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# STEREOCHEMISTRY OF AMINO-CARBONYL COMPOUNDS—VII[a,b]

## ABSOLUTE AND RELATIVE CONFIGURATION OF SOME DIASTEREOMERIC 1,3-AMINO-ALCOHOLS.

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**Abstract**—The absolute configuration of (+)-4-dimethylamino-2,4-diphenyl-butan-2-ol and (+)-4-piperidino-2-phenyl-pentan-2-ol, the predominant diastereomers obtained by reaction of (+)-3-dimethylamino-1,3-diphenyl-propan-1-one with MeLi and (+)-3-piperidino-1-phenyl-butan-1-one with MeMgI, respectively, was determined by chemical correlation. The relative configurations of the diastereomers afforded by such reactions were thus assigned.

In continuation of earlier work[3-5] on asymmetric induction in LAH reductions and Grignard reactions of various amino-ketones, an analogous research with organometallic reagents was jointly undertaken on β-asymmetric β-amino-ketones.[6]

The present paper deals with the configurational assignment of the amino-alcohols **4** and **7** obtained by reaction of the amino-ketones **3** and **6** with organometals, respectively.

This knowledge was required in order to establish, by physical methods, the relative configurations of a series of compounds to be described in a forthcoming communication,[6] so as to define the predominant direction of attack by the entering group.

The principle of the configurational assignment, already applied to other amino-alcohols,[2,7] starts with optically active compounds and establishes the absolute configuration of each asymmetric center and thereby, their relative configuration.

Scheme 1 shows the chemical correlation by which the configuration of (+)-4-dimethylamino-2,4-diphenyl-butan-2-ol **4** (the predominant diastereomer obtained from (+)-3-dimethylamino-1,3-diphenyl-propan-1-one **3** and MeLi) was proved to be 2*S*,4*S*.

The known[3] (±)-*erythro*-3-dimethylamino-1,3-diphenyl-propan-1-ol **1**, after resolution to the (+)-enantiomer, was submitted to the Horeau method[8] in order to determine the configuration at C-1. This configuration proved to be *R* and therefore (+)-*erythro* **2** is 1*R*,3*S*.

Oxidation of the amino-alcohol (+)-1*R*,3*S* **2** to the corresponding amino-ketone allowed the configurational assignment of (+)-**3** and, therefore, of C-4 in (+)-**4**.

The C-2 configuration in this (+)-amino-alcohol **4** was determined by hydrogenolysis of the enantiomer (−)-**4** to the known[2] S(+)-1,3-diphenyl-butane **5**. Since this reaction occurs with retention of configuration,[9] the assignment of *S* configuration to the C-2 in (+)-**4** is substantiated.

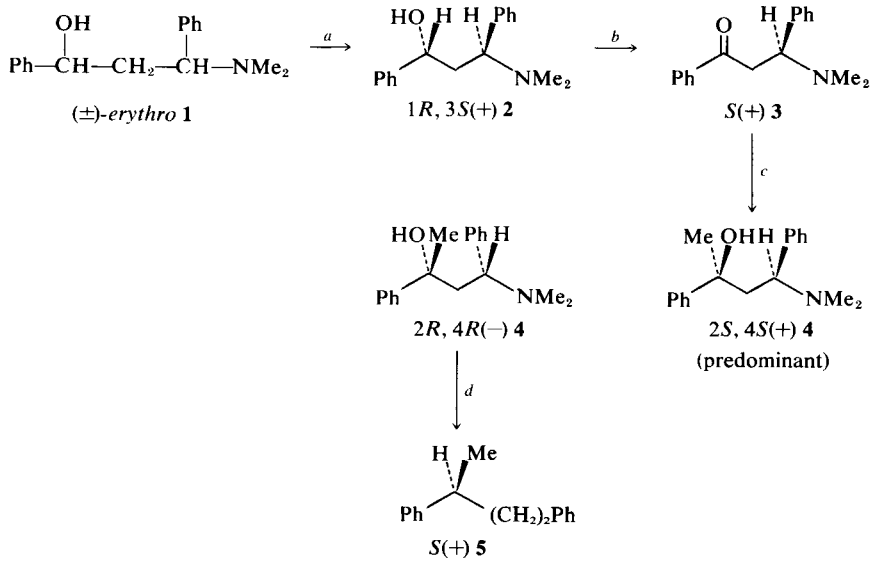
The absolute configuration of (+)-4-piperidino-2-phenyl-pentan-2-ol **7** (the predominant diastereomer afforded by the corresponding *S*(+)-3-piperidino-1-phenyl-butan-1-one **6** and MeMgI) proved to be 2*R*,4*S* by the chemical correlation shown in Scheme 2.

The configuration of the asymmetric center C-4 is *S*, the (+)-amino-alcohol **7** being obtained from the known[1] *S*(+)-amino-ketone **6**.

The configuration at C-2 was assigned by correlating (+)-**7**, obtained with higher optical purity by resolution of the racemic compound, with the known[10] *S*(+)-2-phenyl-pentane **12**. In this case the above (Scheme 1) method of correlation by hydrogenolysis adopted for the benzylamino group in (−)-**4** is not suitable for the elimination of the amino group in (+)-**7** to the corresponding known phenyl-alkane **12**. Elimination of the piperidino group was therefore performed by Hoffman degradation of the corresponding (+)-2-methoxy-2-phenyl-4-piperidino-pentane-methiodide **8**, followed by hydrogenation of the resulting mixture of methoxy-alkenes **9**. The 2-phenyl-2-

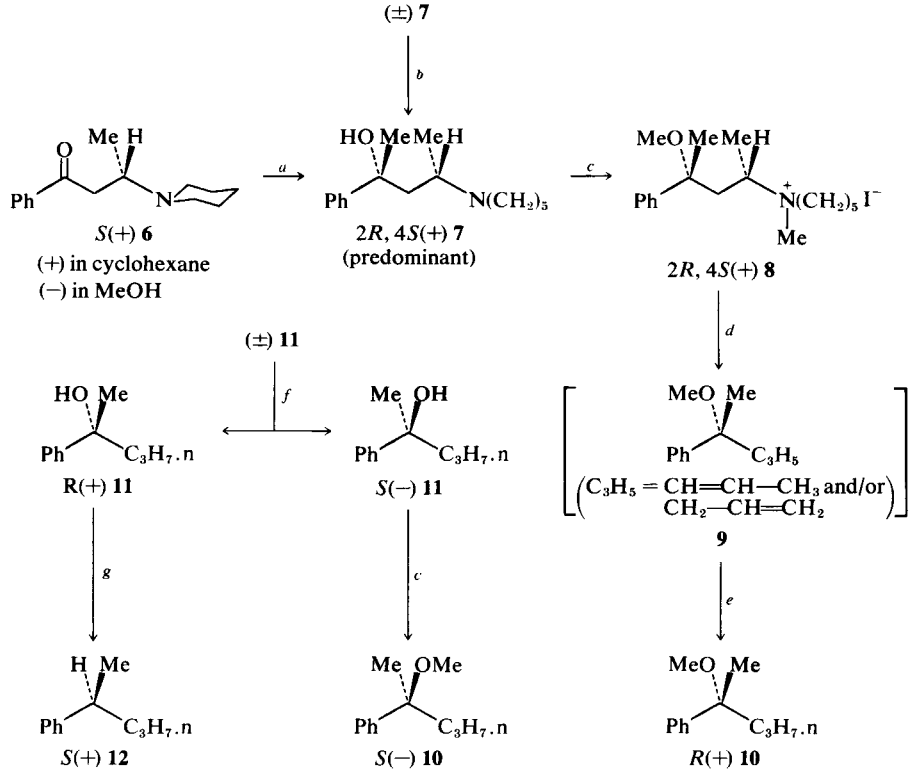
[a] The preceding Note VI, Ref 1, appeared under the title "Stereochemistry of Mannich bases".

[b] Note V of the series *Induction* 1-3 *asymetrique*; Note IV, see Ref 2.




SCHEME 1

[a](−)-Camphoric acid. [b]$CrO_3$, acetone. [c]MeLi, $Et_2O$. [d]Ni-Raney (retention).




SCHEME 2

[a]MeMgI, $Et_2O$. [b](−)-Dibenzoyltartaric acid. [c]K MeI. [d]$Ag_2O$, heat. [e]$H_2$, Pd/C. [f]K, phthalic anhydride/brucine/LAH, $Et_2O$. [g]Ni-Raney (retention).

methoxy-pentane **10** was finally correlated with *S*(+)-**12** through the 2-phenyl-pentan-2-ols (+)- and (−)-**11**. As the configuration of (+)-**11** was shown to be *R* by hydrogenolysis with retention[9] to *S*(+)-**12**, (−)-2-phenyl-pentan-2-ol **11** has therefore configuration *S*. Methylation of *S*(−)-**11** gave *S*(−)-**10**, enantiomer with (+)-**10** which was derived from the (+)-amino-alcohol **7**. The configuration *R* at C-2 of (+)-4-piperidino-2-phenyl-pentan-2-ol **7** is thus assigned.

## EXPERIMENTAL

IR spectra were measured with a Perkin-Elmer Infracord 337 or with a Beckmann IR 5 spectrophotometer. Optical rotations were determined with a Perkin-Elmer 141 micropolarimeter or a Bendix NPL 143 C polarimeter. M.ps were determined with a Kofler apparatus or a Perkin-Elmer DSC 1 microcalorimeter. NMR spectra were measured, at 60 MHz, with a Perkin-Elmer R 12 or a Jeol C-60 HL and, at 100 MHz, with a Varian HA 100 spectrometer (chemical shifts are given in δ (ppm) using TMS as internal reference). Elemental analyses were performed on a F & M Mod. 185 CHN Analyzer, or by the "Service Central de Microanalyse du C.N.R.S."; the elemental formula in the text indicates that the analyses resulted within the 0.2% of the calculated value.

(±)-3-*Dimethylamino*-1,3-*diphenyl*-*propan*-1-*one* **3** *and* (±)-3-*piperidino*-1-*phenyl*-*butan*-1-*one* **6**. Racemic **3** was prepared as reported.[3] Racemic **6**, already described,[11] was better prepared by reaction between phenyl-propenyl-ketone and piperidine (in equimolar ratio) for several hr at room temp. The mixture was treated with cold dil HCl and washed with $Et_2O$. The product was obtained as a crystalline solid (75% yield) by making the highly diluted and ice-cooled acidic solution alkaline, m.p. 37–38° (from light petroleum).

(±)-4-*Dimethylamino*-2,4-*diphenyl*-*butan*-2-*ol* **4**. The amino-ketone (±)-**3** (0·01 mol) in $Et_2O$ (20 ml) was slowly added, at room temp and under $N_2$, to a stirred ethereal soln (40 ml) of MeLi, obtained from MeI (0·03 mol) and Li (0·066 mol) (the amount of metal was in excess in order to avoid quaternization of the amine by the halide). The mixture was then refluxed for 1 hr and, after cooling, poured into sat $NH_4Cl$ aq and ether extracted. After elimination of neutral by-products, the crude mixture of diastereomeric aminoalcohols (55% yield) was isolated.

Pure (±)-**4** was in part obtained by direct fractional crystallization of the crude mixture from n-hexane and, in part, as oxalate from the mother liquors. The total yield was 73% (based on the diastereomeric mixture); oxalate, m.p. 119° (from AcOEt followed by acetone); free base, m.p. 80° from n-hexane, after vacuum drying. $C_{18}H_{23}NO$: NMR (solv. $CDCl_3$): 1·50(s), $CH_3$—C—O; 2·02(s), $CH_3$—N; 3·33(m), H—C—N.

(±)-4-*Piperidino*-2-*phenyl*-*pentan*-2-*ol* **7**. The reaction with amino-ketone (±)-**6** was performed with MeMgI as described for (±)-**3** (reaction time, 2·5 hr).

The unreacted amino-ketone was eliminated from the mixture by the method described[3] or by reaction with hydroxylamine to give the corresponding oxime, then extracted with 10% NaOH aq. From the so obtained mixture of amino-alcohols (70% yield) (±)-**7** was isolated and purified as the hydrochloride. The salt, washed 3 times with boiling methyl-ethyl ketone, contained less than 1% (by GLC) of its diastereomer (60% yield, based on the diastereomeric mixture), m.p. 239–241° (from AcOEt/EtOH). $C_{16}H_{26}NOCl$: NMR (solv. $CS_2$): 1·30(s), $CH_3$—C—O; 0·75(d), $CH_3$—C—N.

*Absolute configuration of* 2S,4S(+)-4-*dimethylamino*-2,4-*diphenyl*-*butan*-2-*ol* **4** (*Scheme* 1).

1S,3R(−)- *and* 1R,3S(+)-3-*dimethylamino*-1,3-*diphenyl*-*propan*-1-*ols* **2**. (±)-*Erythro*[3] **1**[3] (11·8 g) and (+)-camphoric acid (9·25 g) in MeOH/$H_2O$ 2:1 (120 ml) gave, after 30 min at −20°, the corresponding salt (14·12 g), which was crystallized from the same solvent (90 ml). The camphorate (3·73 g) obtained afforded (−)-**2** (2 g), $[\alpha]_J^{28} = -28·3$ ($c = 2·8$, $CCl_4$), m.p. 83–88°.

The aminoalcohol recovered from the mother liquor, $[\alpha]_J^{27} = +5·5$ ($c = 2$, $CCl_4$), was treated with (−)-camphoric acid and afforded, after crystallization and hydrolysis, the enantiomer (+)-**2**, $[\alpha]_J^{27} = +31·5$ ($c = 1·4$, $CCl_4$). The optical purity (by calorimetric methods) was 97%.

This aminoalcohol, treated according to the Horeau method,[8] gave (+)-phenyl-butyric acid (23% optical yield).

S(+)-3-*Dimethylamino*-3-*phenyl*-*propan*-11-*one* **3**. To the (+)-amino-alcohol **2** (90% optical purity; 1·014 g), in acetone (8·5 ml), Djerassi reactive[12] (1·7 ml) was added with cooling. The mixture was kept 20 min at room temp, a few drops of EtOH were added and the ppt which formed after 5 min was filtered off and washed with acetone (8 ml). The filtrate was treated with ice-cooled dil $NH_4OH$ and ether extracted. The ethereal soln, washed with cold water and dried, gave, after vacuum evaporation in the cold, the (+)-amino-ketone **3** (0·969 g), which spontaneously solidified, m.p. 61° (from n-hexane), $[\alpha]_J^{27} = +4·85$ ($c = 1·3$, $CCl_4$).

2R,4R(−)-4-*Dimethylamino*-2,4-*diphenyl*-*butan*-2-*ol* **4**. Racemic **4** (5 g) was treated with (+)-tartaric acid (2·8 g), giving the corresponding salt (1·19 g), m.p. 177°(dec) (after two crystallizations from acetone followed by acetone/MeOH). Hydrolysis of the tartrate gave 0·92 g of (−)-amino-alcohol **4**, m.p. 90° (from n-hexane); $[\alpha]_D^{26} = -156$, $[\alpha]_J^{26} = -163·5$ ($c = 1·5$, $CCl_4$), $[\alpha]_J^{26} = -131$ ($c = 1·8$, MeOH), optical purity, 98·6% (by calorimetry).

2S,4S(+)-4-*Dimethylamino*-2, 4-*diphenyl*-*butan*-2-*ol* **4**. The crystalline *S*(+)-amino-ketone **3** (0·869 g), added in small portions to an ethereal soln of MeLi (Li, 0·19 g; MeI, 0·75 ml; $Et_2O$, 25 ml), gave a crude diastereomeric mixture (0·686 g, 74%) which was crystallized from n-hexane, giving (+)-**4** (0·125 g), m.p. 91°, $[\alpha]_J^{27} = +160$ ($c = 1·1$, $CCl_4$), optical purity 98% (by calorimetry).

S(+)-2,4-*Diphenyl*-*butane* **5**. The enantiomer (−)-**4** (optical purity 95%; 0·543 g) in EtOH (60 ml) was stirred overnight with Ni-Raney (from 40 g of Ni/Al alloy). After filtration and washing with EtOH and $Et_2O$, the soln was evaporated to dryness, the residue redissolved in $Et_2O$, washed with $H_2O$ and dried. After evaporation of the solvent, the crude product (0·368 g, 87%) was distilled in a bulb tube, b.p. (0·5 mm Hg) 90–100°, decoloured on $Al_2O_3$ (10 g) by elution with hexane and submitted again to distillation (bulb tube), b.p. (1 mm Hg) 110–120°; purity checked by GLC (Aerograph 200) column (l = 3m) SE 30 10% on Chromosorb W, t = 220°. $[\alpha]_J^{26} = +14·7$, $[\alpha]_D^{26} = +14·25$ ($c = 2·1$, $CHCl_3$).

*Absolute configuration of* 2R,4S(+)-4-*piperidino*-2-*phenyl*-*pentan*-2-*ol* **7** (*Scheme* 2).

2R,4S(+)-4-*Piperidino*-2-*phenyl*-*pentan*-2-*ol* **7** *by Grignard reaction on* S(+)-**6**. The reaction was carried out on the known[1] amino-ketone *S*(+)-**6** (4·2 g), $[\alpha]_D^{25} = +1·5$

(c = 2·5, cyclohexane, −8 (c = 1, MeOH), −12 (c = 1, MeOH/HCl).

The mixture of diastereomeric amino-alcohol hydrochlorides (2·65 g, 52%), $[\alpha]_D^{25} = +10·6$ (c = 2, MeOH), submitted to the treatment with methyl-ethyl ketone adopted for the racemic compound, afforded 1·55 g (59% yield, based on the diastereomeric mixture) of (+)-**7** hydrochloride, contaminated with less than 1% (by GLC) of diastereomeric impurity; GLC (C. Erba Fractovap GV): column (1 = 2 m) Versamid 10% on Chromosorb W, t = 200°, m.p. 220–222°, $[\alpha]_D^{25} = +15$ (c = 2, MeOH).

2R,4S(+)-4-*Piperidino*-2-*phenyl-pentan*-2-*ol* **7** *by optical resolution.* A soln of (±)-**7** (29·6 g, 0·12 mol) and (−)-dibenzoyltartaric acid (22·5 g, 0·06 mol) in acetone (150 ml), gave after a few hr 22·5 g of the corresponding salt, m.p. 147°(dec), which was suspended in EtOH (160 ml), refluxed for a few min and then cooled and filtered. The treatment repeated twice finally gave 15 g of product with a molar composition aminoalcohol/acid = 2:1, m.p. 171°(dec) from EtOH. Anal. $C_{50}H_{64}N_2O_{10}$.

Hydrolysis of the salt afforded 8·8 g (29·5%) of (+)-**7**, $[\alpha]_D^{25} = +23$ (c = 1, MeOH), +39 (c = 1, MeOH/HCl).

2R, 4S(+)-4-*Piperidino*-2-*phenyl*-2-*methoxy-pentane methiodide* **8**. The (+)-amino-alcohol **7** obtained from the above resolution (8·8 g, 0·036 mol) was added to a suspension of K (1·4 g, 0·036 mol) in toluene (120 ml). The mixture was refluxed 20 hr, cooled, treated with a large excess of MeI (10 ml) and kept at room temp for 1 hr with occasional stirring. A further amount of MeI (10 ml) was then added and the mixture left standing for 2 more hr. The soln was decanted and the soild material, triturated with AcOEt and filtered, was then extracted with $CH_2Cl_2$ (2× 40 ml) and the undissolved KI removed. The filtrate was finally evaporated to dryness and gave 11·2 g (78%) of (+)-methiodide **8**, m.p. 138–140° (from acetone), $[\alpha]_D^{25} = +52·5$ (c = 1·7, MeOH). Anal. $C_{18}H_{30}NOI$.

R(+)-2-*Phenyl*-2-*methoxy-pentane* **10**. (+)-Methiodide **8** (11·0 g) was submitted to Hoffman degradation following the procedure previously described[7] for a similar compound. After washing with dil HCl in order to eliminate any aminic material, a maxture of alkenes **9** (3·5 g, 70%) was obtained, $[\alpha]_D^{25} = -7·4$ (neat, l = 0·1), which was submitted without any further treatment to hydrogenation.

The alkenes **9** (3·5 g), in 95% EtOH (90 ml), were hydrogenated at room temp on 5% Pd/C (1 g). The reaction was continued until the amount of consumed hydrogen was 1·5 times the calculated. The crude product, containing a large amount of 2-phenyl-pentane (by NMR), was submitted to repeated fractional distillation giving 1·7 g (48%) of R(+)-**10**, b.p. (20 mm Hg) 107–112°, $[\alpha]_D^{25} = +25$ (neat). IR and NMR spectra identical with those of the (−)-enantiomer (see below).

R(+)- *and* S(−)-2-*Phenyl-pentan*-2-*ols* **11**. (±) **11**, b.p. (2 mm Hg) 84–86°, Lit.[13] 112–113° (14 mm Hg), was allowed to react, as a potassium alcoholate, with phthalic anhydride in benzene, as described[14] for a similar compound. The product was a very viscous oil (48–56% yield) which was submitted without any further treatment to optical resolution with brucine.

(±)-2-Phenyl-pentan-2-ol monophthalate (31·3 g) and brucine (39·4 g) in 95% EtOH (140 ml) gave the corresponding salt (30 g), m.p. 115–120°. After two crystallizations from EtOH, the m.p. 122–124° remained unchanged after further crystallization. Anal. $C_{42}H_{46}N_2O_8$.

The monophthalate obtained from the crystallized brucine salt was treated with LAH according to the method described[14] for *R*(+)-2-phenyl-butan-2-ol, giving (+)-**11** in 78% yield (based on the phthalate), b.p.(1·4 mm Hg) 77–78°, $[\alpha]_D^{25} = +9·6$ (neat), +5·8 (c = 4·5, MeOH). Anal. $C_{11}H_{16}O$.

Enantiomer (−)-**11** was obtained in the same manner from the mother liquors of the brucine salt, b.p.(1·3 mm Hg) 72·5–75°, $[\alpha]_D^{25} = -4·8$ (neat), −4·0 (c = 5·5, MeOH). Anal. $C_{11}H_{16}O$.

S(+)-2-*Phenyl-pentane* **12**. Ni-Raney W2[15] (30 g) was suspended in a soln of *R*(+)-**11** (4·7 g) in abs EtOH (100 ml) and the mixture was refluxed for 5 hr. The soln was then filtered, diluted with $H_2O$ and extracted with light petroleum. After drying and evaporation of the solvent, an oil was obtained which still contained an appreciable amount of starting material (by IR). The mixture was then purified on $Al_2O_3$ (10 g) by elution with light petroleum and the crude product (52% yield) distilled, b.p. (19 mm Hg) 83–85°, $[\alpha]_D^{26} = +10·7$ (neat), +12·6 (c = 5, MeOH). Anal. $C_{11}H_{16}$. NMR (neat): 7·1(m) aromatic protons; 2·63(m) H—2; 1·78–1·02(m) methylenic protons; 1·18(d) $CH_3$—1; 0·8(m) $CH_3$—5.

*R*(−)-2-Phenyl-pentane previously described[10] showed $[\alpha]_D^{25} = -15·0$ (neat) and b.p.(760 mm Hg) 193°.

S(−)-2-*Phenyl*-2-*methoxy*-*pentane* **10**. *S*(−)-**11** (3·8 g, 0·023 mol) in benzene (10 ml) was added during 30 min with stirring, to a suspension of K (0·9 g, 0·023 mol) in benzene (25 ml) at 60–70°. The mixture was stirred with heating for 4 hr, then cooled and an excess of MeI (5 ml) added. After 12 hr at room temp the suspension was washed with $H_2O$ and dried. Elimination of the solvent under reduced press afforded an oil which was purified on $Al_2O_3$ (10 g) by elution with light petroleum. The crude methyl-ether **10** (70% yield) was then distilled, b.p.(16 mm Hg) 105–108°, $[\alpha]_D^{25} = -15·3$ (neat), −14·3 (c = 5·5, MeOH). Anal. $C_{12}H_{18}O$. NMR ($CS_2$): 7·25(m) aromatic protons; 2·95 (s) $OCH_3$; 1·9–1·0(m) methylenic protons; 1·42(s) $CH_3$–1; 0·85(m) $CH_3$–5.

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