Tetrahedron Vol 25, pp 4147 to 4151. Pergamon Press 1969. Printed in Great Britain

STEREOCHEMISTRY OF MANNICH BASES—I

ABSOLUTE CONFIGURATION OF SOME α-METHYL-β-AMINO-KETONES.

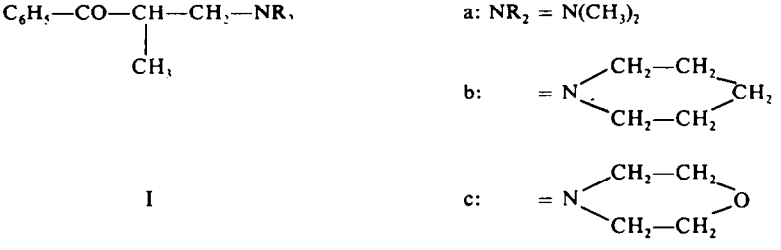
A. S. ANGELONI, G. GOTTARELLI and M. TRAMONTINI

Istituto di Chimica degli Intermedi della Universita', Bologna Italy

(*Received in U.K.* 10 *March* 1969; *Accepted for publication* 19 *March* 1969)

Abstract—The absolute configuration of (+)-α-methyl-β-dimethylaminopropiophenone (Ia) was found to be *S* by chemical correlation with *R*(−)-α-methyl-β-alanine. The absolute configuration of (+)-α-methyl-β-piperidino- and of (−)-α-methyl-β-morpholinopropiophenone (Ib and Ic) was found to be *S* and *R*, respectively, by comparison of their ORD spectra with that of the keto-base (Ia).

IN ORDER to clarify the stereochemistry of the stereospecific reactions between α-substituted β-aminoketones and Grignard or hydrogenating reagents, concerning which a preliminary communication has already appeared,[1] we have determined, by chemical and spectroscopic methods, the absolute configurations of some Mannich keto-bases (f. Ia, b, c). α-Methyl-β-aminopropiophenones (Ia, b, c) were resolved by



crystallization of the (−)-acid dibenzoyltartrates. (+)-α-Methyl-β-dimethylaminopropiophenone (Ia) was related chemically to *R*(−)-α-methyl-β-alanine (II), the absolute configuration of which was determined by Balenović and Bregant.[2] The sequence of reactions is reported in Fig. 1.

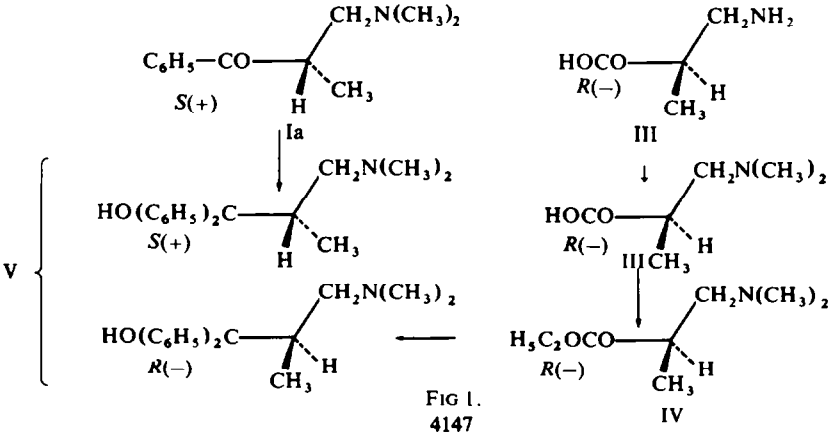


FIG 1.

Racemic α-methyl-β-alanine was synthesized by reaction of methyl methacrylate and ammonia in methanol, followed by acid hydrolysis. This reaction is more convenient than other methods previously reported; [3,4] optical resolution was performed following Balenović *et al.*[2]

R(−)-α-Methyl-β-alanine (II) was methylated with formaldehyde and hydrogen over a palladium catalyst; (−)-N,N-dimethyl-α-methyl-β-alanine(III) thus obtained was esterified with ethanol and gaseous hydrogen chloride to give the (−)-ethyl-ester(IV)* which, by reaction with phenylmagnesium bromide, afforded (−)-1,1-diphenyl-2-methyl--3-dimethylaminopropanol(V).

On the other hand, (+)-α-methyl-β-dimethylaminopropiophenone(Ia), by reaction with phenylmagnesium bromide, gave a (+)-1,1-diphenyl-2-methyl-3-dimethylaminopropanol(V); the absolute configuration of (+)-keto-base(Ia) is therefore *S*.

Once the absolute configuration of (+)-α-methyl-β-dimethylaminopropiophenone (Ia) had been established by chemical transformations it was possible to find the configurations of the other keto bases (Ib, c) by comparison of their ORD spectra (Fig. 2).

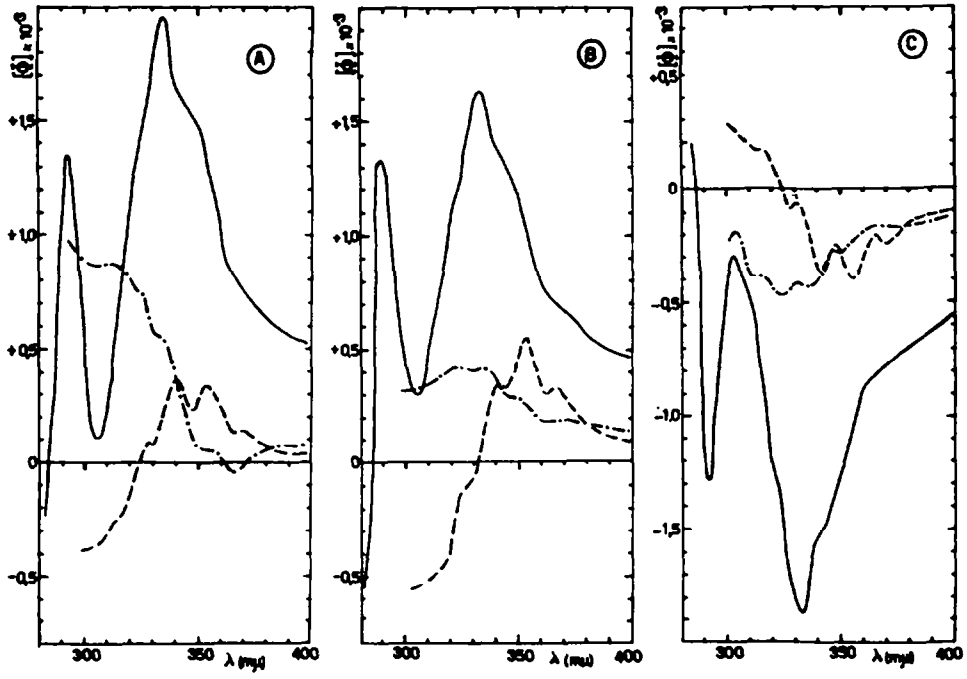


FIG. 2. ORD curves of: (A), (+)-α-methyl-β-dimethylamino-, (B), (+)-α-methyl-β-piperidino-, (C), (−)-α-methyl-β-morpholino-propiophenone (form. Ia, b, c). (— — hydrochlorides in methanol; —·—·— free bases in methanol; — — — — — free bases in cyclohexane).

* Once the absolute configuration of the acid III had been established, in order to obtain the intermediate required for the correlation, we resolved the racemic ester IV, whose antipodes are directly related to the acid III by hydrolysis.

In going from the hydrochlorides (in methanol), which show the most intense Cotton effect, to the free bases in methanol and cyclohexane, a change in shape and intensity is observed, which is more dramatic for the less rigid N,N-dimethylamino derivative(Ia). The wavelengths of the extrema are in agreement with those of other aryl-ketones previously reported.[5] The blue shift observed in going from cyclohexane to methanol is consistent with the assignment of the band to an $n\rightarrow\pi^*$ transition, although such a band and shift are not detectable in the UV spectra.[6]

Large changes in conformer populations or the formation of solvated species may cause the Cotton effect to change sign even though the absolute configuration remains constant, and so give rise to errors in correlations of this type.[7] We consider that such a phenomenon can be ruled out in this series of hydrochlorides and free bases in hexane, since the wavelengths of extrema are constant (within the limits of accuracy of the instrument) and amplitudes and shapes of the curves are strictly similar. Normally, when changes in conformation or solvation occur, the different species absorb at different wavelengths and the shapes and intensities of the curves display remarkable variations.[8]

Therefore, as the Cotton effect of the known *S*(+)-α-methyl-β-dimethylaminopropiophenone(Ia) is positive, and the Cotton effect of (+)-α-methyl-β-piperidinopropiophenone (Ib) and of (−)-α-methyl-morpholinopropiophenone (Ic) is positive and negative respectively, the absolute configurations of (+)-Ib and (−)-Ic are *S* and *R* respectively.

EXPERIMENTAL

Optical resolution of α-methyl-β-aminopropiophenones (Ia, b, c)

(+)-α-*Methyl*-β-*dimethylaminopropriophenone* (Ia) *hydrochloride*. m.p. 171–173°, $[\alpha]_D$ +48 (*c* 1, water) was obtained following Pohland *et al.*[9]

(+)-α-*Methyl*-β-*piperidinopropiophenone* (Ib) *hydrochloride*, obtained in the same way, had a m.p. 167–168° (from EtOH/Et_2O) and $[\alpha]_D$ +45 (*c* 1, MeOH). (Found: C, 67·3; H, 8·55; N, 5·25. $C_{15}H_{22}NOCl$ requires: C, 67·25; H, 8·3; N, 5·25%).

(−)-α-*Methyl*-β-*morpholinopropiophenone* (Ic) *hydrochloride* was prepared analogously; only the fraction of (−)-dibenzoyl-tartrate m.p. 90–118° was collected which, when recrystallized from acetone, had a m.p. 94–100°. The free base obtained from this salt was converted to the hydrochloride, m.p. 163–166°, $[\alpha]_D$ −45·8 (*c* 1, EtOH). (Found: C, 62·5; H, 7·2; N, 5·4. $C_{14}H_{20}NO_2Cl$ requires: C, 62·3; H, 7·4; N, 5·2%). Further crystallization of the hydrochloride did not improve the purity of the compound.

The free bases (Ia, b, c) were obtained by treating hydrochlorides with conc ammonia at 0°. The ethereal extract was dried and the solvent carefully removed at room temp under reduced pressure. The free bases are themselves optically unstable and particularly alkaline treatment causes racemization.

S(+)-1,1-*Diphenyl*-2-*methyl*-3-*dimethylaminopropanol* (V)

(Compound Ia (1·2 g; 0·0063 mole) obtained from the corresponding hydrochloride having $[\alpha]_D$ +44 (*c* 1, MeOH) in 25 ml Et_2O was added in 30 min to a soln of 0·019 mole PhMgBr in 25 ml Et_2O. After refluxing for 90 min, the mixture was treated with dil HCl and extracted with ether. The aqueous layer was made alkaline and extracted with ether. The organic phase was washed with water and dried over Na_2SO_4, and after removal of solvent gave 1·6 g of V, m.p. 91–93°, (from EtOH), $[\alpha]_D$ +9 (*c* 1·9, $CHCl_3$). (Found: C, 79·6; H, 8·7; N, 5·2. $C_{18}H_{23}NO$ requires: C, 80·25; H, 8·6; N, 5·2%).

Racemic V had m.p. 92–93° (from EtOH). (Found: C, 80·35; H, 8·55; N, 5·2%).

(−)-α-*Methyl*-β-*alanine*

25 g of methyl methacrylate were added to MeOH previously saturated with ammonia (obtained from gaseous ammonia and MeOH at 0°). The mixture was heated in an autoclave at 100–110° for 6 hr. Excess ammonia and MeOH were eliminated by distillation and the residue refluxed with 80 ml of conc HCl for 12 hr. Excess HCl and water were removed under reduced press. The remaining salt after dilution with

1000 ml water, was passed through a column containing Amberlite IR 120, previously regenerated with 2N HCl. The resin, containing the amino acid, was eluted with water, then with 2N NH_4OH until alkaline and finally with water again until the eluent gave a neutral reaction with univ. indic. After removing the water from the neutral and alkaline fractions, under reduced press, an oily residue was obtained which, after recrystallization from acetone–water (3:1), gave 11 g of product, m.p. 176–178°. The mother liquor was evaporated to dryness, the residue dissolved in 45 ml acetone/water (3:1) and the soln cooled, whereupon 6 g of product were obtained; total yield 60–65%.

R(−)-N,N-*Dimethyl-α-methyl-β-alanine* (III)

Compound II (0·5 g) obtained by the method of Balenović *et al.*[2] was methylated using Bowman and Stroud's technique[10] for the α-amino acids.

The crude product was treated with MeOH and the insoluble part filtered off. The methanolic phase was evaporated to dryness and the residue crystallized from acetone with charcoal. The hygroscopic amino acid III was obtained in a 75% yield, m.p. 112–116°, $[\alpha]_D$ −35 (*c* 2, EtOH). (Found: C, 54·0; H, 9·6; N, 10·2. $C_6H_{13}O_2N$ requires: C, 54·9; H, 10·0; N, 10·7%).

Racemic III had m.p. 121–123° (from acetone). (Found: C, 54·9; H, 10·0; N, 10·65%).

S(+)-III, m.p. 111–116°, $[\alpha]_D$ +43 (*c* 1, EtOH) was obtained from the (+)-IV, $[\alpha]_D$ +24 (see below) by acid hydrolysis, followed by purification on Amberlite IR 120 and crystallization from acetone.

R(−)-N,N-*dimethyl-α-methyl-β-alanine ethylester* (IV)

A soln of 0·45 g of III ($[\alpha]_D$ −35) in 25 ml of EtOH was treated with a slow steam of dry HCl for 30 min. The soln was cooled to −5°, saturated with the same reagent and left overnight at room temp. The solvent was removed under reduced press and the residue was quickly extracted with ether, after adding ice and making alkaline with 20% NaOH aq. The dried organic layer gave, after removing the solvent, 0·35 g of product $[\alpha]_D$ −20 (*c* 2, EtOH). The amino ester IV obtained was directly treated with Grignard reagent.

R(−)-1,1-*Diphenyl-2-methyl-3-dimethylaminopropanol* (V)

Compound IV (0·35 g; from the reaction described above) in 20 ml of Et_2O was added to a soln of 0·013 mol PhMgBr and treated as described for V.

0·36 g of V was obtained, m.p. 73–83° (from EtOH), $[\alpha]_D$ −18 (*c* 2, $CHCl_3$). (Found; C, 79·9; H, 8·7; N, 5·3. $C_{18}H_{23}NO$ requires: C, 80·25; H, 8·6; N, 5·2%).

Another reaction, using IV, $[\alpha]_D$ −4 afforded V having m.p., 89–91°, $[\alpha]_D$ −3·9 (*c* 3, $CHCl_3$).

Optical resolution of (±)-N,N-*dimethyl-α-methyl-β-alanine ethylester* (IV)

Compound IV (6·9 g) and an equimolar amount of (−)-dibenzoyl-tartaric acid in 150 ml EtOH were left at room temp overnight, giving 13·7 g of (−)-dibenzoyl-tartrate, m.p. 140–143°, $[\alpha]_D$ −78 (*c* 1, MeOH). After two crystallizations from EtOH, 6 g of (−)-dibenzoyl-tartrate, m.p. 144–146°, $[\alpha]_D$ −71 (*c* 1, MeOH) were obtained. (Found: C, 60·35; H, 6·0; N, 2·55. $C_{26}H_{31}O_{10}N$ requires: C, 60·35; H, 6·05; N, 2·7%). This salt gave IV having $[\alpha]_D$ +24 (*c* 2, EtOH).

The residue obtained from the mother liquor of the first two crystallizations was crystallized from EtOH. The (−)-dibenzoyl-tartrate so obtained (7 g) had a m.p. 127–129°, $[\alpha]_D$ −84·7 (*c* 1, MeOH) and gave IV $[\alpha]_D$ = −4 (*c* 2, EtOH).

ORD spectra were recorded with a Perkin Elmer mod. P 22 spectropolarimeter. M.ps are uncorrected.

Acknowledgement—We thank the "Consiglio Nazionale delle Ricerche" for a grant.

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