl-3-(4-aminophenyl)piperidine-2,6-dione [(*R*)-aminoglutethimide] [(*R*)-1]

A suspension of (*R*)-(+)-**6** (0.5 g) and 10% Pd/C in ethyl acetate (10 mL) was stirred in a hydrogen atmosphere at r.t. for 1.5 h. The catalyst was filtered off and washed with ethyl acetate. Evaporation of solvent left 0.44 g (100%) of (*R*)-**1** as a colorless solid, $[\alpha]_D$ +163° (c 1, MeOH), *ee* > 99% (HPLC), (lit.[5] $[\alpha]_D$ +163.5°).

(*S*)-(-)-3-Ethyl-3-(4-aminophenyl)piperidine-2,6-dione [(*S*)-aminoglutethimide] [(*S*)-1]

Reduction of (S)-**6** according to the above procedure gave (*S*)-**1**, $[\alpha]_D$ -163° (c 1, MeOH), *ee* > 99% (HPLC), (lit.[5] $[\alpha]_D$ -163.5°).

Acknowledgement: We thank Mrs. A. Wiśniewska for skillful technical assistance.

REFERENCES AND NOTES

1. Negwer, M. *Organic Chemical Drugs and their Synonyms, 7th Edition*; Akademie-Verlag GmbH: Berlin, Vol. I, 1994; p. 760.
2. Salhanick, H. *Cancer Research (Suppl.)* **1982**, *42*, 3315-3321.
3. Santen, R.J. *J.Enz.Inhibit.* **1990**, *4*, 79-99.
4. a.Graves, P.E.; Salhanick, H.A. *Endocrinology* **1979**, *105*, 52-57. b. Popper, C.; Smith, H.J.; Nicholls, P.J.; Barrell, K.J.; Ahmadi, M. *Chirality* **1995**, *7*, 376-380.
5. Finch, N.; Dziemian, D.; Cohen, J.; Steinetz, B.G. *Experientia* **1975**, *31*, 1002-1003.
6. Hoffmann, K.; Urech, E. U.S. Patent, 2,848,455 Aug.15, 1955; CA **53**; P7103i.
7. Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, and Resolutions*; John Wiley &Sons: New York, 1981; pp. 295-299.
8. Only structures of (*R*) enantiomers are depicted.
9. Knabe, J.; Koch, W. *Arch.Pharm.* **1972**, *305*, 849-854.
10. Duax, W.L.; Norton, D.A. *Atlas of Steroid Structures*; Plenum Press: New York, 1975; pp. 16-22.
11. Van Roey, P.; Bullion, K.A.; Osawa, Y.; Braun, D.G. *Acta Cryst.* **1991**, *C47*, 829-832.
12. Czarnocki, Z.; Maurin, J.K.; Paluchowska, B.; Winnicka-Maurin, M. *Acta Cryst.B*, **1997**, in press.
13. Sheldrick, G.M. *Acta Cryst.* **1990**, *A46*, 467-473.
14. Sheldrick, G.M. *Program for the Refinement of Crystal Structures*; University of Göttingen, Germany, 1993.
15. Flack, D.H. *Acta Cryst.* **1983**, *A39*, 876-881.
16. The tables containing full experimental data are deposited with Cambridge Crystallographic Data Center (CCDC), UK.
17. Chu, T.-T.; Marvell, C.S. *J.Am.Chem.Soc.*, **1933**, *55*, 2841-2850.

(*Received in UK* 4 *March* 1997; *revised* 22 *April* 1997; *accepted* 24 *April* 1997)