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STEREOCHEMISTRY OF MANNICH BASES—II

STEREOSPECIFIC SYNTHESIS AND ABSOLUTE CONFIGURATION OF DIASTEREOISOMERIC 1-PHENYL-1,2-DIMETHYL-3-DIMETHYLAMINO-PROPAN-1-OLS*

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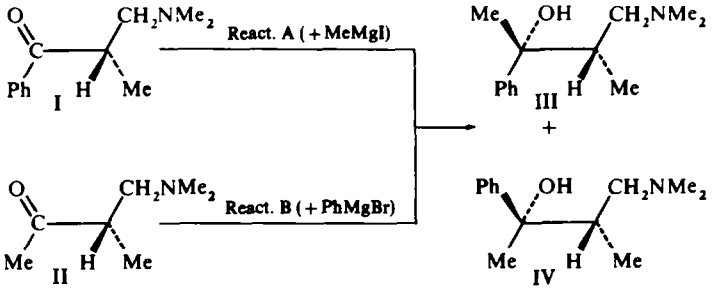
Abstract—During the stereospecific synthesis of diastereoisomeric (±)-1-phenyl-1,2-dimethyl-3-dimethylamino-propan-1-ols (III and IV), obtained by reaction of suitable Grignard reagents on α-methyl-β-dimethylamino-propiophenone (I) or on 3-methyl-4-dimethylamino-butan-2-one (II) respectively, the absolute configuration of (—)-amino-alcohol (III) was shown to be 1*R*, 2*S*. It was also established that (—)-amino-alcohol (IV) has the 1*S*, 2*S* configuration.

DURING research on the stereochemistry of the Grignard reactions with α-substituted-β-amino-ketones,[1,2] a very high stereospecificity was observed.

In order to obtain a deeper understanding of this subject, the stereospecific synthesis of the (±)-1-phenyl-1,2-dimethyl-3-dimethylamino-propanols (III and IV) was undertaken by reaction of suitable Grignard reagent with phenyl-keto-base (I) or methyl-keto-base (II) (Table 1). In this manner the absolute configuration of the diastereoisomeric amino-alcohols (III and IV) was determined by chemical correlations (Tables 2 and 3).

TABLE 1†



React. A: III 100%, IV 0%
React. B. III 14%, IV 86%

† Only one enantiomer of the racemic pair is here represented.

* Part I, see Ref. 2.

These reactions (Table 1) are highly stereospecific, phenyl-keto-base (I) (Reaction A) yielding only amino-alcohol (III) and methyl-keto-base (II) (Reaction B) mainly the diasteroisomer amino-alcohol (IV).

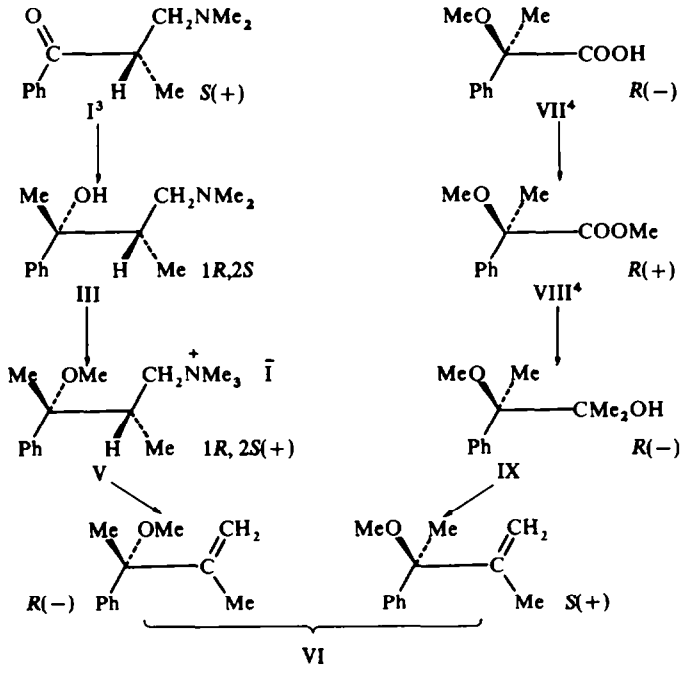
The course of these reactions is consistent with a cyclic intermediate in which the Mg atom of the organo-metallic reagent coordinates both the carbonyl oxygen and the amine nitrogen. The organic group then approaches from the least sterically hindered side of the molecule.[3]

In order to confirm this hypothesis it was necessary to establish the relative configuration of the two asymmetric centers of the reaction products. This was made possible by determining the absolute configuration of the (−)-amino-alcohol (III) obtained from the (+)-keto-base (I) (Table 2).

The absolute configuration of the asymmetric center in position 2 of (−)-1-phenyl-1,2-dimethyl-3-dimethylamino-propan-1-ol (III) is the same as in the known (+)-keto-base (I).[2]

The configuration of the asymmetric center in position 1 was established by chemical correlation (Table 2) with the known *R*(−)-atrolactic-acid-methylether-VII.[4]

TABLE 2



3

(+)-α-Methyl-β-dimethylamino-propiophenone-(I) reacted with MeMgI, but the (−)-1-phenyl-1,2-dimethyl-3-dimethylamino-propan-1-ol (III) was optically impure because of the optical instability of the starting material.[2] It was purified by crystallization of its salt with (+)-dibenzoyl-tartaric acid and then methylated to the corresponding (+)-methyl-ether-iodomethylate (V). Hofmann elimination on the cor-

responding quaternary amonium base gave (−)-1-methoxy-1-phenyl-1,2-dimethyl-prop-2-ene (VI).

The atrolactic-acid-methyl ether (VII) racemate was resolved with brucine.* *R*(−)-Atrolactic-acid-methyl ether (VII), esterified with diazomethane, gave *R*(+)-atrolactic-acid-methylether-methyl ester (VIII), which, by treatment with MeMgI, afforded (−)-1,1-dimethyl-2-methoxy-2-phenyl-propan-1-ol (IX). This (−)-alcohol (IX), by reaction with thionyl chloride and then with alkali, gave (+)-1-methoxy-1-phenyl-1,2-dimethyl-prop-2-ene (VI) enantiomeric with the compound derived from (−)-amino-alcohol (III).

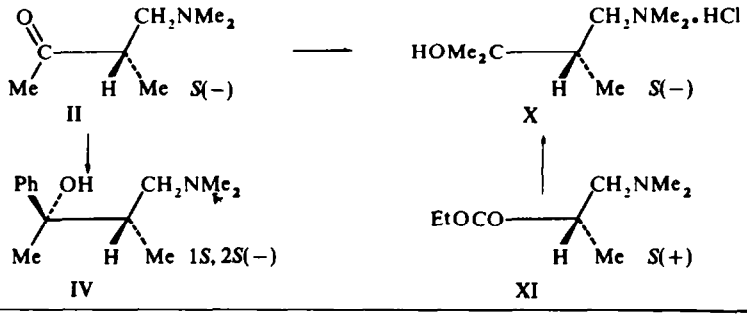
The absolute configuration at C-1 in (−)-1-phenyl-1,2-dimethyl-3-dimethylamino-propan-1-ol (III) is therefore *R*, consistent with the postulated cyclic intermediate in the Grignard reaction with *S*(+)-phenyl-keto-base (I).

The absolute configuration of (−)-amino-alcohol (III) is therefore 1*R*,2*S*.

It follows that the configuration of (±)-amino-alcohol (III) is 1*R*,2*S*/1*S*,2*R* and the diastereoisomer (±)-amino-alcohol (IV) is 1*R*,2*R*/1*S*,2*S*.

This result and the absolute configuration of the methyl-keto-base (II) (Table 3) also afforded the configuration of (−)-amino-alcohol (IV) by chemical correlation with the known S(+)-N,N-dimethyl-α-methyl-β-alanine-ethylester (XI).[2]†

TABLE 3



Racemic methyl-keto-base (II), resolved by crystallization of its salt with (−)-dibenzoyl-tartaric acid, gave the (−)-methyl-keto-base-hydrochloride (II). The corresponding free base, with MeMgI, afforded (−)-1,1,2-trimethyl-3-dimethylamino-propanol-hydrochloride (X).

On the other hand *S*(+)-amino-ester (XI) afforded the same (−)-amino-propanol-hydrochloride (X).

It follows that the absolute configuration of (−)-3-methyl-4-dimethylamino-butan-2-one-hydrochloride (II) and the configuration at C-2 in (−)-1-phenyl-1,2-dimethyl-3-dimethylamino-propan-1-ol (IV), derived from (+)-II, is *S*. The absolute configuration of (−)-amino-alcohol (IV), diastereoisomer of III, is therefore 1*S*,2*S*.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were recorded on a Beckmann IR-5 spectrophotometer.

* This method seems more convenient and rapid than the one with quinine previously reported.[4]

† The aminoester (XI) was obtained by a new and more convenient method than the one previously reported[2] (Experimental).

(±)-1-*Phenyl*-1,2-*dimethyl*-3-*dimethylamino-propan*-1-*ols* (III and IV)

A soln of I (0·01 mol) in Et_2O (30 ml) was added to an ethereal soln (40 ml) containing MeMgI (0·025 mol). The mixture was refluxed for 90 min, poured in 200 ml dil HCl and extracted with ether. The aqueous layer was made alkaline and extracted with ether; the organic layer, washed with water, was dried and the solvent removed under reduced press. The residue, obtained in 90–95% yield, was analysed by GLC: only III was present, m.p. 47–48° from pet. ether. (Found: C, 75·7; H, 10·5; N, 6·85. $C_{13}H_{21}NO$ requires: C, 75·3; H, 10·2; N, 6·75%); hydrochloride, m.p. 184–185° from EtOH, (Found: C, 64·1; H, 9·3; N, 5·8. $C_{13}H_{22}NOCl$ requires: C, 64·05; H, 9·1; N, 5·75%); picrate, m.p. 188–189° from EtOH, (Found: C, 52·2; H, 5·6; N, 12·8. $C_{19}H_{24}N_4O_8$ requires: C, 52·3; H, 5·55; N, 12·85%).

The base II was treated with PhMgBr as described above. The residue, analysed by GLC, was a mixture of two diastereoisomeric amino-alcohols in the ratio (III/IV) 1 :6·5, together with small amounts of unreacted II.*

Several crystallizations of the mixture of III and IV hydrochlorides from EtOAc–EtOH gave the pure IV hydrochloride, m.p. 176–177°. (Found: C, 64·4; H, 9·3; N, 5·8. $C_{13}H_{22}NOCl$ requires: C, 64·05; H, 9·1; N, 5·75%); picrate, m.p. 162–163° from EtOH, (Found: C, 52·5; H, 5·6; N, 12·95. $C_{19}H_{24}N_4O_8$ requires: C, 52·3; H, 5·55; N, 12·85%).

The quantitative evaluation of diastereoisomeric amino-alcohols was made by GLC using Versamid 10% on Chromosorb W; carrier gas: He; temp 180°.

1R,2S(−)-1-*Phenyl*-1,2-*dimethyl*-3-*dimethylamino-propan*-1-*ol* (III)

This compound obtained from *S*(+)-α-methyl-β-dimethylamino-propiophenone (I),[2] had m.p. 39–41°, $[\alpha]_D$ −3° (*c* = 2, MeOH); hydrochloride m.p. 168–170°, $[\alpha]_D$ +27° (*c* = 1, MeOH).

Optical enrichment of (−)-1-*phenyl*-1,2-*dimethyl*-3-*dimethylamino-propan*-1-*ol* (III)

Compound III (6·7 g, 0·032 mol) and an equimolecular amount of (+)-dibenzoyl-tartaric acid emihydrate in EtOH (150 ml) gave the corresponding salt, m.p. 155° (dec) after two recrystallizations from EtOH, $[\alpha]_D$ +113° (*c* = 1, MeOH). This salt gave 3·7 g of (−)-III, m.p. 56–57° from pet. ether, $[\alpha]_D$ −6° (*c* = 2, MeOH). (Found: C, 75·75; H, 10·9; N, 6·8. $C_{13}H_{21}NO$ requires: C, 75·3; H, 10·2; N, 6·75%); hydrochloride, m.p. 183–184°, $[\alpha]_D$ +43° (*c* = 1, MeOH). (Found: C, 63·7; H, 9·1; N, 5·8. $C_{13}H_{22}NOCl$ requires: C, 64·05; H, 9·1; N, 5·75%).

(+)-(1-*Phenyl*-1,2-*dimethyl*-3-*dimethylamino*)-*propyl-methyl-ether-iodomethylate* (V)

To a soln of (−)-III (5 g, 0·024 mol) in dry toluene (80 ml), K (1·23 g, 0·031 mol) was added and the mixture refluxed for 2 hr. MeI was then added (10·6 g, 0·75 mol) in two portions, refluxing for a total of 3–4 hr.[5]

The ppt was filtered off, washed with EtOAc and dissolved in CH_2Cl_2 (80–100 ml). The insoluble KI was removed by filtration and the filtrate, after removal of the solvent, afforded 8·1 g (92%) of V, m.p. 184–189°, $[\alpha]_D$ +38° (c = 1, MeOH). Two recrystallizations from 95% EtOH gave (+)-V emihydrate, m.p. 198–199°, $[\alpha]_D$ +42° (*c* = 1, MeOH). (Found: C, 48·35; H, 7·25; N, 3·9. $C_{15}H_{26}NOI.\frac{1}{2}H_2O$ requires: C, 48·25; H, 7·25; N, 3·75%).

(−)-1-*Methoxy*-1-*phenyl*-1,2-*dimethyl-prop*-2-*ene* (VI)

A soln of (+)-V (5·8 g, 0·016 mol, $[\alpha]_D$ +42°, MeOH) in an aqueous (200 ml) suspension of Ag_2O (0·03 mol) was stirred for 15 min at room temp. The solid was removed by filtration and most of the water evaporated at 50°, under reduced press. The viscous residue was warmed in a distillation apparatus at 100° and 15–17 mm Hg press: a mixture of water and the product distillate slowly at 70–80°.

The distillate was extracted with pet. ether and dried. After removal of the solvent under reduced press, the residue (1·6 g) was purified by chromatography on aluminium oxide with pet. ether. The first fractions gave (−)-VI in 40% yield, b.p. (13 mmHg) 87–89°, $[\alpha]_D$ −60° (*c* = 1, MeOH). (Found: C, 81·65; H, 9·1. $C_{12}H_{16}O$ requires: C, 81·75; H, 9·15%).

Optical resolution of (±)-2-*methoxy*-2-*phenyl-propionic-acid* (VII) (*atrolactic-acid-methylether*)

Compound (±)-VII (20·45 g, 0·11 mol) and an equimolecular amount of brucine in acetone (100 ml)

* Keto-base, when present, can be eliminated by steam distillation of the aqueous soln (pH 6-7) of the hydrochlorides.

gave, after 1–2 hr, 54 g of the corresponding salt, which was then suspended in 100 ml boiling acetone and the warm mixture filtered. The solid was again treated as above with 70 ml acetone. The residual brucine salt (23 g) had m.p. 178–180°, $[\alpha]_D$ −11° (*c* = 1, MeOH). (Found: C, 69·1; H, 6·7; N, 4·95. $C_{33}H_{38}N_2O_7$ requires: C, 68·95; H, 6·65; N, 4·85%). Free *R*(−)-acid-VII[4]: $[\alpha]_D$ −32·5° (Neat, l = 0·1 dm), = −26° (*c* = 1, MeOH).

From the first two acetone mother liquors, 25 g of salt were obtained, m.p. 110–112°, $[\alpha]_D$ +3° (*c* = 1, MeOH). (Found: C, 68·0; H, 6·4; N, 4·7%). Free S(+)-acid VII[4]: $[\alpha]_D$ +31·5° (neat, l = 0·1 dm), = +25° (*c* = 1, MeOH).

R(+)-2 *Methoxy-2-phenyl-methylpropionate* (VIII)

The above *R*(−)-VII was esterified with diazomethane,* B.p. (0·6 mmHg) 74°, $[\alpha]_D$ +43° (neat, l = 0·1 dm), = −12° (*c* = 1, MeOH).

(−)-1,1,2-*Trimethyl-2-methoxy-2-phenyl-propan-1-ol* (IX)

(+)-Methyl ester VIII (6 g, 0·03 mol) and MeMgI (0·15 mol) in ether, were refluxed for 5 hr. The mixture was then poured in 0·5N cold H_2SO_4 and rapidly extracted with ether. The organic layer was dried and the solvent removed: the residual oil was shaken for some minutes with a neutral conc hydroalcoholic soln of hydroxylamine. The mixture was made alkaline (pH 8–9) with NaOH and extracted with pet. ether.

The crude product (5 g), obtained after removal of the solvent, gave by distillation (−)-alcohol-IX (2·3 g), b.p. (0·8 mmHg) 78°, $[\alpha]_D$ −52° (neat, l = 0·1 dm), = −43° (*c* = 1, MeOH). (Found: C, 74·5; H, 9·7. $C_{12}H_{18}O_2$ requires: C, 74·03; H, 9·34%).

(+)-1-*Methoxy*-1-*phenyl*-1,2-*dimethyl-prop*-2-*ene* (VI)

Thionyl chloride (0·06 mol) in pyridine (5 ml) was added dropwise, during 30 min, to a stirred soln of (−)-IX (6·15 g, 0·032 mol) in 25 ml pyridine, cooled in ice-bath at 0°. The mixture was then stirred for 30 min at room temp and extracted with pet. ether. The solvent was removed under reduced press and the residual oil treated with alcoholic KOH (50 ml) for 20 min at room temp. The soln was then diluted with water and extracted with pet. ether. The organic layer was washed, dried and the solvent removed on a fractionating column. The residual oil was eluted on aluminium oxide with pet. ether and the first fractions gave (+)-VI (yield 20%), b.p. (13 mmHg) 88–90°, $[\alpha]_D$ +69° (neat, l = 0·1 dm), = +24° (*c* = 1, MeOH); IR spectrum and elemental analysis agreed with that of (−)-VI.

Optical resolution of (±)-3-*methyl*-4-*dimethylamino-butan*-2-*one* (II)

Compound (±)-II (6·9 g, 0·053 mol) and an equimolecular amount of (−)-dibenzoyl-tartaric acid in acetone (50 ml) gave, after 2–3 hr, 13·5 g of the corresponding salt, m.p. 124–127°. After recrystallization from EtOH 7·5 g of product, m.p. 134–135° was obtained. (Found: C, 61·0; H, 6·1; N, 3·05; $C_{25}H_{29}NO_9$ requires: C, 61·6; H, 6·0; N, 2·85%).

The free base (1·2 g), $[\alpha]_D$ −26° (*c* = 1, MeOH/conc. HCl 10:1), so obtained, was not further purified.

(−)-1-*Phenyl*-1,2-*dimethyl*-3-*dimethylamino-propan*-1-*ol* (IV)

This compound was obtained from (−)-II (1·4 g, 0·011 mol) and PhMgI. The crude product (2·1 g), containing 14% of diastereoisomer III, had $[\alpha]_D$ −14° (*c* = 1, MeOH) = −19° (*c* = 1, MeOH/conc. HCl

salt, so obtained, had m.p. 132–134°. (Found: C, 65·5; H, 6·1; N, 2·6. $C_{31}H_{35}NO_9$ requires: C, 65·8; H, 6·2; N, 2·5%); free base: $[\alpha]_D$ −16 (*c* = 1, MeOH), = −23 (*c* = 1, MeOH/conc. HCl 10:1).

10:1) was purified as (+)-dibenzoyl-tartrate, isolating the portion (30%) soluble in warm acetone. The

(−)-1,1,2-*Trimethyl*-3-*dimethylamino-propan*-1-*ol-hydrochloride* (X)

(a) *From* (−)-*methyl-keto-base* (II). Compound (−)-II (1·7 g, 0·013 mol) and MeMgI gave 1·3 g of (−)-X, $[\alpha]_D$ −1·8 (*c* = 3, MeOH/conc HCl 10:1), hydrochloride, m.p. 131–133° from EtOAc/EtOH, $[\alpha]_D$ −1·9° (*c* = 3, MeOH/HCl). (Found: C, 52·8; H, 10·9; N, 7·8, $C_8H_{20}NOCl$ requires: C, 52·9; H, 11·1; N, 7·7%).

(b) *From* (+)-*amino-ester* (XI).[2*] Compound XI (2g)([$\alpha]_D$ +18°, MeOH) and MeMgI gave (−)-X

* Racemic N,N-dimethyl-α-methyl-β-alanine, employed for the synthesis of (+)-amino-ester-XI was prepared from methylmethacrylate (24 g) and dimethylamine (17 g) in methanol (200 ml). Working in the same conditions previously reported[2] for α-methyl-β-alanine, 19 g of crude amino-acid were obtained. The reaction to (±)-amino-ester-XI (b.p. 53–55°, 15 mm Hg) and its subsequent optical resolution were carried out as described.[2]

(yield 76%) $[\alpha]_D$ −3·2° (c = 3, MeOH/conc HCl 10:1); hydrochloride: m.p. 137–145° from EtOAc/EtOH $[\alpha]_D$ −3·9° (c = 3, MeOH/HCl) (Found: C, 53·0; H, 11·05; N, 7·8. $C_8H_{20}NOCl$ requires: C, 52·9; H, 11·1; N, 7·7%).

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