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STEREOCHEMISTRY OF MANNICH BASES—III*

THE ABSOLUTE CONFIGURATIONS AND PREFERRED CONFORMATIONS OF 1-PHENYL-2-METHYL-3-DIMETHYLAMINO-PROPAN-1-OL AND OF DIASTEREOMERIC 1-PHENYL-2-METHYL-3-PIPERIDINO-PROPAN-1-OLS

L. ANGIOLINI and G. GOTTARELLI†
Istituto di Chimica degli Intermedi della Università, Bologna, Italy

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Abstract—By means of the Horeau method, ORD, IR and NMR spectra the 1*R*, 2*S* absolute configuration is assigned to (+)-1-phenyl-2-methyl-3-dimethylamino-propan-1-ol (III-α form) and the 1*R*, 2*S* and 1*S*, 2*S* absolute configurations are assigned to (+)-1-phenyl-2-methyl-3-piperidino-propan-1-ols (IV-α form) and (IV-β form) respectively.

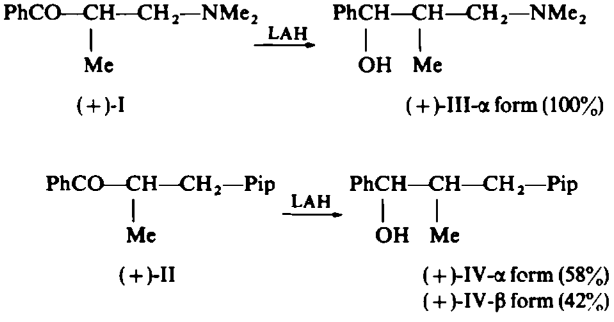
On the basis of IR and NMR spectra, preferred conformations of the above amino-alcohols are deduced.

IN THE course of our studies on LAH stereospecific reduction of β-amino-ketones (Mannich bases) bearing an asymmetric center in the α position with respect to the CO group,[2] we have made configurational assignments of the amino alcohols so obtained. Such an assignment was necessary in order to elucidate the steric course of the reaction.

In the present work the absolute configurations are assigned by means of independent methods which lead to results in perfect agreement.

The absolute configurations of (+)-α-methyl-β-dimethylamino-propiophenone (I) and of (+)-α-methyl-β-piperidino-propiophenone (II) were known to be *S* from preceding work.[3] Reduction by ethereal LAH of *S* (+)-I affords only one diastereomer, and reduction of *S*(+)-II affords both diastereomeric amino-alcohols (Chart 1):

CHART 1



$$\mathrm{PhCO{-}\underset{\underset{Me}{|}}{CH}{-}CH_2{-}NMe_2} \xrightarrow{\mathrm{LAH}} \mathrm{Ph\underset{\underset{OH}{|}}{CH}{-}\underset{\underset{Me}{|}}{CH}{-}CH_2{-}NMe_2}$$

(+)-I → (+)-III-α form (100%)

$$\mathrm{PhCO{-}\underset{\underset{Me}{|}}{CH}{-}CH_2{-}Pip} \xrightarrow{\mathrm{LAH}} \mathrm{Ph\underset{\underset{OH}{|}}{CH}{-}\underset{\underset{Me}{|}}{CH}{-}CH_2{-}Pip}$$

(+)-II → (+)-IV-α form (58%)
(+)-IV-β form (42%)

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* Part II, see Ref. 1.

† Present address: School of Chemical Sciences, University of East Anglia, Norwich.

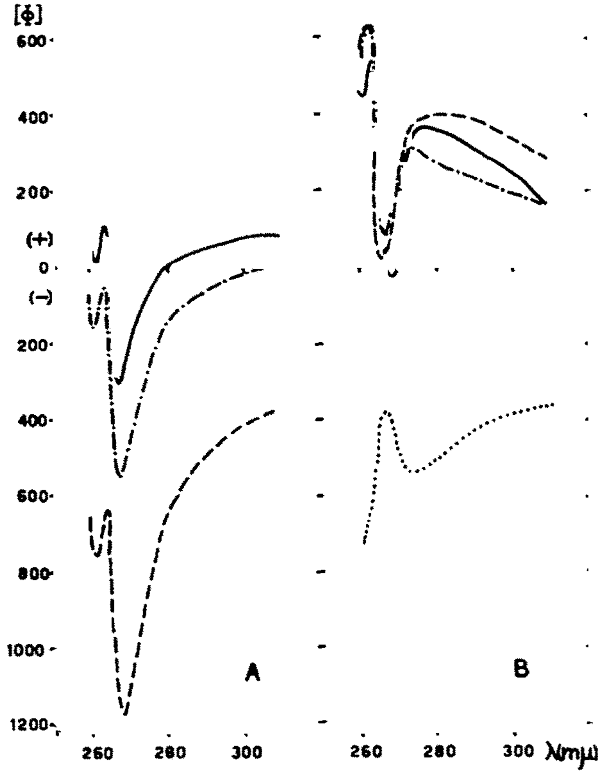


FIG. 1 ORD Spectra of III-α, IV-α and IV-β. A: III-α hydrochloride in MeOH (———); free base in MeOH (—·—·—·—) and in Cyclohexane (— — — —). B: IV-α hydrochloride in MeOH (————); free base in MeOH (—·—·—·—) and Cyclohexane (— — — —). IV-β hydrochloride in MeOH (·········).

The absolute configurations at C-2 in (+)-1-phenyl-2-methyl-3-dimethylamino-propan-1-ol (III-α form) and in (+)-1-phenyl-2-methyl-3-piperidino-propan-1-ols (IV-α and β forms) are therefore *S*.

The absolute configuration at C-1 in (+)-III-α and (+)-IV-α was found to be *R* by means of the Horeau method, using racemic α-phenyl-butyric anhydride.[4] In this assignment we have considered the Ph group as the largest substituent according to Horeau's work on the phenyl-alkyl-carbinols series.[4c]

Further evidence of the absolute configuration at C-1 in (+)-III-α, (+)-IV-α and (+)-IV-β was obtained from ORD correlations (Fig. 1).

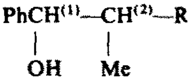
The aromatic ^1L_B transition is optically active and it is possible to relate the sign of the multiple Cotton effect to the absolute configuration of the centre bonded with the aromatic chromophore.[5] In particular, it is possible to relate the negative Cotton effect of (+)-III-α and (+)-IV-α and the positive Cotton effect of (−)-IV-β (hydrochloride) to the absolute configuration *R* and *S*, respectively, at the asymmetric centre C-1.

Changes of solvent as well as protonation of the amine nitrogen seem to affect very little both intensity and sign of Cotton effects, in agreement with other work on the ^1L_B transition in analogous aromatic systems.[5]

The IR spectra in CCl_4 of III-α, IV-α and IV-β indicate that such amino alcohols exist in intramolecularly hydrogen bonded conformations (Chart 2). In fact, even at high dilutions ($\sim 3{\cdot}10^{-3}$ M) no variation in position and intensity of bonded OH stretching (at 3240 ± 10 cm^{-1} for III-α, 3230 ± 10 cm^{-1} for IV-α and 3185 ± 10 cm^{-1} for IV-β) is observed.*

This conclusion rules out every conformation without intramolecular H-bonding and allows an easier analysis of the NMR spectra (Table 1).

TABLE 1. $H^{(1)}$ CHEMICAL SHIFTS AND $J_{H^{(1)}H^{(2)}}$ COUPLING CONSTANTS IN

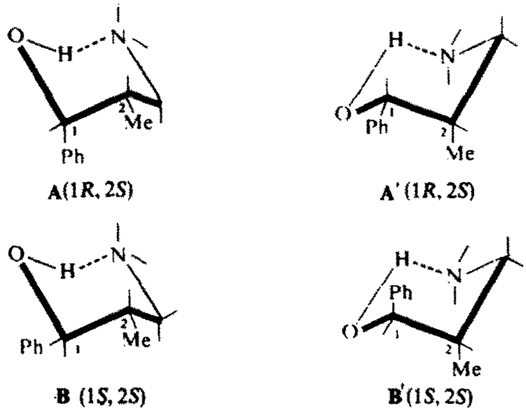

$$\underset{OH}{PhCH^{(1)}}—\underset{Me}{CH^{(2)}}—R$$

Comp.	R	$\delta_{H^{(1)}}$†	$J_{H^{(1)}H^{(2)}}$ (c/s)	Solv.
(+)-IV-α	CH_2Pip	4·80	3·5	$CDCl_3$
(+)-IV-α	CH_2Pip	4·66	3·0	CCl_4
(+)-IV-β	CH_2Pip	4·36	9·0	$CDCl_3$
(+)-IV-β	CH_2Pip	4·22	8·5	CCl_4
(+)-III-α	CH_2NMe_2	4·70	2·5	CCl_4

† In ppm from TMS internal standard.

Ignoring the higher energy conformations we may consider for the diastereomeric amino-alcohols the following "chair" conformations (Chart 2):

CHART 2



A(1*R*, 2*S*) A′(1*R*, 2*S*)

B (1*S*, 2*S*) B′(1*S*, 2*S*)

It seems reasonable to consider conformer **A** to be more stable than **A′**, the former having less severe steric interactions due to the "ring" substituents. 1–3 diaxial interaction between Me and the axial N-substituent group in **A′** is, in fact, the most destabilizing of the **A**–**A′** system.[6] A larger difference in stability should exist in system

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* We have determined IR spectra using the following molar concentrations and cell thicknesses in mm (in parenthesis): III-α, 0·10 (0·1), 0·01 (1·0), 0·0027 (3·0); IV-α, 0·10 (0·1), 0·01 (1·0), 0·0032 (3·0); IV-β, 0·11 (0·1), 0·01 (1·0), 0·0035 (3·0).

B–**B′**, since **B** not only lacks the 1–3 diaxial interaction present in **B′** but also has both the Ph and Me groups in equatorial positions.

The $J_{H(1)H(2)}$ of isomer (+)-IV-β-indicates an ax/ax relation and therefore the conformation **B** is the most appropriate.

Concerning (+)-IV-α isomer, $J_{H(1)H(2)}$ indicates either an eq/ax or an eq/eq relation. As we have related **B′** structure (eq/eq) to the previously discussed (+)-IV-β isomer, we can exclude **B′** for (+)-IV-α. Between **A** and **A′** conformers, both showing ax/eq relations, **A** seems to be more stable, as discussed above, and therefore it should be the preferred conformation of (+)-IV-α.

It is moreover noteworthy that the $H(^1)$ (eq) resonance in (+)-IV-α is downfield of the $H^{(1)}$ (ax) resonance in (+)-IV-β.[7]

The absolute configuration being *S* at C-2 in (+)-IV-α and (+)-IV-β, the configuration of (+)-IV-α and (+)-IV-β will be therefore 1*R*, 2*S* (**A** conformation) and 1*S*, 2*S* (**B** conformation), respectively.

We have then analogously interpreted and correlated to (+)-IV-α NMR data of (+)-1-phenyl-2-methyl-3-dimethylamino-propan-1-ol (III-α) (Table 1).[*] This leads to the conclusion that the absolute configuration of (+)-III-α is 1*R*, 2*S* and **A** its preferred conformation (Chart 2).

Since the different and independent methods used have given results in full agreement, we can therefore conclude that the above assigned absolute configurations are unequivocable.

EXPERIMENTAL

NMR spectra were determined on a Varian A-60A spectrometer, ORD spectra on a Perkin–Elmer Model P 22 spectropolarimeter (conc 1–3 mg/ml; cell thickness 0·5–1 cm), optical rotations on a Bendix N.P.L. Automatic Polarimeter and IR spectra on a Perkin–Elmer Model 225 spectrophotometer. M.ps are uncorrected.

(+)-1-*Phenyl-2-methyl-3-dimethylamino-propan-1-ol* (III-α form). Compound I (0·03 mol), obtained as previously reported,[3] dissolved in dry ethyl ether (30 ml), was dropped into a magnetically stirred suspension of LAH (0·03 mol) in dry ethyl ether (50 ml). The mixture was refluxed for 1 hr and cooled in an ice-bath. The complex was then cautiously hydrolyzed with water and the ethereal layer, washed and dried, gave, after removal of the solvent, the crude III (95% yield).

GLC analysis of the crude material was carried out using either a Silicon Oil or Versamid 900 10% on Chromosorb W column at 180° and gave only one peak.

(+)-III-α was crystallized from light petroleum, m.p. 84–86° (*dl* m.p. 87–89°); $[\alpha]_D^{21}$ +1° (*c*, 3in MeOH); hydrochloride, m.p. 167–168° (*dl* m.p. 168–170°); $[\alpha]_D^{21}$ + 32·4° (*c*, 1 in MeOH).[†] (Found: C, 62·73; H, 9·15; N, 6·18. $C_{12}H_{20}NOCl$ requires: C, 62·73; H, 8·78; N, 6·10%).

(+)-1-*Phenyl-2-methyl-3-piperidino-propan-1-ols* (IV-α and β forms). Compound II[3] was reduced as described above. The crude reaction product (90% yield) was analyzed by GLC using a Versamid 900 10% on Chromosorb W column (programmed temp: 180–210°; increase 1°/min), and showed two peaks having an area ratio of 58:42 corresponding to the diasteromeric α and β amino alcohols (IV) respectively.

The two pure isomers were separated by fractional crystallization of their hydrochlorides from abs EtOH. (+)-IV-α Hydrochloride (less soluble) is first obtained: m.p. 223–225° (*dl* m.p. 233–235°); $[\alpha]_D^{21}$

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[*] NMR measurements in CCl_4 of a number of similar diastereomeric amino-alcohols give for the 1*R*, 2*S*/1*S*, 2*R* ("erythro") series $\delta_{H(1)}$ and $J_{H(1)H(2)}$ values ranging from 4·66 to 4·92 ppm and from 2·0 to 3·6 cps, respectively. The corresponding values in the 1*S*, 2*S*/1*R*, 2*R* ("threo") series are ranging from 4·22 to 4·43 ppm and from 7·2 to 8·5 cps (L.A., unpublished results).

Analogous correlations were previously referred.[8]

[†] The characteristics of the hydrochloride obtained by catalytic hydrogenation of the same starting amino-ketone have been reported[9] as: m.p. 121–124° (dl m.p. 169–171°); $[\alpha]_D^{21}$ −25·9° (H_2O).

+21·7° (*c*, 1 in MeOH). (Found: C, 67·09; H, 9·23; N, 5·20. $C_{15}H_{24}NOCl$ requires: C, 66·77; H, 8·97; N, 5·19%). Free base (oil) (*dl* m.p. 50–51°); $[\alpha]_D^{21}$ +25·5° (*c*, 1 in MeOH).[*]

By evaporating the mother liquors and by further crystallization from acetone (−)-IV-β hydrochloride (more soluble) was obtained: m.p. 141–143° (*dl* m.p. 171–173°); $[\alpha]_D^{21}$ −20·9° (*c*, 1 in MeOH). (Found: C, 67·09; H, 9·19; N, 5·28%). Free base (oil) $[\alpha]_D^{21}$ +11·7° (*c*, 1 in MeOH).[*]

Absolute configuration at C-1 *in* (+)-1-*phenyl-2-methyl-3-dimethylamino-propan*-1-*ol* (III-α) *and* (+)-1-*phenyl-2-methyl-3-piperidino-propan*-1-*ol* (IV-α) *by the method of Horeau.*

This determination was performed as described[4b] from 0·3194 g of (+)-III-α ($[\alpha]_D^{21}$ +1·0°) and 1·042 g of α-phenyl-butyric anhydride. Esterification yield 89%. Optical yield of the (+)-α-phenyl-butyric-acid 56%.

The determination on (+)-IV-α ($[\alpha]_D^{21}$ +25·5°) was performed using 0·1235 g of amino alcohol and 0·3762 g of anhydride. Esterification yield 91%. Optical yield of the (+)-α-phenyl-butyric-acid 51%.

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[*] The Authors previously mentioned[9] (see footnote on p. 4) gave the characteristics of the hydrochloride obtained by catalytic reduction of the same Mannich base used in this work: m.p. 164–167° (*dl* m.p. 226°); $[\alpha]_D^{30}$ −22·5° (H_2O).

As in the preceding footnote, we can offer no explanation for these discrepancies.