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SYNTHESIS OF RACEMIC ERYTHRO 2.3-DIMETHYL-VALERIC ACID AND MAXIMUM VALUES OF SPECIFIC ROTATORY POWERS OF (2R.3S) AND(2S.3S) 2.3-DIMETHYL VALERIC ACIDS

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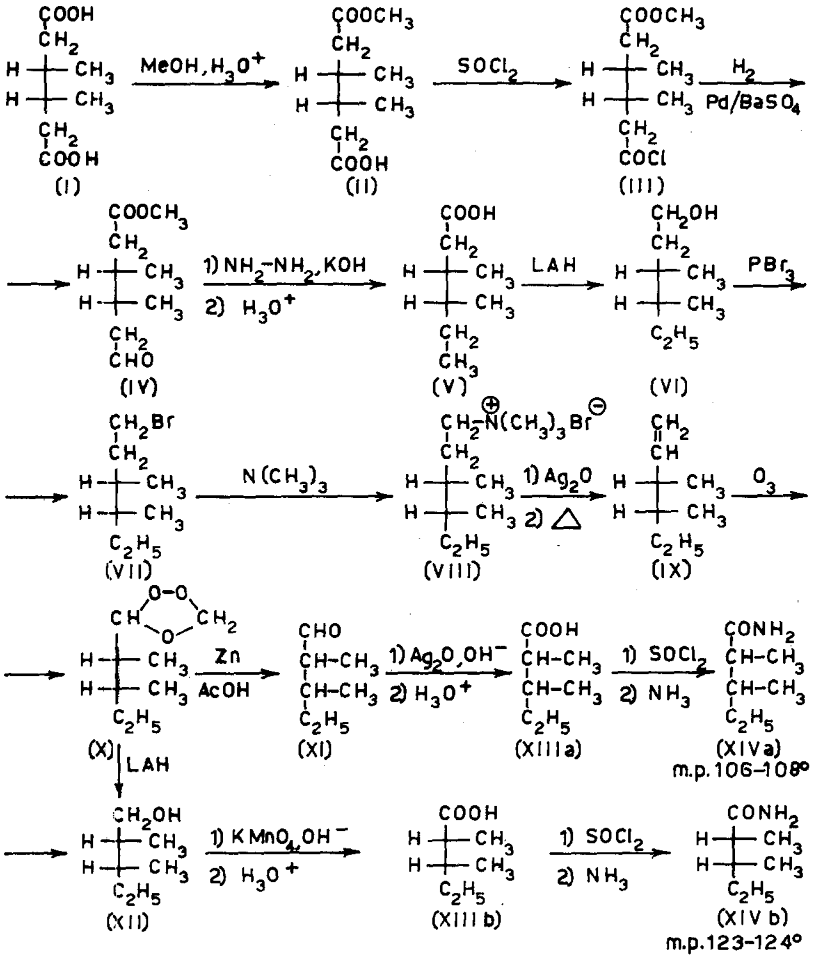
During the investigation of the asymmetric induction of sec.butyl group in a series of reactions (hydroformylation (1,2), propylene addition to sec.butyl lithium (3), disubstituted malonic acids decarboxylation (4)), quick methods for the determination of the optical purity of the two diastereoisomers of 2.3-dimethyl-valeric acid, readily obtainable from the reaction products were extremely useful.

In the present communication we report the preparation of the racemic erythro 2.3-dimethyl-valeric acid amide, the N.M.R. quantitative analysis of mixtures of erythro and threo 2.3-dimethyl-valeric acid amides and the relationships between $[\alpha]_D$ and optical purity (5) for the above erythro and threo compounds.

Starting from meso-3.4-dimethyl-adipic acid (I) (m.p. 133-134°) (6), erythro 2.3-dimethyl-valeric acid (XIIIb) has been prepared in 12 steps with 10% overall yield, and characterized as amide (Scheme 1).

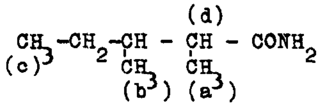
SCHEME 1 (7)


(I)
MeOH, H3O+
(II)
SOCl2
(III)
H2
Pd/BaSO4
(IV)
1) NH2-NH2, KOH
2) H3O+
(V)
LAH
(VI)
PBr3
(VII)
N(CH3)3
(VIII)
1) Ag2O
2) △
(IX)
O3
(X)
Zn
AcOH
(XI)
1) Ag2O, OH−
2) H3O+
(XIIIa)
1) SOCl2
2) NH3
(XIVa)
m.p. 106-108°
LAH
(XII)
1) KMnO4, OH−
2) H3O+
(XIIIb)
1) SOCl2
2) NH3
(XIVb)
m.p. 123-124°

From the standpoint of the stereospecificity the most sensitive step is the decomposition of ozonide (X). In fact the N.M.R. spectrum of amide (XIVa) (m.p. 106-108°) of 2.3-dimethyl-valeric acid obtained decomposing (X) in acid medium and successively oxidizing with Ag_2O the aldehyde thus obtained shows 8 bands corresponding to $-CH_3$ and to $-\underset{|}{C}H-$ in α position with respect to $-\underset{\underset{O}{\|}}{C}-$ group (Table I, Case B).

TABLE I (i)

Chemical Shifts of $-CH_3$ (a),(b),(c) and $-\underset{|}{C}H-$ (d) Appearing in N.M.R. Spectra of Erythro and Threo 2.3-Dimethyl-Valeric Acid Amides and Their Mixture



$$\underset{(c)}{CH_3}-CH_2-\underset{\underset{(b)}{CH_3}}{\underset{|}{C}H}-\overset{(d)}{\underset{\underset{(a)}{CH_3}}{\underset{|}{C}H}}-CONH_2$$

Diastereoisomer	Chemical Shifts (p.p.m.)			
	δ_a	δ_b	δ_c	δ_d
A) Erythro (ii)	1.13	0.94	0.88	2.11
B) Mixture of Erythro and Threo (iii)	1.13-1.09	0.94-0.89	0.88-0.89	2.11-2.19
C) Threo (iiii)	1.09	0.89	0.89	2.19

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i) All N.M.R. spectra were determined on a Varian HA-100 I spectrometer at 100 Mc; as solvent chloroform-d was used.

ii) Obtained from meso-3.4-dimethyl-adipic acid, according to (Scheme I) and from methyl-sec.butyl-malonic acid, by thermal decarboxylation followed by fractional crystallization of the corresponding amides.

iii) Obtained from meso-3.4-dimethyl-adipic acid, by acid decomposition of ozonide (VIII) or from methyl-sec.butyl-malonic acid by thermal decarboxylation.

iiii) Determined on the basis of the N.M.R. spectra of erythro and of mixtures of erythro and threo amides containing different percent of erythro diastereoisomer.

N.M.R. spectra containing the same bands have been obtained from the mixture of diastereoisomeric amides (m.p. 106-110°) of 2.3-dimethyl-valeric acids prepared according to Chichibabin (8).

On the contrary, amide (m.p. 123-124°) (XIVb) of 2.3-dimethyl-valeric acid obtained reducing the ozonide (X) with LAH and oxidizing 2.3-dimethyl-1-pentanol thus obtained by $KMnO_4$ shows a N.M.R. spectrum in which only 4 bands can be attributed to methyl groups (a),(b),(c) and to $-\underset{|}{C}H-$ group in α position with respect to $-\underset{\underset{O}{\|}}{C}-$ group (Table I, Case A).

The same N.M.R. spectrum is shown by the amide (m.p.123-124°) obtained by fractional crystallization from MeOH (40%) and water starting with the amides mixture prepared according to Chichibabin (8).

Since in none of the steps performed to convert *meso*-3.4-dimethyl-adipic acid into 2.3-dimethyl-valeric acid inversion of asymmetric carbon atoms configuration should take place, we have attributed to 2.3-dimethyl-valeric acid (XIIIb) and its amide (XIVb) (m.p. 123-124°) the *erythro* steric structure.

Using N.M.R. spectra to determine the ratio between *erythro* and *threo* diastereoisomers of 2.3-dimethyl-valeric acid in their mixture, maximum value of optical rotation of the diastereoisomers has been determined as follows:

a mixture of optically active diastereoisomeric 2.3-dimethyl-valeric acids (XVI), with known optical purity of the asymmetric carbon atom in β position with respect to -COOH group has been prepared by $KMnO_4$ oxidation of (3S)-2.3-dimethyl-1-pentanols (9) (XV) having known optical purity of the asymmetric carbon atom 3S (9) (Scheme 2).

The diastereoisomers have been partially separated by fractional distillation of the corresponding mixture of methyl esters (XVII).

From the first and last fraction of the fractional distillation the corresponding amides were prepared and their diastereoisomeric composition were determined by N.M.R. analysis.

TABLE II

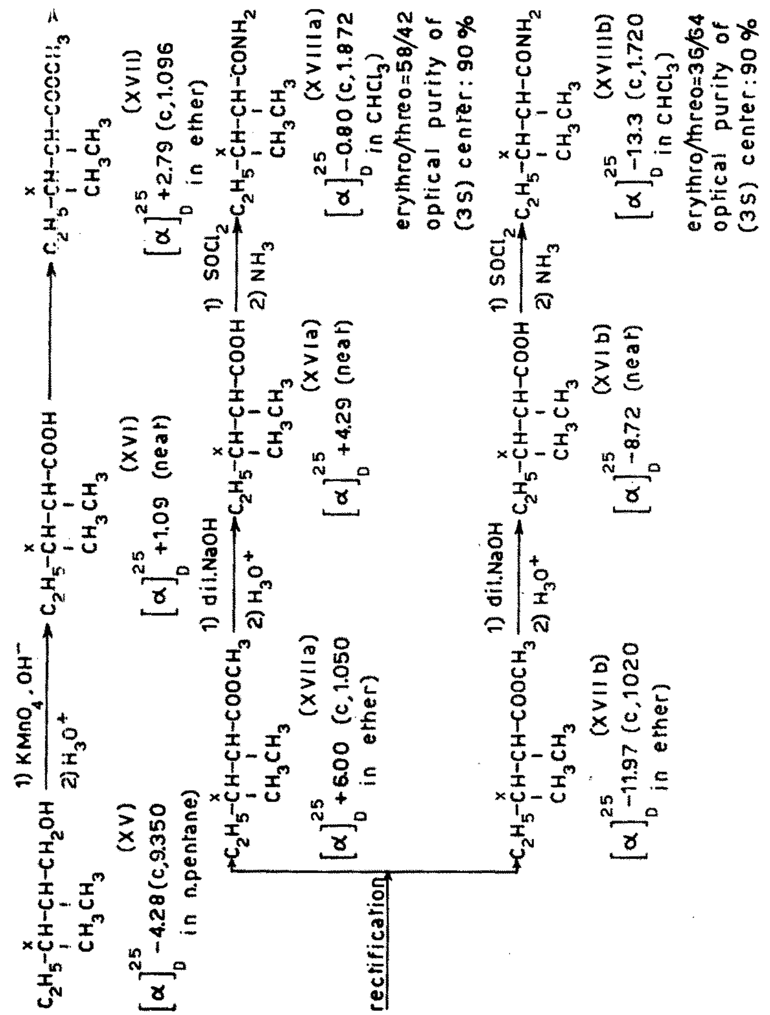
Maximum Values of Specific Rotatory Power of the (3S)-2.3-Dimethyl-Valeric Acids, Esters and Amides

Compound	Diastereoisomer	$[\alpha]_{D\,max}^{25}$
Acid	Erythro	+ 29.5 (neat)
Acid	Threo	- 32.4 (neat)
Ester	Erythro	+ 31.9 (c,1.050 in ether)
Ester	Threo	- 37.0 (c,1.020 in ether)
Amide	Erythro	+ 23.4 (c,1.872 in $CHCl_3$)
Amide	Threo	- 35.0 (c,1.920 in $CHCl_3$)

The acid mixture regenerated from the amides, prepared from the original diastereoisomeric esters mixture, showed the same optical activity and the same diastereoisomeric composition observed in the acids mixture used for preparing esters(10), proving that no racemization takes place in the preparation of the amides from the 2.3-dimethyl-valeric acids.

Plotting % erythro measured by N.M.R. analysis against $[\alpha]_D$ for the mixture of diastereoisomeric amides having optical purity of the 3S center of 90%, $[\alpha]_D$ for the erythro and threo diastereoisomer having optical purity of 90% can be eva

SCHEME 2


C2H5-CH-CH-CH2OH (CH3 CH3) (XV) [α]D25 −4.28 (c,9.350 in n.pentane)
1) KMnO4, OH⁻ 2) H3O⁺
C2H5-CH-CH-COOH (CH3 CH3) (XVI) [α]D25 +1.09 (neat)
C2H5-CH-CH-COOCH3 (CH3 CH3) (XVII) [α]D25 +2.79 (c,1.096 in ether)
rectification
C2H5-CH-CH-COOCH3 (CH3 CH3) (XVIIa) [α]D25 +6.00 (c,1.050 in ether)
1) dil.NaOH 2) H3O⁺
C2H5-CH-CH-COOH (CH3 CH3) (XVIa) [α]D25 +4.29 (neat)
1) SOCl2 2) NH3
C2H5-CH-CH-CONH2 (CH3 CH3) (XVIIIa) [α]D25 −0.80 (c,1.872 in CHCl3)
erythro/threo=58/42
optical purity of (3S) center: 90 %
C2H5-CH-CH-COOCH3 (CH3 CH3) (XVIIb) [α]D25 −11.97 (c,1020 in ether)
1) dil.NaOH 2) H3O⁺
C2H5-CH-CH-COOH (CH3 CH3) (XVIb) [α]D25 −8.72 (neat)
1) SOCl2 2) NH3
C2H5-CH-CH-CONH2 (CH3 CH3) (XVIIIb) [α]D25 −13.3 (c,1.720 in CHCl3)
erythro/threo=36/64
optical purity of (3S) center: 90 %

luated.

From the above data, $[\alpha]_{D\ max}$ for the erythro and threo acids esters and amides can be extrapolated (Table II) and therefore knowing $[\alpha]_D$ of a mixture of diastereoisomers of general formula C_2H_5-CH(CH_3)-CH(CH_3)-COX (X= OH, OCH_3, NH_2) and the diastereoisomeric composition of the mixture from N.M.R. analysis, it is possible to evaluate the optical purity of both diastereoisomers present in the mixture.

REFERENCES

1. P.Pino, S.Pucci and F.Piacenti, Chem.& Ind.(London) 294 (1963).
2. R.Rossi, L.Lardicci, F.Piacenti and P.Pino, Chimica e Industria, **46**, 828 (1964).
3. L.Lardicci, P.Salvadori and P.Pino, Atti Acc.Naz.Lincei (1966) in press.
4. V.Scartoni, Thesis, Pisa (1965).
5. The optical purity of the compounds we have prepared have been estimated assuming optical purity of 100% for (-)-2-methyl-1-butanol having $[\alpha]_D^{25}$- 5.82 (R.M.Ikeda, R.E.Kepner and A.Webb, Anal.Chem., **28**, 1335 (1956).
6. S.Ställberg-Stenhagen, Arkiv för Kemi, **3**, 257 (1950).
7. Although the synthesis described in (Scheme 1) gives rise to couple of enantiomers (II-X,XII,XIIIb,XIVb), only one enantiomer of each couple is reported.
8. A.E.Chichibabin and M.M.Katznelson, Bull.Akad.Sci.U.R.S.S. Classe Sci.Math.Nat., 267 (1933).
9. L.Lardicci, R.Rossi and P.Pino, Chimica e Industria, **44**, 1002 (1962).
10. N.M.R. spectra of 2.3-dimethyl-valeric acids, methyl esters and amides are similar in the region between 0.8 and 1.2 p.p.m. in which the bands corresponding to methyl protons appear. Therefore on the basis of N.M.R. spectra, the composition of the diastereoisomeric mixtures can be evaluated not only in the case of the 2.3-dimethyl-valeric amides but also in the case of the corresponding acids and esters.