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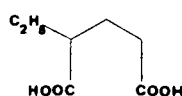
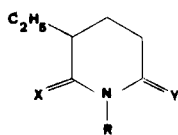
(-)-3-Ethylpiperidine and (R)-(-)-2-ethylglutaric acid have been chemically correlated through *N*-substituted α -ethylglutarimides obtained from the oxidation of optically active *N*-ethyl- and *N*-benzyl-3-ethylpiperidine with ruthenium tetroxide. The (R)-(-) configuration of (-)-3-ethylpiperidine was confirmed by CD measurements. The selective oxidation of endocyclic methylenes linked to the nitrogen atom was explained in term of different conformational freedom of endo- and exocyclic methylene groups.

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In the past (1) we proposed the oxidation of *N*-benzyl-3-substituted cyclic amines, by means of ruthenium tetroxide, as an alternative reaction to the von Braun degradation. In fact, ruthenium tetroxide oxidizes selectively the endocyclic methylene groups adjacent to the nitrogen atom giving imides which can be easily converted in the corresponding dicarboxylic acids. The low reactivity of the *N*-benzyl protecting group could be due either to the nature of the benzylic methylene or rather, to steric factors associated with the different conformational freedom of exo- and endocyclic methylenes.

In order to investigate the influence of steric factors on the oxidation and then to gather further information for the study of the reaction mechanism, we compared the reactivity of cyclic amines *N*-substituted with a benzyl or an ethyl group.

According to our previous studies on the absolute configuration of amino compounds, determined through chemical correlation (2a,b) and circular dichroism (3) measurements, *N*-benzyl and *N*-ethyl derivatives of optical active 3-ethylpiperidine were oxidized with ruthenium tetroxide. These reactions, in fact, besides giving informations on different reactivities of endo and exocyclic methylene independently on the nature of the groups linked to the exocyclic methylene, allow the correlation



R	X=Y=H	X=Y=O
CH ₃ -CH ₂ -	I	IV
H	II	-
O ₂ N-C ₆ H ₄ -CO-	III	-
C ₆ H ₅ -CH ₂ -	IIa	V

VI

of 3-ethylpiperidine to 2-ethylglutaric acid of known absolute configuration (4).

1,3-Diethylpiperidine (I) and 3-ethylpiperidine (II) were obtained by reduction with Raney nickel of 3-ethylpyridine dissolved in ethanol or dioxane, respectively. It is known (5a-c) that this reduction gives *N*-ethylpiperidines in the presence of ethanol as a solvent. The purification of the amine (II) was performed by crystallization of the corresponding *p*-nitrobenzoyl derivative (III).

Amines I and II were resolved by means of dibenzoyl-D-tartaric acid and (-)-diacetone-2-keto-L-gulonic acid hydrate (DAG), respectively; in both cases the *l*-isomer was isolated. Partially resolved *l*-isomer of I and *d*-isomer of II recovered from the mother liquors of the fractional crystallization were used for the oxidation reactions.

(-)-1,3-Diethylpiperidine (I) and (+)-*N*-benzyl-3-ethylpiperidine (IIa) obtained from (+)-(II) were oxidized with ruthenium tetroxide to the corresponding imides with no isolation of the intermediate lactames. The hydrolysis of imides (+)-(IV) and (-)-(V), isolated from the oxidation mixture in 60% yields, gave (R)-(-) and (S)-(+)-2-ethylglutaric acid (4), respectively.

Furthermore, amine (-)-(II) was condensed (3) with 2-fluoropyridine *N*-oxide and the circular dichroism curve of the condensation product showed, in agreement with the same derivative obtained from R(-)-3-methylpiperidine (3), a negative Cotton effect. The chiroptical properties of 3-ethyl and 3-methylpiperidine dithiocarbamates have already been compared by other authors (6).

The CD results obtained from these two different chromophoric amino derivatives are coherent and indicate that (-)-3-ethylpiperidine has an absolute configuration which agrees with the chemical correlation here reported. From the above results it is possible to conclude that: (i) *l*-isomers of the amines I and II both have R configuration. (ii) Benzyl or ethyl groups can be used indifferently as protecting groups of the amino function in the oxidation reactions with ruthenium tetroxide. (iii)

The different reactivity of the methylene groups linked to the nitrogen atom is mainly dependent on a difference in conformational freedom; endocyclic methylenes are oxidized preferentially with respect to the exocyclic ones.

EXPERIMENTAL

Microanalyses were carried out by Dr. A. Reho, Istituto di Chimica Farmaceutica, Bari, with a Hewlett-Packard Model 185 C,H,N analyzer. The melting points, determined with a Buchi-Tottoli capillary melting point apparatus, are uncorrected. Optical rotations ($[\alpha]_D$ and ORD) were determined on a Perkin-Elmer Model 241 MC polarimeter. CD and uv spectra were recorded in methanol with a Cary 61 dichrograph and with Cary 15 spectrophotometer, respectively; cells of 10 mm path length and concentrations about 0.01 mg./ml. were used. Ir and nmr spectra were determined with a Perkin-Elmer Model 257 and Varian HA-100 spectrometers, respectively. Nmr chemical shifts are expressed in τ (s = singlet, d = doublet, t = triplet, m = multiplet), using deuteriochloroform and TMS as the internal standard. The glc analysis were made with a gas chromatograph (Hewlett-Packard Model 5750G Research Chromatograph).

(R)-(-)-3-Ethylpiperidine (II).

3-Ethylpyridine (20 g.) was reduced with Raney nickel (4.5 g.) in ethanol 95° (500 ml.) at 80 atmospheres and heated at 160° for 22 hours. After filtration and evaporation of the solution, a colorless liquid was obtained. After distillation (b.p. 170-172°/760 mm; 60-62°/9 mm; yield 80%) [Lit. (7) b.p. 175°] it showed only one peak in glc analysis; nmr: 7.0-7.36 (2H, m, 2 and 6 heterocyclic-H), 7.50-9.26 (17H, superimposed signals area), 7.64 (2H, q, J = 7 Hz, CH_3-CH_2-N), 8.92 (3H, t, J = 7 Hz, CH_3-CH_2-N), 9.11 (3H, t, J = 7 Hz, 3- CH_2-CH_3). The hydrochloride had m.p. 189-191° dec. (absolute ethanol-ethyl ether); nmr: -1.07 (1H, broad, NH^+), 6.40-6.74 (2H, m, 2 and 6 heterocyclic-H), 6.76-9.20 (17H, superimposed signals area), 8.53 (3H, t, J = 7 Hz, $N-CH_2-CH_3$), 9.05 (3H, t, J = 7 Hz, 3- CH_2-CH_3).

Anal. Calcd. for $C_9H_{19}N \cdot HCl$: C, 60, 82; H, 11.34; N, 7.88. Found: C, 61.24; H, 11.42; N, 7.91.

Equimolecular amounts of racemic (I) and dibenzoyl-D-tartaric acid were crystallized 9 times from absolute ethanol. The free amine was obtained from the salt as a colorless oil [(R)-(I)], b.p. 150°/760 mm; d = 0.828; ORD (neat): $[\alpha]_{589} -0.14^\circ$, $[\alpha]_{530} -0.12^\circ$, $[\alpha]_{500} -0.10^\circ$, $[\alpha]_{450} \pm 0$, $[\alpha]_{400} +0.22^\circ$, $[\alpha]_{350} +0.85^\circ$, $[\alpha]_{330} +1.27^\circ$; nmr: identical with that of the racemic compound.

The hydrochloride had m.p. 188-189° (absolute ethanol ethyl ether); ir (nujol mull): ν max 2700-2350 (series of bands NH^+) cm^{-1} ; nmr: identical with that of the racemic hydrochloride.

Anal. Calcd. for $C_9H_{19}N \cdot HCl$: C, 60.82; H, 11.34; N, 7.88. Found: C, 60.95; H, 10.99; N, 7.99.

(R)-(-)-3-Ethylpiperidine (II).

3-Ethylpyridine was reduced with Raney nickel (4.5 g.) in dioxane (320 ml.) at 67 atmospheres and heated at 150° for 16 hours. The reduction mixture worked as usual, yielded for distillation (b.p. 152-154°/760 mm) a liquid showing three peaks on glc analysis (110°, 80% of II; 113°, 16% of starting amine; 120°, 4% of I). It was purified through the corresponding *N*-(*p*-nitrobenzoyl)derivative (III), m.p. 47-48° (petroleum ether), b.p. 190°/0.15 mm.

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.24; H, 7.20; N, 10.75.

Compound III (m.p. 44-47°) was hydrolyzed with ethanol 95° and concentrated hydrochloric acid. The mixture after evaporation to dryness, and addition of water was extracted with ethyl ether. The evaporated water layer afforded II hydrochloride as a white solid, m.p. 143-145° (yield 77% from III; 58% from 3-ethylpyridine); after two crystallizations from absolute ethanol-ethyl ether it showed m.p. 146-147° (8); ir (nujol mull): ν max 3180 (bonded NH), 2600-2150 (series of bands NH_2^+), 1620 and 1600 (NH_2^+ deformation) cm^{-1} ; nmr: 0.70 (2H, broad, NH_2^+), 6.44-6.82 (2H, broad, 2 and 6 heterocyclic-H), 7.07-9.20 (12H, superimposed signals area), 9.06 (3H, t, J = 7 Hz, CH_3-CH_2).

Anal. Calcd. for $C_7H_{15}N \cdot HCl$: C, 56.17; H, 10.78; N, 9.36. Found: C, 56.62; H, 10.61; N, 9.64.

From II hydrochloride (m.p. 143-145°) by alkalization with sodium hydroxide and extraction with ethyl ether, the base was obtained as a colorless liquid (8) (II) (b.p. 153-155°/760 mm) that showed only one peak on glc analysis; ir (neat): ν max 3380 (secondary amine), 1650 (NH deformation of secondary amine) cm^{-1} ; nmr: 6.88-7.20 (2H, m, 2 and 6 heterocyclic-H), 7.34-9.30 (13H, superimposed signals area), 9.13 (3H, t, J = 7 Hz, CH_3-CH_2).

Equimolecular amounts of racemic II and (-)-diacetone-2-keto-L-gulonic acid hydrate (DAG) were crystallized 7 times from acetone. The free amine was obtained from the salt as a colorless oil [(R) - (II)], b.p. 152°/760 mm; d = 0.847; ORD (neat): $[\alpha]_{589} -6.09^\circ$, $[\alpha]_{550} -7.19^\circ$, $[\alpha]_{500} -9.02^\circ$, $[\alpha]_{450} -12.02^\circ$, $[\alpha]_{400} -16.4^\circ$, $[\alpha]_{350} -23.13^\circ$, $[\alpha]_{320} -25.40^\circ$ [lit. (6) b.p. 150°; $[\alpha]_D -6.0^\circ$ (d = 0.855)].

The hydrochloride [(R) - (II) hydrochloride] had m.p. 167° (absolute ethanol-ethyl ether); ORD (c 1.66 methanol): $[\alpha]_{589} \pm 0$, $[\alpha]_{550} +0.80^\circ$, $[\alpha]_{500} +1.81^\circ$, $[\alpha]_{450} +2.81^\circ$, $[\alpha]_{400} +4.62^\circ$, $[\alpha]_{350} +7.63^\circ$, $[\alpha]_{300} +10.24^\circ$, $[\alpha]_{290} +12.65^\circ$, $[\alpha]_{270} +18.1^\circ$; nmr: identical with that of the racemic hydrochloride.

Anal. Calcd. for $C_7H_{15}N \cdot HCl$: C, 56.17; H, 10.78; N, 9.36. Found: C, 56.46; H, 11.05; N, 9.37.

The free amine [(S)-(II)] (recovered from the mother liquors of the DAG-salt fractional crystallization and having optical purity = 37%) had b.p. 152°/760 mm; ORD (neat): $[\alpha]_{589} +2.21^\circ$, $[\alpha]_{550} +2.61^\circ$, $[\alpha]_{500} +3.30^\circ$, $[\alpha]_{450} +4.35^\circ$, $[\alpha]_{400} +6.10^\circ$, $[\alpha]_{350} +9.38^\circ$, $[\alpha]_{320} +13.02^\circ$. The hydrochloride [(S)-(II)-HCl] had m.p. 141-142° (absolute ethanol-ethyl ether); ir and nmr spectra identical with those of the racemic hydrochloride.

Anal. Calcd. for $C_7H_{15}N \cdot HCl$: C, 56.17; H, 10.78; N, 9.36. Found: C, 56.61; H, 10.79; N, 9.23.

1-[2'-Pyridyl *N'*-oxide]-3-ethylpiperidine.

N-[2-pyridyl *N*-oxide] derivative was obtained reacting the hydrochloride of (R)-(-)-3-ethylpiperidine (0.48 g.) with 2-fluoropyridine *N*-oxide as usual (3). The dark oily residue (yield 91%) was distilled to give a pale yellow oil (0.19 g.; 29% yield; b.p. 100-102° (0.8 mm); ORD (c 1.93 methanol): $[\alpha]_{589} -35.9^\circ$, $[\alpha]_{550} -41.03^\circ$, $[\alpha]_{500} -71.79^\circ$, $[\alpha]_{400} -110.26^\circ$, $[\alpha]_{365} -161.54^\circ$; CD: λ max (ν) = 350 (± 0), 312 (-780), 275 (± 0), 266 (-275), 252 (+2202), 232 nm (-1835); uv: λ max (ϵ) = 312 (3700), 254 nm (16600); nmr: 1.80-1.98 (1H, m, 6'-pyridyl-H), 2.54-2.82 (1H, m, 4'-pyridyl-H), 3.34-3.66 (2H, m, 3',5'-pyridyl-H), 5.74-6.04 (2H, m, α -piperidine-H), 7.08-9.26 (12H, superimposed signals area), 7.08-7.72 (2H, m, α -piperidine-H), 9.08 (3H, t, J = 7 Hz, CH_3-CH_2).

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 70.27; H, 8.68; N, 14.02.

(S)(+)-N-Benzyl-3-ethylpiperidine (IIa).

(S)(+)-3-Ethylpiperidine (II) (7.5 g.; optical purity 37%) was refluxed for 4 hours in benzene with equimolecular amounts of benzyl chloride and triethylamine and gave a colorless oil, b.p. 85°/4 mm, yield 82%, $[\alpha]_D^{25} +1.7^\circ$ (neat), $d^{25} = 0.929$; ORD (c 11.62 methanol): $[\alpha]_{589} +1.1^\circ$, $[\alpha]_{550} +1.2^\circ$, $[\alpha]_{500} +1.4^\circ$, $[\alpha]_{450} +1.7^\circ$, $[\alpha]_{400} +1.9^\circ$, $[\alpha]_{350} +1.8^\circ$, $[\alpha]_{330} +1.5^\circ$; nmr: 2.67-2.96 (5H, m, aromatic-H), $\nu_A = 6.55$, $\nu_B = 6.62$ (2H, q, $J_{AB} = 13.1$ Hz, N-CH₂-C₆H₅), 7.14-7.42 (2H, m, 2 and 6 heterocyclic-H), 8.04-9.32 (12H, superimposed signals area), 9.17 (3H, t, $J = 7$ Hz, CH₃-CH₂-).

Anal. Calcd. for C₁₄H₂₁N: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.48; H, 10.11; N, 7.19.

The hydrochloride [(S)(+)(IIa)hydrochloride], m.p. 146-147° (from absolute ethanol-ethyl ether); ir (nujol mull): ν max 2700, 2600 and 2480 (large salt band) cm⁻¹; nmr: -1.57 (1H, broad, NH⁺), 2.22-2.42 and 2.55-2.80 (2 + 3H, m, aromatic-H), 5.75 (2H, d, $J = 6$ Hz, C₆H₅-CH₂-NH⁺), 6.56-6.88 (2H, m, 2 and 6 heterocyclic-H), 6.94-9.34 (12H, superimposed signals area), 9.14 (3H, t, $J = 7$ Hz, CH₃-CH₂-).

Anal. Calcd. for C₁₄H₂₁N·HCl: C, 70.12; H, 9.25; N, 5.84. Found: C, 69.94; H, 9.35; N, 5.80.

(R)(+)-1,3-Diethylpiperidine 2,6-Dione (IV).

(R)(-)-1,3-Diethylpiperidine (I) (3.05 g.) having $[\alpha]_D -0.14^\circ$ was oxidized as described (1). The imide (IV) was obtained (yield 64%) by distillation of the crude reaction mixture, b.p. 87-88°/1 mm; optical rotation at 589 nm + 0.57° (neat); ir (neat): ν max 1730 and 1675 (C=O imide) cm⁻¹; nmr: 6.22 (2H, q, $J = 7$ Hz, N-CH₂-CH₃), 7.12-9.12 (13H, superimposed signals area), 8.89 (3H, t, $J = 7$ Hz, N-CH₂-CH₃), 8.98 (3H, t, $J = 7$ Hz, 3-CH₂-CH₃).

Anal. Calcd. for C₉H₁₅NO₂: C, 63.87; H, 8.93; N, 8.28. Found: C, 63.66; H, 8.61; N, 8.16.

The imide [(R)(+)(IV)] (1.54 g.) by hydrolysis (1) with concentrated hydrochloric acid gave the ethylamine hydrochloride (100%; m.p. 105-108° from ethanol-ethyl ether) and (R)(-)-2-ethylglutaric acid (VI) (80%) with an optical purity of 12%, m.p. 50-51° (from ligroin-benzene); ORD (c 5.17 absolute ethanol): $[\alpha]_{589} -1.74^\circ$, $[\alpha]_{550} -1.74^\circ$, $[\alpha]_{500} -1.93^\circ$, $[\alpha]_{450} -2.51^\circ$, $[\alpha]_{400} -3.10^\circ$, $[\alpha]_{350} -3.87^\circ$, $[\alpha]_{330} -4.06^\circ$ [lit (9) racemic compound m.p. 60-61°; d-isomer m.p. 42°, $[\alpha]_D +14^\circ$ (absolute ethanol)]; ir (nujol mull): ν max 1700 (large band) cm⁻¹; nmr: -1.85 (2H, s, COOH), 7.48-7.80 (3H, m, CH-COOH and CH₂-COOH), 7.96-8.70 (4H, m, CH₃-CH₂- and -CH₂-CH-COOH), 9.03 (3H, t, $J = 7$ Hz, CH₃-CH₂-).

Anal. Calcd. for C₇H₁₂O₄: C, 52.49; H, 7.55. Found: C,

52.86; H, 7.64.

(S)(-)-N-Benzyl-3-ethylpiperidine 2,6-Dione (V).

(S)(+)-N-Benzyl-3-ethylpiperidine (IIa) (4 g.) having $[\alpha]_D +1.7^\circ$ (neat) was oxidized as described (1). The imide (V) was obtained (yield 60%) by distillation of the crude reaction mixture, b.p. 128°/0.2 mm: $[\alpha]_D -9.1^\circ$ (neat), $d = 1.124$; ORD (c 4.64 methanol): $[\alpha]_{589} -4.5^\circ$, $[\alpha]_{550} -5.5^\circ$, $[\alpha]_{500} -6.9^\circ$, $[\alpha]_{450} -8.9^\circ$, $[\alpha]_{400} -11.9^\circ$, $[\alpha]_{350} -16.8^\circ$, $[\alpha]_{335} -18.3^\circ$; ir (neat): ν max 1725 and 1670 (C=O imide) cm⁻¹; nmr: 2.62-2.94 (5H, m, aromatic-H), 5.10 (2H, s, C₆H₅-CH₂-N(CO)₂), 7.10-9.15 (10H, superimposed signals area), 9.05 (3H, t, $J = 7$ Hz, CH₃-CH₂-).

Anal. Calcd. for C₁₄H₁₇NO₂: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.63; H, 7.60; N, 6.15.

The imide [(S)(-)(V)] (1.3 g.) by hydrolysis (1) performed as described above, gave (S)(+)-2-ethylglutaric acid (VI) (90%) with an optical purity of 30.7%: ORD (c 6.92 absolute ethanol): $[\alpha]_{589} +4.3^\circ$, $[\alpha]_{550} +5.1^\circ$, $[\alpha]_{500} +6.0^\circ$, $[\alpha]_{450} +7.4^\circ$, $[\alpha]_{400} +9.5^\circ$, $[\alpha]_{350} +12.3^\circ$, $[\alpha]_{330} +13.7^\circ$, $[\alpha]_{300} +16.6^\circ$; m.p. ir and nmr spectra are identical with those above described for (R)(-)-2-ethylglutaric acid.

Anal. Calcd. for C₇H₁₂O₄: C, 52.49; H, 7.55. Found: C, 52.81; H, 7.58.

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