Tetrahedron Vol. 27, pp. 5247 to 5254 Pergamon Press 1971. Printed in Great Britain

STEREOCHEMISTRY OF MANNICH BASES—VI*

ABSOLUTE CONFIGURATION OF β-PIPERIDINO-BUTYROPHENONE AND OF SOME 1-PHENYL-3-DIALKYLAMINO-BUTHANES

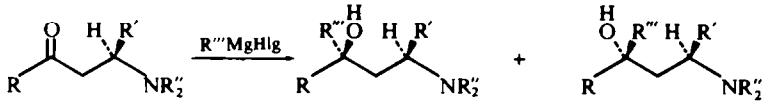
V. CANNATA, B. SAMORI and M. TRAMONTINI

Istituto Chimica Intermedi—Università di Bologna, Italy

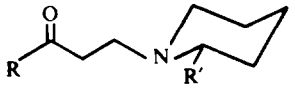
(*Received in the UK* 2 *June* 1971; *Accepted for publication* 12 *July* 1971)

Abstract—The S absolute configuration was assigned to (+)-β-piperidino-butyrophenone by chemical correlation with S(+)-1-phenyl-3-piperidino-butane. The absolute configuration of S(+)-1-phenyl-3-piperidino-butane was obtained by comparison of its CD spectra with those of R(-)-1-phenyl-3-dimethylamino-butane, obtained by methylation of the (−)-1-phenyl-3-amino-butane, whose absolute configuration was already known to be R. The room and low-temperature CD spectra of these three alkylamino-derivatives are reported together with O_1 the vibronic analysis of L_1b transition of the benzyl chromophore.

IN A PRECEDING report[2] concerning the stereochemistry of Mannich bases, the study of the Grignard reaction on β-amino-ketones (I), bearing an asymmetric centre in the β position to the carbonyl group, was announced. Preliminary experiments showed clearly the reaction to be stereospecific, as the composition of the mixture of the diastereoisomeric amino-alcohols (II) and (III) was considerably different from 50%. Analogous results were obtained with keto-bases (IV) having the asymmetric centre in the amino-group.



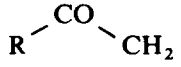
I II III



IV

R, R′ and R‴ = alkyl or aryl
NR''_2 = piperidino or dimethylamino group

An analogous study concerning LAH reduction of derivatives I has shown a prevalence of amino-alcohols III (R‴ = H) in the diastereoisomeric mixture.[3]

In order to obtain a better understanding of the mechanism of the asymmetric induction in the Grignard reaction, the steric configuration of the diasteroisomers obtained needs to be known, as it should demonstrate the direction of attack of R‴ with respect to the  plane.

In preceding studies about the 1-2 asymmetric induction in α-substituted β-amino-

* Part V, see Ref. 1.

ketones the problem was solved by determining the absolute configuration of one of the diastereoisomeric amino-alcohols. the absolute configuration of the starting keto-bases being previously determined.[4,5]

The scope of this work is to determine the absolute configuration of keto-base V (I. R = Ph. R′ = Me. NR''_2 = piperidine residue) by chemical and CD spectroscopic correlation with S (+)-1-phenyl-3-amino-butane (IX).[6]

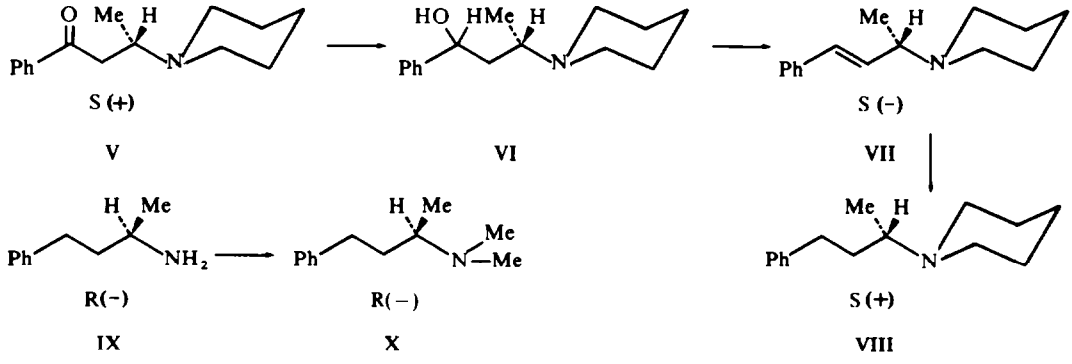
The S-base IX is given[6] as levorotatory, on the basis of the left-hand rotatory power of its hydrochloride.

The use of the dimethylamino-keto-base (I, R = Ph. R′ = R″ = Me) instead of the corresponding piperidine base (V) would have given a direct chemical correlation with the amine IX; however, our and other authors'[7] attempts to resolve the dimethyl-amino base into optical antipodes were unsuccessful, and further, the piperidine derivative is more suitable for the stereochemical studies which are in progress.

$NaBH_4$ reduction of (+)-piperidino-butyrophenone (V) gave the corresponding amino-alcohol (VI). which is probably a mixture of erythro and threo diasteroisomers [LAH reduction of the same ketone affords a mixture with 35% of threo and 65% of erythro-amino-alcohol (VI)[3]]. The mixture was directly dehydrated to (−)-1-phenyl-3-piperidino-but-1-ene (VII). The NMR spectrum of VII agrees with the proposed structure; however. the investigation on the *cis* or *trans* stereochemistry was not carried out. as it was not relevant to this work.

Hydrogenation of VII gives (+)-1-phenyl-3-piperidino-butane (VIII). whose structure is in agreement with NMR data (experimental).

On the other side. formaldehyde/formic acid methylation of R(−)-1-phenyl-3-amino-butane (IX) afforded (−)-1-phenyl-3-dimethylamino-butane (X). having the same R absolute configuration.



The S absolute configuration was assigned to (+)-1-phenyl-3-piperidino-butane (VIII) by comparing its CD spectra in the zone corresponding to the L_1b and L_1a benzene transitions. with the ones of R(−)-1-phenyl-3-dimethylamino-butane (X) (Figs. 1. 3. 4).

The CD spectra of derivatives S(+)-VIII and R(−)-X in cyclohexane or P_3M_1* are very similar to each other. They consist of three bands. each of which have opposite

* The solvent used for low temperature measurement was isophenthane/methyl-cyclohexane 3:1 (P_3M_1).

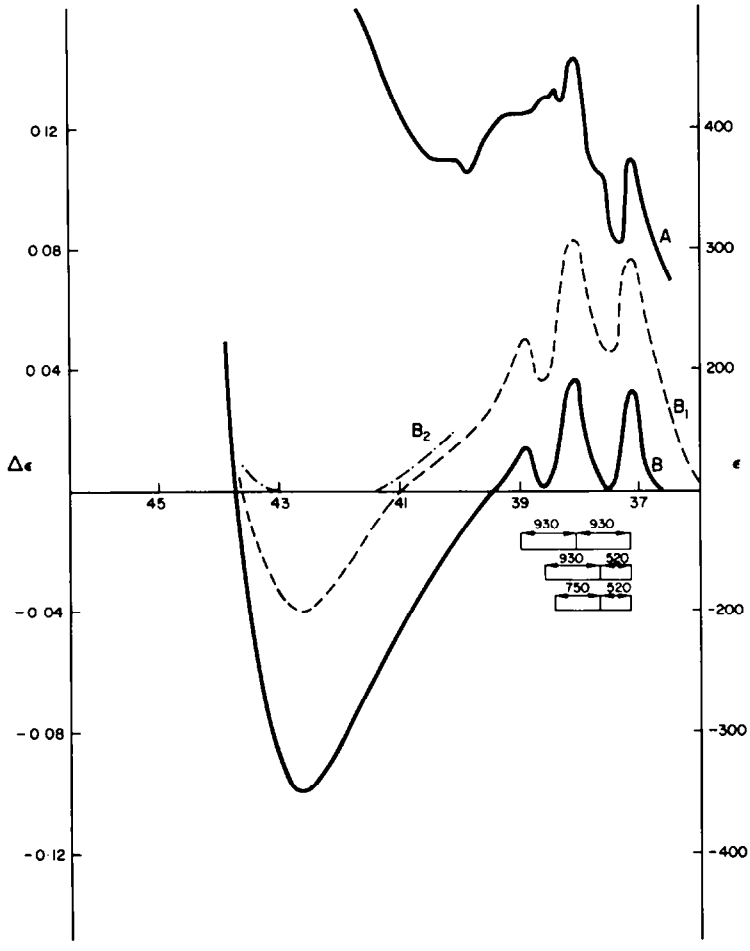


FIG. 1. The absorption (A. ———) and CD (B. ———) spectra of (+)-1-phenyl-3-piperidinobutane (VIII) in cyclohexane at room temp. The CD spectrum in P_3M_1 at $-70°$ (B_1, – – – – –) and at $-120°$ (B_2, – · – · –).

signs in each of the two derivatives. Two of them near 38.000 and 48.000 cm^{-1} are directly corresponding to L_1b and L_1a benzene transition and the band between the two (near 43,000 cm^{-1}) is caused by the presence of conformational equilibria.

The absolute configuration assignment is put on a more solid basis by the extension of the comparison to both of the transitions. In fact. the optical activity of the L_1b transition in analogous systems seems to be caused by a "one electron" mechanism. while in the L_1a transition a dipole-dipole mechanism seems to be relevant: the symmetry rules governing the two transitions are therefore different.[8]

The hypothesis of duality of mechanism responsible for the optical activity of the two bands is further confirmed by the different sensitivity of L_1b and L_1a bands to solvent changes. In fact. in the spectra of derivatives R(−)-X and R(−)-IX. the protonation of the amino group and the change of the solvent from cyclohexane to MeOH causes the inversion only of the L_1a band. (It was not possible to observe the same

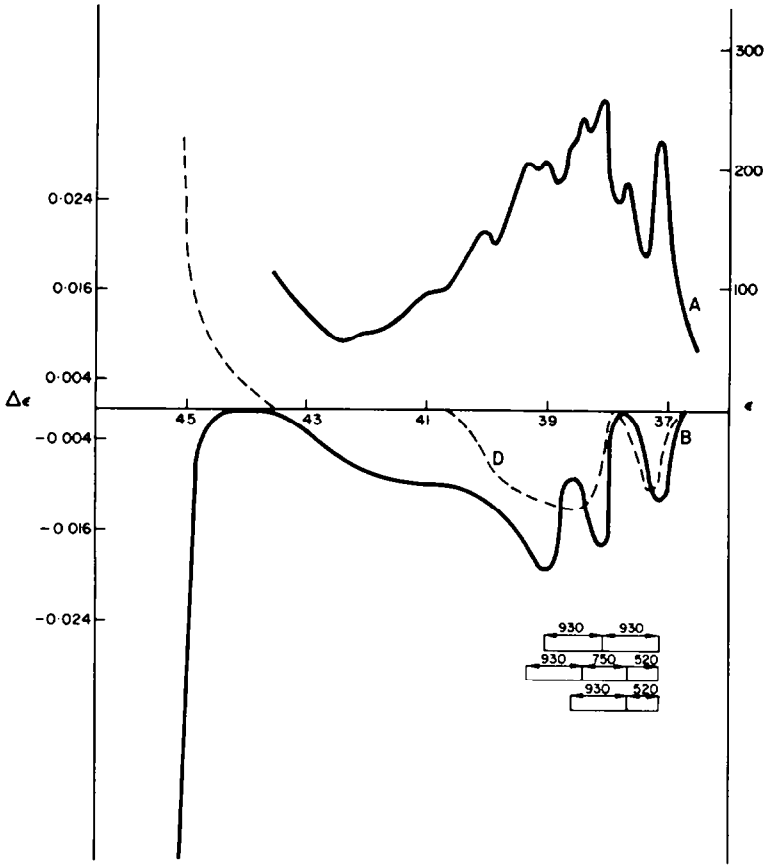


FIG. 2. The absorption (A. ———) and CD (B. ———) spectra of (−)-1-phenyl-3-amino-butane (IX) in cyclohexane at room temp. CD of (IX) hydrochloride in water at room temp. (D. – – – –).

phenomenum also for S(+)-VIII owing to its low optical purity; in fact an increase of the polarity of the solvent causes a decrease of the optical activity and the determination of the spectra becomes problematic).

The conformational homogeneity in derivatives S(+)-VIII and R(−)-X was verified by low-temperature CD spectra and by a vibronic analysis of the resolved part of L_1b transition, as conformational changes could invert the sign of the same progression.[9]

Vibronic analysis allowed us to exclude the contribution of a forbidden progression from the part of the spectra under investigation. We were therefore able to avoid the correlation of an allowed progression in one derivative. with a forbidden one in another derivative. In fact it could possibly cause a mistake in the assignment of the absolute configuration. if the non totally symmetric vibration involved had caused an inversion of sign in the CD spectrum.

The results of vibronic analysis of derivatives (S)-(+)-VIII. R(−)-IX. R(−)-X (Figs. 1. 2. 3) are in agreement with those which were previously reported in the literature[8, 10] for the benzyl chromophore: the CD spectra are based on the allowed progression

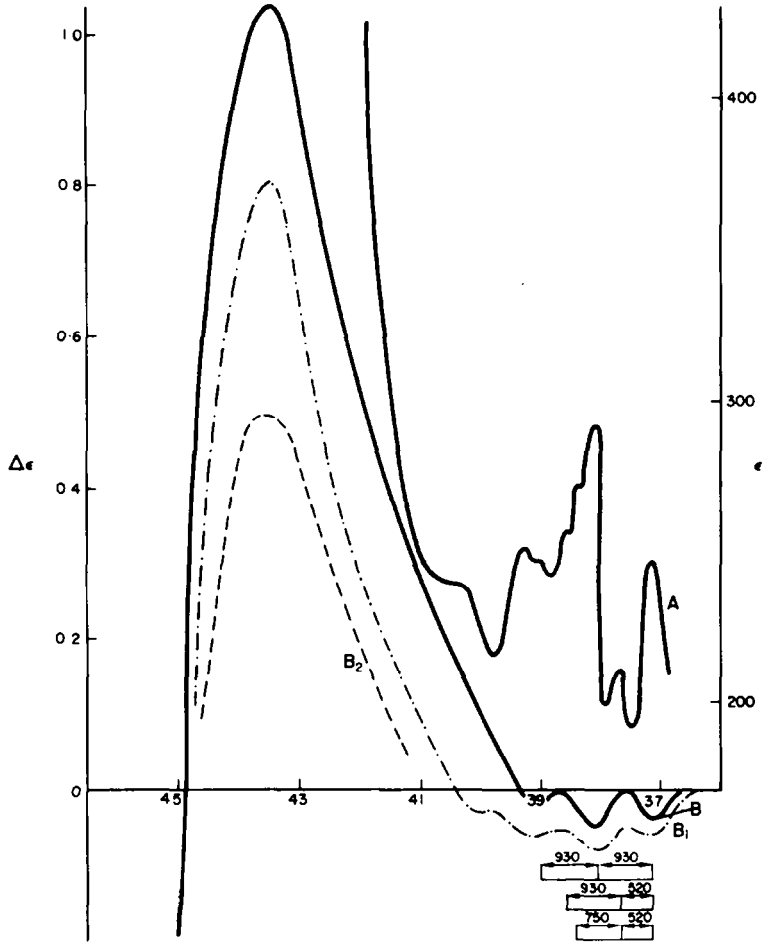


Fig. 3. The absorption (A. ———) and CD (B. ———) spectra of (−)-1-phenyl-3-dimethylamino-butane (X) in cyclohexane at room temp. CD in P_3M_1 at −80° (B_1. – · – · –) and at −130° (B_2. – – – – –).

0 + n930 cm^{-1}, whilst the UV spectra show also the presence of forbidden progressions 0 + 520 + n930.[11] and 0 + 520 + 750 cm^{-1}.

Low-temperature CD spectra show clearly the existence of conformational equilibria[12] in the series of compounds studied. as the band near 43.000 cm^{-1} suffers a decrease of intensity with lowering of temperature: on the contrary. the L_1b transition increases, without, however, a change in its vibronic structure.

The conformational equilibrium responsible for the 43.000 cm^{-1} band seems to be dependent on the nature of the amino-group. as in the spectra of compounds R(−)-X and S(+)-VIII the lowering of the temperature affects the 43.000 cm^{-1} band intensity in a different way; in fact. in compound S(+)-VIII this band disappears at −120°. whereas in R(−)-X it suffers a decrease of 50% at −130°.

In derivative R(−)-IX this band is not detectable.

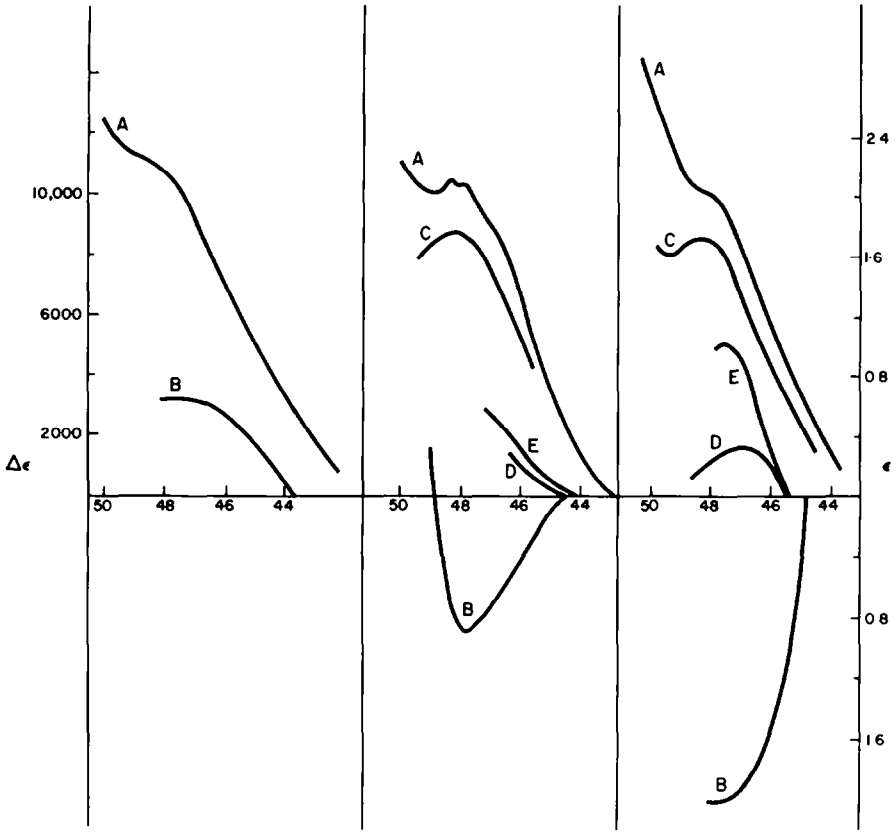


FIG. 4. Spectra corresponding to L_1a benzenoid transition of derivatives (+)-VIII. (−)-IX. (−)-X at room temp. Absorption of the bases in cyclohexane (A). and of hydrochloride in water (C). CD of the base in cyclohexane (B) and in MeOH (E). and of hydrochloride in water (D).

On this basis it seems sound to invoke the conformational homogeneity of derivatives R(−)-X and S(+)-VIII. even if the relative stability of the different conformers are different. Derivative R(−)-IX. on the other hand. behaves in quite a different way. Therefore the correlation of configuration directly with compound R(−)-IX could have been misleading, even with the help of vibronic analysis.

From this analysis it follows that the dimethylamino base (−)-X has an absolute configuration opposite to the piperidine base (+)-VIII. Therefore the S absolute configuration must be assigned to (+)-β-piperidino-butyrrophenone (V).

EXPERIMENTAL

M.ps are uncorrected. IR spectra were measured using a Beckman IR-5 spectrophotometer. NMR spectra were measured in CCl_4 using a Jeol C-60 HL spectrograph. $[\alpha]_D$ were measured with a Bendix NPL 143C polarimeter. CD spectra were recorded using a Roussel–Jouan Dicrograph (calibrated with a mercury lamp). UV spectra were recorded using a Unicam SP 700A spectrophotometer (the wave-length range. corresponding to L_1b benzenoid absorption. was calibrated using a vapour phase spectrum of benzene as a reference).

(−)-β-*Piperidino-butyrophenone hydrochloride*. The titled compound was synthesised following a previous procedure:[13] the corresponding base (V) was obtained from the hydrochloride by treatment with diluted NaOH at 0°: it shows $[\alpha]_D = +1{\cdot}5$ ($c = 2{\cdot}5$ cyclohexane) and $[\alpha]_D = -8$ ($c = 1$ MeOH). The base is by no means optically stable.

(−)-1-*Phenyl*-3-*piperidino-but*-1-*ene* (VII). (a) Reduction of (+)-β-piperidino-butyrophenone. $NaBH_4$ (0·4 g) was added in small amounts to a solution of (+)-V ($[\alpha]_D = +1$. cyclohexane) in MeOH/water 9:1 (2 g in 25 ml) at the room temp., and the mixture set aside for 5 hr. The mixture, diluted with water, was extracted several times with light petroleum and the organic phase afforded, after evaporation of solvent, 1·8 g of 1-phenyl-3-piperidino-butan-1-ol (VI) (90%). The IR spectrum showed the band characteristic of the OH group and no longer showed carbonyl absorption. The compound was used directly for the next reaction.

(b) Dehydration of 1-phenyl-3-piperidino-butan-1-ol (VI).

Compound VI (1·7 g) was added with stirring to 25 ml of a conc. H_2SO_4/water (1:1) solution at 80–90° and the mixture stirred for 15 min. Ice was added to the mixture which was then washed with light petroleum.

The aqueous phase was basified with solid NaOH and extracted with light petroleum; the organic phase, after distillation of solvent, afforded 0·9 g (53%) of 1-phenyl-3-piperidino-but-1-ene (VII) $[\alpha]_D = -9°$ ($c = 2$ cyclohexane), picrate m.p. 132–133° (the m.p. decreased to 126–127° and to 120–122° after crystallisation from abs. EtOH).

NMR spectrum of the free base showed the following multiplets: $\delta = 7{\cdot}12$: (5, Ar protons); $\delta = 6{\cdot}15$: (2, ethylenic protons); $\delta = 3{\cdot}02$, 2·4, 1·43, 1·15: (1:4:6:3, alkyl protons) respectively. The IR spectrum no longer shows OH group. The (±)-1-phenyl-3-piperidino-but-1-ene picrate has m.p. 133–134° (from abs. EtOH).

(±)-1-*Phenyl*-3-*piperidino-butane* (VIII). A solution of (−)-1-phenyl-3-piperidino-but-1-ene (VII) (0·9 g) in EtOH (25 ml), acid by a small excess of HCl, was hydrogenated at room temp. using 0·3 g of 5% Pd/C catalyst. One mole of hydrogen was absorbed in about one hr. The alcoholic solution, diluted with water and basified, afforded, using the same procedure described above, 0·7 g (78%) of 1-phenyl-3-piperidino-butane (VIII) $[\alpha]_D = +7{\cdot}5$ ($c = 4$, cyclohexane). (The same base shows $[\alpha]_D = -3$ in MeOH and its hydrochloride $[\alpha]_D = -5{\cdot}5$ in MeOH). The picrate has m.p. = 120–121° (EtOH). NMR spectrum of the free base showed a series of multiplets centred at $\delta = 6{\cdot}95$ (5, aromatic protons); $\delta = 2{\cdot}4$, 1·5 and 0·85 (7, 8 and 3, alkyl protons) respectively.

(±)-1-Phenyl-3-piperidino-butane picrate has m.p. = 110–111° (EtOH).

R(+)-1-*Phenyl*-3-*amino-butane hydrochloride*. The compound was synthesised following the literature[6] and showed $[\alpha]_D = +13$ ($c = 1$, water:). The corresponding free base (IX) had $[\alpha]_D = -18$ ($c = 1$, cyclohexane).

(−)-1-*Phenyl*-3-*dimethylamino-butane* (X). (−)-1-Phenyl-3-amino-butane (IX) ($[\alpha]_D = -18$). (4·0 g, 0·027 mol) was added with stirring and cooling to 5·15 g (0·134 mol) of 98% formic acid.

Aqueous formaldehyde 40% (0·059 mol, 4 ml) was then added always with stirring and cooling. The mixture was heated on a steam bath until no more gas was evolved (6–8 hr), 4 ml of diluted HCl (1:1) added, and the mixture concentrated under reduced pressure. The viscous residue was mixed with water, basified with aq NaOH and extracted with light petroleum. The organic phase after drying and evaporation of the solvent, gave 3·6 g (90%) of 1-phenyl-3-dimethylamino-butane (X), $[\alpha]_D = -28$ ($c = 2$, cyclohexane). The product was characterised as a picrate m.p. 127–128° (EtOH). NMR spectrum of the base showed a series of multiples centred respectively at $\delta = 6{\cdot}98$ (5, aromatic protons): $\delta = 2{\cdot}5$, 2·13, 1·65 and 0·9 (3, 6, 2, and 3, alkyl protons).

(±)-1-phenyl-3-dimethylamino-butane picrate has m.p. = 111–112° (EtOH).

The analysis of the picrates of the bases VII, VIII and X, either optically active or racemate, are in a good agreement with the proposed structures.

Acknowledgement—We thank the C. N. R. for a grant. Dr. Giovanni Gottarelli for helpful discussion and Dr. Giuliana Salvadori for NMR Spectra.

REFERENCES

[1] R. Andrisano and L. Angiolini, *Tetrahedron* **26**, 5247 (1970)
[2] R. Andrisano, P. Costa Bizzarri and M. Tramontini, *Ibid.* **26**, 3959 (1970)

[3] M. J. Brienne, C. Fouquey and J. Jacques, *Bull. Soc. Chim. France* 2395 (1969)
[4] A. S. Angeloni. G. Gottarelli and M. Tramontini. *Tetrahedron* **25**. 4147 (1969)
[5] L. Angiolini. P. Costa Bizzarri and M. Tramontini. *Ibid.* **25**. 4211 (1969)
[6] J. VanFijk. V. G. Keizer and H. D. Moed. *Recueil* **82**. 189 (1963)
[7] R. J. McConaill and F. L. Scott. *Tetrahedron Letters* 2993 (1970)
[8] G. Gottarelli and B. Samori, *Substituent effect on CD of α-phenylaethyl-amines, J. Chem. Soc.* (B) (in press)
[9] O. E. Weigang. Jr.. *J. Chem. Phys.* **43**. 3609 (1965)
[10] R. D. Gillard and P. R. Mitchell. *Trans. Faraday Soc.* **65**. 2611 (1969)
[11] H. Sponer. *J. Chem. Phys.* **10**. 672 (1942)
[12] W. Scott Briggs and C. Djerassi. *Tetrahedron* **21**. 3455 (1965)
[13] R. Andrisano. A. S. Angeloni. P. De Maria and M. Tramontini. *J. Chem. Soc.* (C) 2307 (1967)