Tetrahedron, 1966, Vol. 22, pp. 1991 to 2001. Pergamon Press Ltd. Printed in Northern Ireland

SYNTHESIS OF SOME OPTICALLY ACTIVE α-ALKYLACRYLIC COMPOUNDS CONTAINING A SEC-BUTYL GROUP

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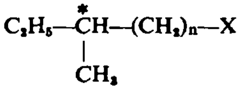
(*Received* 15 *November* 1965; *in revised form* 24 *January* 1966)

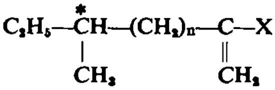
Abstract—α-alkylacroleins of general formula $C_2H_5-\overset{*}{\underset{CH_3}{CH}}-(CH_2)_{n-1}-\underset{\underset{CH_2}{\|}}{C}-CHO$ (n = 1,2,3) have been prepared by a Mannich reaction between optically active aldehydes of general formula $C_2H_5-\overset{*}{\underset{CH_3}{CH}}-(CH_2)_n-CHO$ (n = 1,2,3) and formaldehyde. From these compounds the corresponding acids, nitriles and the branched paraffins of general formula $C_2H_5-\overset{*}{\underset{CH_3}{CH}}-(CH_2)_n-\underset{CH_3}{CH}CH_3$ (n = 0,1,2) have been obtained. The racemization encountered in these syntheses is evaluated and on this basis the maximum molecular rotatory power of the new compounds calculated.

THE relationship between the sign of optical rotation, absolute configuration, optical purity and rotatory power of compounds of general formula I has been extensively investigated,[1–10] but data concerning compounds of formula II, are not available.



$C_2H_5-\overset{*}{\underset{CH_3}{CH}}-(CH_2)_n-X$

I



$C_2H_5-\overset{*}{\underset{CH_3}{CH}}-(CH_2)_n-\underset{\underset{CH_2}{\|}}{C}-X$

II

n = 0,1,2,3, etc.

(X = $-CHO$, $-CH_2OH$, $-COOH$, $-CN$, $-CH_2Cl$, etc.)

In such compounds the functional group X is conjugated with a double bond and the conjugated system is α, β or γ with respect to the asymmetric carbon atom.

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[1] P. A. Levene and R. E. Marker, *J. Biol. Chem.* **103**, 302–3 (1933).
[2] P. A. Levene, R. E. Marker and M. Kuna, *J. Biol. Chem.* **111**, 739 (1935).
[3] K. B. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.* **78**, 1642 (1956).
[4] P. Pino, L. Lardicci and L. Centoni, *J. Org. Chem.* **24**, 1399 (1959).
[5] L. Lardicci and P. Pino, *Gazz. Chim. Ital.* **91**, 441 (1961).
[6] L. Lardicci, *Gazz. Chim. Ital.* **91**, 458 (1961).
[7] L. Lardicci and L. Conti, *Ann. Chim.* **51**, 828 (1961).
[8] L. Lardicci and R. Rossi, *Atti Soc. Tosc. Sc. Nat.* **68A**, 23 (1961).
[9] L. Lardicci and L. Conti, *Gazz. Chim. Ital.* **92**, 428 (1962).
[10] L. Lardicci and R. Rossi, *Atti Soc. Tosc. Sc. Nat.* **69B**, 20 (1962).

These compounds (II) are, therefore, not only interesting intermediates in preparative chemistry, but serve as models for the investigation of the relationship between chemical structure and optical activity. They also may be used as optically active vinyl monomers in the preparation of optically active high polymers.[11–17]

The present paper reports the synthesis, some properties and the relationship between optical purity and [α] of the compounds (II; X = —CHO, —COOH, —CN).

Synthesis of optically active α-sec-butylacrylic compounds

The synthesis of α-alkylacroleins (II; X = —CHO) from glycerol ethers,[18] aldols[19–20] and the reaction of aliphatic aldehydes with formalin[21–24] has been described. The preparation of α-alkylacrylic acids (II; X = —COOH) has been carried out by dehydration of the β-hydroxyacids[25] and cyanohydrins of methylketones,[26,27] from the α-alkylmalonic esters,[28,29] and by oxidation of the corresponding α-alkylvinyl methyl ketones.[30]

The α-alkylacrylic acids (II) may be prepared by mild oxidation of the corresponding α-alkylacroleins,[31] and, via their oximes, it is possible to obtain the desired α-alkylacrylonitriles.[23]

The synthesis of II (X = —CHO) was achieved from the corresponding optically active aldehydes (I) (scheme 2), according to Marvel *et al.*[22]

The intermediates of the scheme 2 (I; X = —CHO) have been prepared according to scheme 1, with certain modifications of the procedures described in the literature.[2,6,9,32]

Compound II (X = —CHO) was oxidized with silver oxide[6,9] (scheme 3) and the

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[11] P. Pino, G. P. Lorenzi and L. Lardicci, *Chimica e Industria* **42,** 712 (1960).

[12] P. Pino and G. P. Lorenzi, *J. Amer. Chem. Soc.* **82,** 4745 (1960).

[13] P. Pino, G. P. Lorenzi, L. Lardicci and F. Ciardelli, *Vysokomolekul. Soedin.* **3,** 1597 (1961).

[14] P. Pino, F. Ciardelli, G. P. Lorenzi and G. Montagnoli, *Makromol. Chem.* **61,** 207 (1963).

[15] P. Pino, G. P. Lorenzi and S. Previtera, *Rend. Acc. Naz. Lincei* [8], **29,** 562 (1960).

[16] P. Pino, G. P. Lorenzi and E. Chiellini, *Ric. Sci.* **34,** 193 (1964).

[17] O. Pieroni, Thesis, University of Pisa, 1964; F. Ciardelli, E. Benedetti, O. Pieroni and P. Pino, *Chimica e Industria* **46,** 826 (1964).

[18] M. Sommelet, *Bull. soc. chim. Fr.* [4], **1,** 393, 409 (1907).

[19] T. Mitsui, M. Kitahara and Y. Miyatake, Rika Gaku Kenkyusho Hokoku, **38,** 205 (1962) [*Chem. Abstr.* **59,** 3762e (1963)].

[20] S. Malinowski, H. Jablczynska-Jedrzejewska, S. Basinski and S. Benbenek, *Chim. et Ind.* **85,** 885 (1961).

[21] C. Mannich and W. Krosche, *Arch. Pharm.* **250,** 647 (1912).

[22] C. S. Marvel, R. L. Myers and J. H. Saunders, *J. Amer. Chem. Soc.* **70,** 1694 (1948).

[23] C. S. Marvel, W. R. Miller and L. C. Chou, *J. Amer. Chem. Soc.* **72,** 5408 (1950).

[24] I. Farberov, G. S. Mironov and M. A. Korshunov, *Zh. Prikl. Khim.* **35,** 2483 (1962).

[25] E. E. Blaise and A. Luttringer, *Bull. soc. chim. Fr.* [3], **33,** 635, 760 (1905).

[26] J. Heyboer and A. J. Staverman, *Rec. Trav. Chim.* **69,** 790 (1950).

[27] This last method, according to a previous literature the suggestion,[28] could lead to mixtures of isomers.

[28] C. Mannich and K. Ritsert, *Ber. Dtsch. Chem. Ges.* **57,** 1116 (1924); C. Mannich and M. Bauroth, *Ber. Dtsch. Chem. Ges* **55,** 3504 (1922); C. Mannich and E. Ganz, *Ber. Dtsch. Chem. Ges.* **55,** 3486 (1922).

[29] F. F. Blicke, *Organic Reactions* Vol. I. p. 318, Wiley, New York (1943).

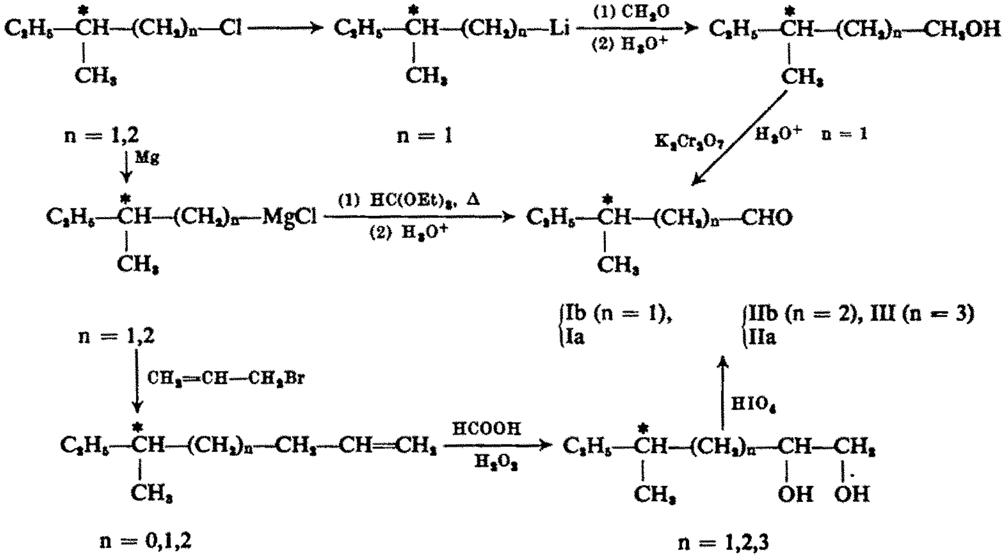
[30] T. White, *J. Chem. Soc.* 238 (1943).

[31] A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.* **2355** (1928).

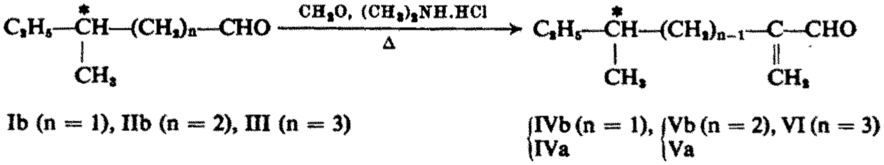
[32] P. Pino, L. Lardicci and L. Centoni, *Gazz. Chim. Ital.* **91,** 427 (1961).

α-alkylacrylonitriles (II; X = —CN) prepared (scheme 3) according to Marvel *et al.*[23] The yields obtained (scheme 1, 2 and 3) are summarized in the Table 1.

SCHEME 1



SCHEME 2



SCHEME 3

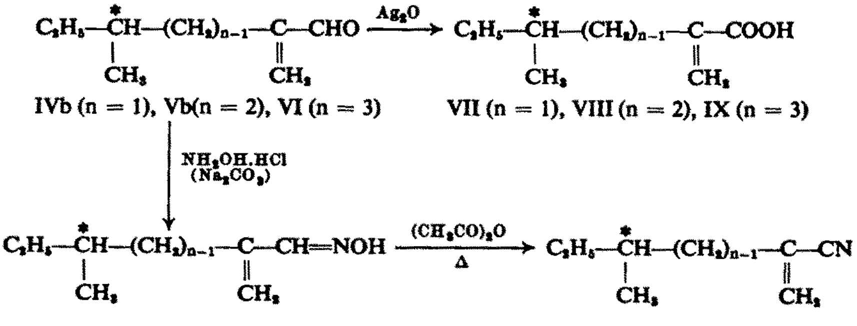
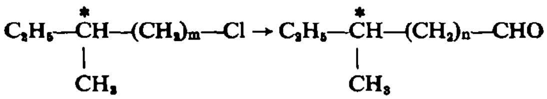
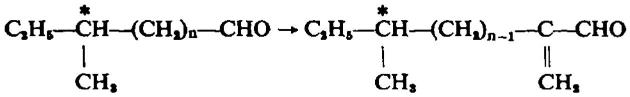
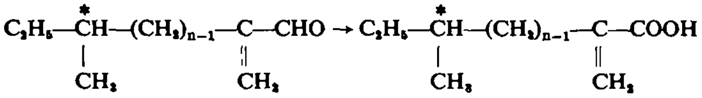
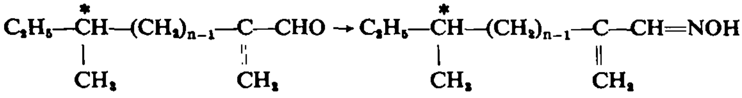
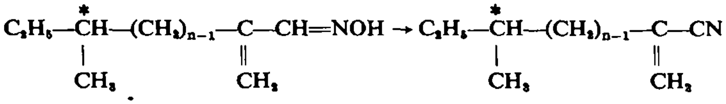
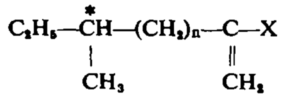


TABLE 1. YIELDS IN THE PREPARATION OF OPTICALLY ACTIVE α-SEC-BUTYLACRYLIC COMPOUNDS AND PRINCIPAL INTERMEDIATES

	n	Yield %
 $C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_m-Cl \rightarrow C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_n-CHO$	1	22[a,d]; 28[b]; 40[c]
	2	36[a,d]; 59[c]
	3	51[a]
 $C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_n-CHO \rightarrow C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_{n-1}-\underset{\underset{CH_2}{\parallel}}{C}-CHO$	1	45[d]; 68
	2	57[d]; 58
	3	55
 $C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_{n-1}-\underset{\underset{CH_2}{\parallel}}{C}-CHO \rightarrow C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_{n-1}-\underset{\underset{CH_2}{\parallel}}{C}-COOH$	1	53
	2	63[d]; 67
	3	41
 $C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_{n-1}-\underset{\underset{CH_2}{\parallel}}{C}-CHO \rightarrow C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_{n-1}-\underset{\underset{CH_2}{\parallel}}{C}-CH{=}NOH$	1	53
	2	53[d]; 57
	3	54
 $C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_{n-1}-\underset{\underset{CH_2}{\parallel}}{C}-CH{=}NOH \rightarrow C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_{n-1}-\underset{\underset{CH_2}{\parallel}}{C}-CN$	1	55
	2	54; 58[d]
	3	40

[a] By oxidation of the corresponding α-olefin with performic and periodic acid. [b] By $K_2Cr_2O_7$ oxidation of (+)(S)-3-methyl-1-pentanol. [c] By reaction of the corresponding Grignard reagent with ethyl orthoformate; the yield is calculated on the aldehyde purified through bisulphitic derivative. [d] Reaction carried out with racemic compounds.

TABLE 2. PHYSICAL PROPERTIES OF OPTICALLY ACTIVE α-SEC-BUTYLACRYLIC COMPOUNDS OF GENERAL FORMULA  $C_2H_5-\underset{CH_3}{\overset{*}{C}H}-(CH_2)_n-\underset{\underset{CH_2}{\parallel}}{C}-X$

X	n	B.p.,°(mm)	n_D^{25}	d_4^{25}	$[\alpha]_D^{25}$	MR_D	
						expt.	calc.[a]
—CHO	0	134–135°(760)[b]	1·4311–13[b]	0·8404	+29·63°	34·51	34·07
	1	61–62°(24)[c]	1·4365[c]	0·8415	+ 1·07°	39·18	38·68
	2	77°(20)	1·4406	0·8427	+11·77°	43·84	43·30
—COOH	0	109–110°(22)	1·4439	0·9521	+13·09°	35·70	35·59
	1	123° (14)[d]	1·4460–62[d]	0·9383[d]	+ 4·47°	40·37	40·21
	2	92° (0·9)	1·4494	0·9337	+11·39°	44·84	44·83
—CN	0	47–48° (19)	1·4215–16	0·8119	+18·84°	34·08	33·87
	1	64° (17)[e]	1·4297–99[e]	0·8231[e]	− 4·15°	38·59	38·49
	2	76–77° (20)	1·4340	0·8262	+10·89°	43·18	43·11

[a] Calculated according W. Roth, E. Eisenlohr and F. Lowe, *Refraktometrisches Hilfsbuch*. W. de Gruyter Verlag, Berlin (1952); [b] A sample of (R)(S)-2-methylene-3-methylpentanal showed b.p. 134–135°, n_D^{25} 1·4311; [c] A sample of (R)(S)-2-methylene-4-methylhexanal boiled at 60° (23 mm), n_D^{25} 1·4363–64; [d] A sample of (R)(S)-2-methylene-4-methylhexanoic acid boiled at 128° (20 mm), n_D^{25} 1·4462, d_4^{25} 0·9389; [e] A sample of (R)(S)-2-methylene-4-methylhexanenitrile showed b.p. 62–63° (14 mm), n_D^{25} 1·4294, d_4^{25} 0·8231.

The synthesis of α-alkylacroleins, via the Mannich reaction gives good yields (57–68 %),[22,23] although the corresponding oximes and nitriles are obtained in lower yields (40–57 %) because during the distillation, particularly in the case of the oximes, some decomposition and polymerization of the product takes place.[23,33,34]

The physical properties of the optically active α-alkylacrylic compounds prepared are given in Table 2; the data agree with that for the corresponding racemic compounds (see footnotes, Table 2).

The discrepancy between experimental and additive molar refraction[35] is 0·5 in the case of the α-alkylacroleins but is smaller (0·2–0·1) or even in the range of the experimental error for the corresponding acids and nitriles. The relatively low $[\Delta]MR_D$ observed in the α, β unsaturated compounds is in the range of the refraction increment attributed to the presence of a conjugated system in the molecule,[22,23,36–39]

The UV spectra of the alkyl acrylic compounds, which agree with the spectral behaviour of α, β unsaturated compounds, will be discussed in a future paper.

RESULTS AND DISCUSSION

The relationship between optical purity and $[\alpha]_D$ of (+)(S)-2-methylene-3-methylpentanal (II; X = —CHO; n = 0) has been established by conversion of IVb to (−)(S)-2,3-dimethylpentane (XIII; scheme 4) since the maximum molecular rotatory power of this branched paraffin is known.[40]

As the steps of the selected sequence involve very little racemization, the minimum optical purity thus calculated for α-sec-butylacrolein should be valid.

To evaluate the maximum racemization encountered in the conversion of (−)(S)-3-methylpentanal (Ib) to IVb, the minimum optical purity of Ib has been checked by oxidation to (+)(S)-3-methylpentanoic acid, for which the relationship between optical purity and rotatory power is known.[3,7] On this basis it is possible to extrapolate for the optically pure (S)-3-methylpentanal $[\alpha]^{25}_D$ −7·20° ÷ −7·30°. This rotation is lower than the value given by Levene *et al.*[2] (−8·7°, heptane) but their value is probably too high as the maximum rotatory power of (+)(S)-1-bromo-2-methylbutane

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[33] D. T. Morrow and R. R. Morner, *J. Amer. Chem. Soc.* **69**, 1831 (1947).

[34] Addition of a little amount of hydroquinone facilitates indeed the distillation but also in this case, a very viscous yellow-brown residue, thermally unstable, is formed in the distillation flask.

[35] W. Roth, F. Eisenlohr and F. Lowe, *Refraktometrisches Hilfsbuch*, W. de Gruyter Verlag, Berlin (1952).

[36] K. Auwers and F. Eisenlohr, *Ber. Dtsch. Chem. Ges.* **43**, 815 (1910).

[37] R. Delay and S. Guillot-Allegre, *Bull. soc. chim. Fr.* [4] **53**, 301 (1933).

[38] J. Colonge, *Bull. soc. chim. Fr.* [5] **23**, 2118 (1936).

[39] F. Piacenti and P. P. Neggiani, *Atti Soc. Tosc. Sc. Nat.* **67A**, 30 (1960).

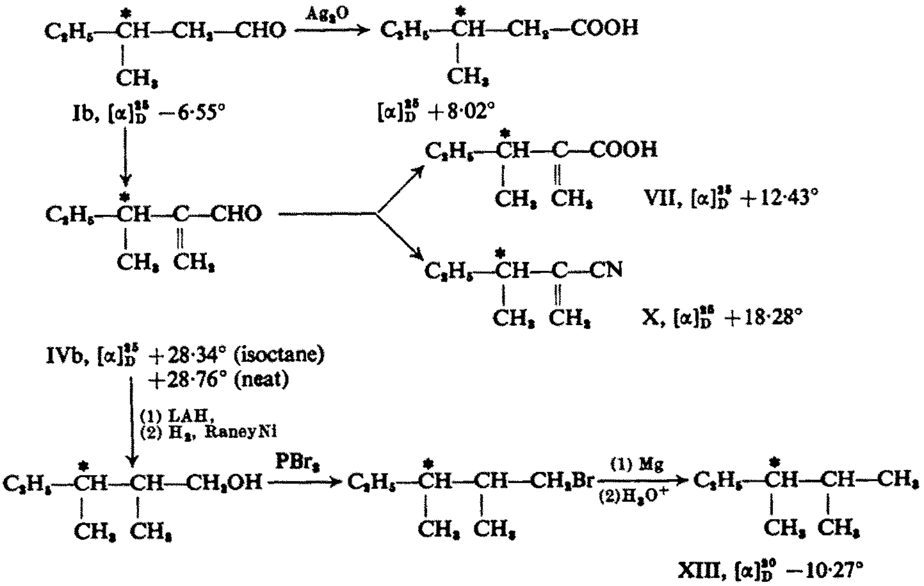
[40] Freudenberg and Lwowski[41] obtained a sample of (S)-2·3-dimethylpentane ($[\alpha]^{20}_D$ −11·4°) starting from (+)(S)-isopropylsuccinic acid ($[\alpha]^{20}_D$ +23·7°, water). As the specific rotatory power of (S)-isopropylsuccinic acid used by these Authors agrees quite well with the value reported by Fredga and Miettinen[42] for the optically pure antipode ($[\alpha]^{20}_D$ −23·36°, water) and as the steps of Freudenberg and Lwowski sequence do not seem to involve a high racemization, the value of −11·4° found for this paraffin is the more plausible value of maximum rotatory power known in literature. In our opinion literature[43] value (28·3°) appears to be too high indeed.

[41] K. Freudenberg and W. Lwowski, *Liebig's Ann.* **587**, 213 (1954).

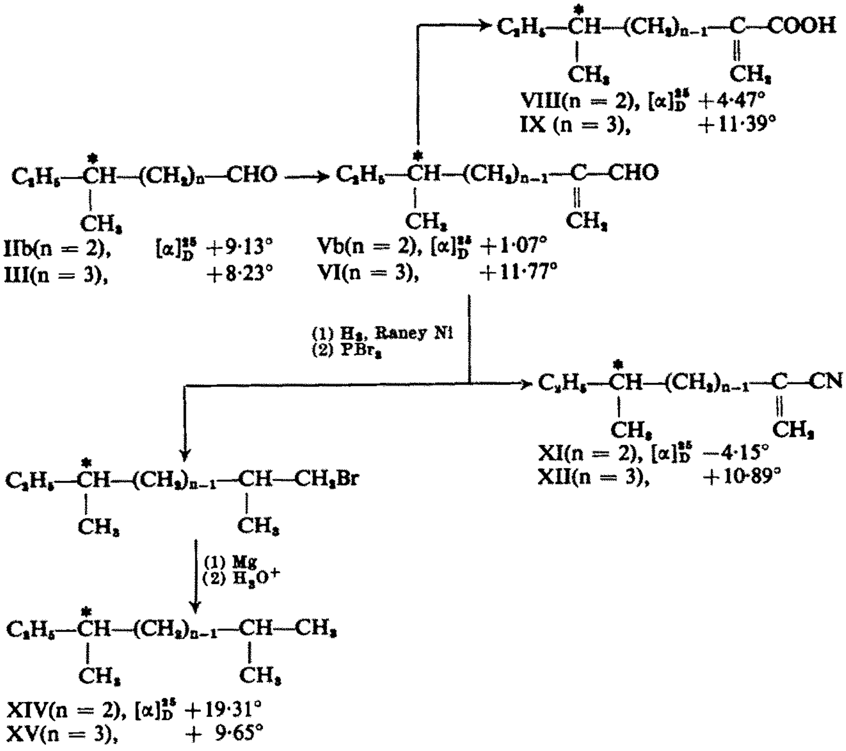
[42] A. Fredga and J. K. Miettinen, *Acta. Chem. Scand.* **1**, 371 (1947).

[43] P. A. Levene and R. E. Marker, *J. Biol. Chem.* **111**, 299 (1935).

SCHEME 4



SCHEME 5



used in the synthesis was taken to be $[\alpha]_D^{25}$ +5·23° instead of 4·1° which is the accepted value.[10,44]

On the basis of the minimum optical purity of (−)(S)-2,3-dimethylpentane recovered from IVb and of (−)(S)-3-methylpentanal used in the synthesis of IVb (scheme 4), it is possible to conclude that in the Mannich reaction between Ib and formaldehyde practically no racemization occurs (Table 3).

Based on these results, the optical purity of the aldehydes (scheme 5; Table 3) used in the syntheses of the other α-alkylacroleins may be taken as the asymmetric carbon atom of these compounds is in the β or γ position with respect to the carbon atom involved in the reaction.

By conversion of (+)(S)-2-methylene-4-methylhexanal (Vb) and (+)(S)-2-methylene-5-methylheptanal (VI) to branched paraffins XIV and XV (scheme 5; sequences not involving racemization) the maximum molecular rotatory powers reported in Table 3 may be extrapolated.

The optical rotations, calculated according to Brewster's semiempiric method, are in good agreement both with the maximum values extrapolated by us and with those reported by Marker.[45]

This general agreement, confirms the high optical purity (>95%) of the α-alkylacrylic aldehydes (Vb and VI) used in the synthesis of the paraffins.

If during the oxidation of α-alkylacroleins to acids and their conversion to oximes and nitriles (scheme 4 and 5) a high degree of racemization does not occur, then the maximum molecular rotatory power of the α-alkylacrylic compounds, can be calculated from the optical purity of the (+)(S)-2-methylene-3-methylpentanal (scheme 4) and the aldehydes used to prepare (S)-2-methylene-4-methylhexanal and (S)-2-methylene-5-methylheptanal respectively (scheme 5) (Table 3).

The general trend of optical activity in the new series is similar to that of alcohols,[1,5] chlorides,[5,9,32] aldehydes,[2,6,8,9] carboxylic acids,[3,5,7,8] methylketones,[10] ethyl ethers,[47] acetylenic hydrocarbons[48] and olefins.[4,6,9,33] In fact the optical rotation shows a maximum value when $n = 0$; this value decreases for $n = 1$ and increases again when $n = 2$ (Table 3).

The new optically active compounds have been correlated with many aliphatic optically active compounds, previously investigated, and containing a terminal sec-butyl group.[1,4,6,7–9,32] Their maximum molecular rotatory power reported in Table 3 is, therefore, dependent on the rotatory power attributed to optically pure (−)(S)-2-methyl-1-butanol.[49]

The lack of racemization in the Mannich reaction between I(X = —CHO) and formaldehyde (Table 3) is in keeping with the accepted mechanism of this reaction,

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[44] (−)(S)-3-methylpentanal is easily oxidized to (+)(S)-3-methylpentanoic acid as showed by the quick increase of the refraction index of a sample of aldehyde by exposure to air. A little amount (2–3%) of the acid in the aldehyde could lower the specific rotatory power of the aldehyde of 4·4–4·6%.

[45] Our data are indeed higher than those reported by Marker,[46] but the discrepancy, that does not exceed 10% of the Marker value, could fall within the range of the experimental errors in the evaluation of minimum optical purity of the starting products.

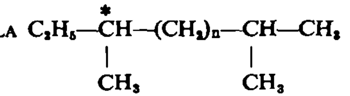
[46] R. Marker, *J. Amer. Chem. Soc.* **58**, 976 (1936).

[47] P. Salvadori and L. Lardicci, *Gazz. Chim. Ital.* **94**, 1205 (1964).

[48] L. Lardicci and L. Conti, *Atti Soc. Tosc. Sc. Nat.* **69B**, 83 (1962).

[49] F. Ciardelli and P. Pino, *Ric. Sci.* **34**, 694 (1964); ref. 1.

TABLE 3. RELATIONSHIP BETWEEN OPTICAL PURITY AND $[\alpha]_D$ OF OPTICALLY ACTIVE α-ALKYLACRYLIC PREPARED COMPOUNDS AND PARAFFINS OF GENERAL FORMULA



$$C_2H_5-\overset{*}{\underset{CH_3}{C}}H-(CH_2)_n-\underset{CH_3}{C}H-CH_3$$

$C_2H_5-\overset{*}{\underset{CH_3}{C}}H-(CH_2)_n-CHO$			$C_2H_5-\overset{*}{\underset{CH_3}{C}}H-(CH_2)_n-\underset{CH_2}{\overset{\Vert}{C}}-X$					$C_2H_5-\overset{*}{\underset{CH_3}{C}}H-(CH_2)_n-\underset{CH_3}{C}H-CH_3$					
											$[M]_D^{25}$ max.		
n	$[\alpha]_D^{25}$	optical purity %	n	X	$[\alpha]_D^{25}$	optical purity %	$[M]_D^{25}$ max.	n	$[\alpha]_D^{25}$	optical purity %	found	calc.	lit.
1	−6·55°	90·8[a]	0	—CHO	+28·76°	90·0[b]	+35·8	0	−10·27°[c]	90·0[d]	—	−15·0[e,f]	−11·4[c,d]
				—COOH	+12·43°	90·0[g]	+17·7						
				—CN	+18·28°	90·0[g]	+22·1						
2	+9·13°	96·0[h]	1	—CHO	+1·07°	96·0[i]	+1·4	1	+19·31°	96·0	+22·9	+20[f]	+21·3[l]
				—COOH	+4·47°	96·0[i]	+6·6						
				—CN	−4·15°	96·0[i]	−5·5						
3	+8·23°	95·0[m]	2	—CHO	+11·77°	95·0[i]	+17·4	2	+9·65°	95·0	+13·1	+13·3[f]	+11·9[l]
				—COOH	+11·39°	95·0[i]	+18·7						
				—CN	+10·89°	95·0[i]	+15·7						

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[a] Calculation based on optically pure (S)-3-methylpentanoic acid, $[\alpha]_D^{25}$ +8·83° [K. B. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.* **78**, 1642 (1956)]; [b] Calculation based on optically pure (S)-2,3-dimethylpentane, $[\alpha]_D^{20}$ −11·4°; [c] At 20°; [d] K. Freudenberg and W. Lwowski, *Leibig's Ann.* **587**, 224 (1954); [e] P. Pino, F. Ciardelli, G. P. Lorenzi and G. Montagnoli, *Makromol. Chem.* **61**, 217 (1963); [f] According Brewster's procedure [*J. Amer. Chem. Soc.* **81**, 5480 (1959)]; [g] The attributed optical purity is the same of the α-sec-butylacrolein used in its preparation; [h] L. Lardicci *Gazz. Chim. Ital.* **91**, 458 (1961); [i] The attributed optical purity is the same of the aldehyde used in its preparation; [l] R. E. Marker, *J. Amer. Chem. Soc.* **58**, 976 (1936); [m] L. Lardicci and L. Conti, *Gazz. Chim. Ital.* **92**, 428 (1962).

the enolization of the carbonylic compound affecting only the methylene group next to the carbonyl, according to the scheme proposed by Cunnings and Shelton.[50]

EXPERIMENTAL

M.ps and b.ps are uncorrected. The former were determined with a Kofler apparatus. Microanalyses were by A. Bernhardt, Mikroanalytisches Laboratorium in Max Planck Institut, Mülheim Ruhr, Germany. Rotations were determined using a Schmidt-Haensch polarimeter with sensitivity of ±0·005 degrees. Tubes 0·5 and 1 dm long, with a glass sleeve for the thermostatic fluid, were used. The optical activity of the aldehydes, in an atmosphere of N_2, was determined by distilling the compounds directly into the polarimetric tube. The α-alkylacrylic compounds were distilled in the presence of small amounts of hydroquinone and stored in sealed vials in the presence of the same inhibitor.

(R)(S)-3-*Methylpentanal* (Ia) *and* (R)(S)-4-*methylhexanal* (IIa)

Compound Ia was prepared by hydroxylation of (R)(S)-4-methyl-1-hexene (b.p. 87°, n_D^{25} 1·3976[5]) with performic acid.[8,9] The 4-methylhexan-1,2-diol obtained (69% yield) was redistilled, b.p. 90–92° (0·7 mm), n_D^{25} 1·4449–51. (Found: C, 63·33; H, 12·17. $C_7H_{16}O_2$ requires: C, 63·59; H, 12·20%.) Oxidative cleavage of the 1,2-glycol with periodic acid, yielded Ia (64%) b.p. 119°, n_D^{25} 1·4010; lit.,[51] b.p. 35–36° (28 mm).

(R)(S)-4-Methyl-1-heptene (65 g, 0·58 mole), obtained from (R)(S)-2-methylbutylmagnesium chloride and allyl bromide,[8] (b.p. 114°, n_D^{25} 1·4075) was hydroxylated; 5-methylheptan-1,2-diol obtained (68·5 g, b.p. 103–104°, (1·6–1·8 mm), n_D^{25} 1·4478–83) by oxidative cleavage with periodic acid gave IIa (79 g; 76%). A fraction of this product, purified through the crystalline bisulphite derivative, had b.p. 144–145°, n_D^{25} 1·4117 (lit.[52], b.p. 144–145°, n_D^{25} 1·412).

(R)(S)-2-*Methylene*-3-*methylpentanal* (IVa) *and* (R)(S)-2-*methylene*-4-*methylhexanal* (Va)

To compound Ia (40 g; 0·4 moles) under N_2 in a 1 l four-necked flask fitted with a mechanical stirrer, thermometer, reflux condenser and dropping funnel, dimethylamine hydrochloride (43 g) and 40% solution of HCHO (42 g) were added with stirring and the mixture, heated at 80° for 3 hr. After steam distillation and the usual procedure,[22] IVa (20·3 g) was obtained.

In a similar manner (mixture heated at 93° for 33 hr.) Va was obtained. (Found: C, 75·63; H, 10·95. $C_8H_{14}O$ requires: C, 76·13; H, 11·18%.)

(−)(S)-3-*Methylpentanal* (Ib)

(a) *From* (+)(S)-3-*methyl*-1-*pentanol.* (+)(S)-3-methyl-1-pentanol (50 g, 0·5 mole; b.p. 152–153°, n_D^{25} 1·4170–73, $[\alpha]_D^{25}$ +8·36°[4]) was oxidized as previously described[8] (48·8 g potassium dichromate in 290 ml water and addition of 40 ml conc. H_2SO_4). From the aldehyde-water azeotropic mixture (b.p. 90·5–91°), Ib (60 g), b.p. 119–120°, n_D^{25} 1·4005 (lit.,[54] b.p. 119°, n_D^{25} 1·4014), $[\alpha]_D^{25}$ −7·02°, was obtained. (Found: C, 72·08; H, 12·09. Calc. for $C_6H_{12}O$: C, 71·95; H, 12·08%.)

The 2,4-dinitrophenylhydrazone, from EtOH, melted at 93–94° (lit.,[51] 93–94°).

(b) *From* (+)(S)-2-*methylbutylmagnesium chloride.* An ethereal Grignard solution was prepared in an atmosphere of dry N_2 from (+)(S)-1-chloro-2-methylbutane (53·2 g; 0·5 mole, b.p. 99–100°, n_D^{25} 1·4101, $[\alpha]_D^{25}$ +1·61°)[7] and Mg (12·2 g; 0·5 mole) in 90% yield. This reagent was added (4 hr.) dropwise with stirring to boiling ethyl orthoformate (66 g, 0·45, mole). The reaction mixture yielded Ib (20·0 g) in accordance with the Levene *et al.* procedure,[8] b.p. 120°, n_D^{25} 1·4002, $[\alpha]_D^{25}$ −7·07°.

(+)(S)-3-*Methylpentanoic acid*

Compound Ib (8 g, $[\alpha]_D^{25}$ −6·84°) was oxidized with Ag_2O[8,9] (freshly precipitated) and yielded (+)(S)-3-methylpentanoic acid, (60%), b.p. 102° (20 mm), n_D^{25} 1·4143, $[\alpha]_D^{25}$ +8·38° (lit.,[7] b.p. 102–103°/20 mm, n_D^{25} 1·4145).

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[50] F. T. Cunnings and J. R. Shelton, *J. Org. Chem.* **25**, 419 (1960).

[51] H. Adkin and G. Krsek, *J. Amer. Chem. Soc.* **71**, 3053 (1949).

(+)(S)-4-*Methylhexanal* (IIb)

(+)(S)-1-Chloro-3-methylpentane (b.p. 128·5–129°, n^{25}_{D} 1·4188–1·4192, $[\alpha]^{25}_{D}$ +19·08°)[5] and Mg in N_2 atmosphere yielded (S)-3-methylpentylmagnesium chloride (88% yield). Ethyl orthoformate freshly distilled (118·6 g, 0·82 mole) was added (40 min) to the Grignard solution (0·78 mole in 500 ml ethyl ether), cooled in an ice bath. The next day, the mixture under N_2 was stirred at room temp (5 hr.) and then heated under reflux for 13 hr. Compound IIb (53 g), b.p. 144–145°, n^{25}_{D} 1·4121–22, $[\alpha]^{25}_{D}$ +9·13° (lit.,[6] b.p. 144–145°, n^{25}_{D} 1·4120), was obtained from the ethereal extracts of the crude aldehyde via the bisulphite compound.

The 2,4-dinitrophenylhydrazone, from EtOH, melted at 89–90° (lit.,[52] 88·5–89°).

(+)(S)-5-*Methylheptanal* (III)

Performic acid hydroxylation of (+)(S)-6-methyl-1-octene, $[\alpha]^{25}_{D}$ +10·3° and oxidative cleavage of the 1,2-diol obtained, yielded III, b.p. 62–63° (19 mm), n^{25}_{D} 1·4177, $[\alpha]^{25}_{D}$ +8·23°.[9]

The 2,4-dinitrophenylhydrazone, from EtOH, melted at 72·5–73·5° (lit.,[52] 72–73·5°).

(+)(S)-2-*Methylene-3-methylpentanal* (IVb), (+)(S)-2-*methylene-4-methylhexanal* (Vb) *and* (+)(S)-2-*methylene-5-methylheptanal* (VI)

From Ib, $[\alpha]^{25}_{D}$ −7·07°, by a procedure similar to that described for IVa, compound IVb was obtained, $[\alpha]^{25}_{D}$ +29·20° (*c*, 3·766 in isooctane).[54]

The 2,4-dinitrophenylhydrazone, from AcOEt and EtOH, melted at 136–137°, $[\alpha]^{25}_{D}$ +7·13° (*c*, 1·102 in $CHCl_3$). (Found: C, 53·40; H, 5·70; N, 19·23. $C_{13}H_{16}N_4O_4$ requires: C, 53·42; H, 5·52; N, 19·17%.) Starting from IIb, compound Vb, $[\alpha]^{25}_{D}$ +1·07°, was obtained. The 2,4-dinitrophenylhydrazone, from AcOEt and EtOH, melted at 133·5–134·5°, $[\alpha]^{25}_{D}$ +17·25° (*c*, 1·043 in $CHCl_3$). (Found: C, 55·01; H, 5·88; N, 18·07. $C_{14}H_{18}N_4O_4$ requires: C, 54·89; H, 5·92; N, 18·29%.)

Compound III, $[\alpha]^{25}_{D}$ +8·23°, was converted to VI in a similar manner. (Found: C, 77·04; H, 11·33. $C_9H_{16}O$ requires: C, 77·09; H, 11·50%.)

The 2,4-dinitrophenylhydrazone, from AcOEt and EtOH, melted at 129–130°, $[\alpha]^{25}_{D}$ +6·91° (*c*, 1·157 in $CHCl_3$). (Found: C, 56·44; H, 6·35; N, 17·52. $C_{15}H_{20}N_4O_4$ requires: C, 56·24; H, 6·29; N, 17·49%.)

(+)(S)-2-*Methylene-3-methylpentanoic acid* (VII), (+)(S)-2-*methylene-4-methylhexanoic acid* (VIII) *and* (+)(S)-2-*methylene-5-methylheptanoic acid* (IX)

Compound IVb (10 g, 0·09 mole), $[\alpha]^{25}_{D}$ +29·82° (*c*, 4·527 in isooctane) was added to $AgNO_3$ (50·6 g) in water (105 ml) with stirring and NaOH (16·3 g) in water (220 ml) was slowly added (4 hr). After another hr stirring at 40–50°, the mixture was stirred at room temp for 2 hr and finally VII (8 g) was obtained, $[\alpha]^{25}_{D}$ +11·86° (*c*, 1·939 in pet. ether).

In another experiment, IVb, $[\alpha]^{25}_{D}$ +29·2° (isoctane) yielded VII, $[\alpha]^{25}_{D}$ +11·70° (*c*, 3·336 in pet. ether). (Found: C, 65·61; H, 9·46; neut. equiv., 128·5. $C_7H_{12}O_2$ requires: C, 65·59; H, 9·44%; neut. equiv., 128·17.)

Compound VIII was obtained from (+)(S)-2-methylene-4-methylhexanal, $[\alpha]^{25}_{D}$ +1·07° by a similar procedure. (Found: C, 67·44; H, 9·74; neut. equiv. 142·8. $C_8H_{14}O_2$ requires: C, 67·57; H, 9·93%; neut. equiv. 142·2.) From VI, $[\alpha]^{25}_{D}$ +11·77°, IX was obtained. (Found: C, 68·76; H, 10·24; neut. equiv., 156·01. $C_9H_{16}O_2$ requires: C, 69·19; H, 10·32%; neut. equiv., 156·21.)

(+)(S)-2-*Methylene-3-methylpentanenitrile* (X), (+)(S)-2-*methylene-4-methylhexanenitrile* (XI) *and* (+)(S)-2-*methylene-5-methylheptanenitrile* (XII)

Compound IVb (12·5 g, 0·11 mole), $[\alpha]^{25}_{D}$ +29·2° (isoctane), with excess hydroxylamine hydrochloride in water,[53] yielded the corresponding oxime (7·6 g), b.p. 56–57° (0·9 mm), n^{25}_{D} 1·4759–61, $[\alpha]^{25}_{D}$ +22·31° (*c*, 1·434 in MeOH).[54] The oxime was dehydrated by heating under reflux with Ac_2O[53] yielding X, $[\alpha]^{25}_{D}$ +18·84°, $[\alpha]^{25}_{D}$ +21·18° (*c*, 1·581 in MeOH).[54]

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[52] M. D. Sutherland, *J. Amer. Chem. Soc.* **75**, 5949 (1953).

[53] C. Djerassi and L. E. Geller, *J. Amer. Chem. Soc.* **81**, 2793 (1959).

[54] L. Lardicci, R. Rossi and P. Pino, *Chimica e Industria* **44**, 1002 (1962); preliminary communication.

[55] J. Dreux, *Bull. Soc. Chim. Fr.* **886** (1955).

In another experiment, the oxime, $[\alpha]_D^{25}$ +21·45° (*c*, 1·212 in MeOH) yielded X, $[\alpha]_D^{25}$ +20·92° (*c*, 1·577 in MeOH).[54] From Vb, $[\alpha]_D^{25}$ +1·07°, the oxime, b.p. 74–75° (0·5–0·6 mm), n_D^{25} 1·4760, d_4^{25} 0·904, $[\alpha]_D^{25}$ +9·77° (according to physical constants of a sample of racemic oxime, b.p. 74–75° (0·6 mm), n_D^{25} 1·4758–59) was recovered. (Found: C, 67·98; H, 10·56; N, 10·05. $C_8H_{15}NO$ requires: C, 68·04; H, 10·71; N, 9·92%.)

Dehydration of this oxime with Ac_2O yielded XI. (Found: C, 77·94; H, 10·73; N, 11·24. $C_8H_{13}N$ requires: C, 77·99; H, 10·64; N, 11·37%.)

Compound VI was converted to its oxime, b.p. 73° (0·8 mm), n_D^{25} 1·4753, d_4^{25} 0·897, $[\alpha]_D^{25}$ +10·83°. (Found: C, 69·52; H, 11·09; N, 9·24. $C_9H_{17}ON$ requires: C, 69·63; H, 11·04; N, 9·02%.)

From (+)(S)-2-methylene-5-methylheptanal oxime, the corresponding nitrile XII was obtained. (Found: C, 78·76; H, 11·15; N, 10·17. $C_9H_{15}N$ requires: C, 78·77; H, 11·02; N, 10·21%.)

(−)(S)-2,3-*Dimethylpentane* (XIII) *from* IVb

Compound IVb, $[\alpha]_D^{25}$ +28·34° (isoctane), by successive reduction with LAH and H_2 over Raney Ni was converted to (+)(3S)-2,3-dimethyl-1-pentanol (63% yield), b.p. 73·5–74° (17 mm), n_D^{25} 1·4284, $[\alpha]_D^{25}$ −3·18° (*c*, 10·067 in pet. ether) (lit.,[55] b.p. 162–164°, n_D^{20} 1·429). Following the Levene and Marker procedure,[56] the alcohol on treatment with PBr_3 yielded (+)(3S)-1-bromo-2,3-dimethylpentane (46%), b.p. 65–66° (30 mm), $[\alpha]_D^{25}$ +3·15° (*c*, 2·538 in ethyl ether).

The Grignard reagent from this alkyl halide was poured on to ice and H_2SO_4 aq in N_2 atmosphere and the hydrocarbon extracted with ether. By distillation of ether extracts from a small piece of Na, XIII (38%) b.p. 90·5°, n_D^{25} 1·3898, $[\alpha]_D^{20}$ −10·27° (lit.,[41] b.p. 89·2°, n_D^{20} 1·3921, d_4^{20} 0·6950, $[\alpha]_D^{20}$ −11·4°) was obtained.

(+)(S)-2,4-*Dimethylhexane* (XIV) *and* (+)(S)-2,5-*dimethylheptane* (XV), *from* Vb *and* VI

Compound Vb, $[\alpha]_D^{25}$ +1·07°, by catalytic reduction over Raney Ni at 120° and 127 atm H_2, was converted to (+)(4S)-2,4-dimethyl-1-hexanol (88%), b.p. 81–82° (15–16 mm), n_D^{25} 1·4278–81, $[\alpha]_D^{25}$ +16·28° (*c*, 11·302 in pet. ether). (Found: C, 73·76; H, 14·02. $C_8H_{18}O$: C, 73·78; H, 13·92%.) By treatment with PBr_3, (+)(4S)-1-bromo-2,4-dimethylhexane (74%), b.p. 73–74° (21 mm), n_D^{25} 1·4510–12, $[\alpha]_D^{25}$ +15·54° (*c*, 6·560 in ethyl ether), was obtained. (Found: C, 49·75; H, 8·93; Br, 41·59. $C_8H_{17}Br$ requires: C, 49·75; H, 8·87; Br, 41·37%.)

The Grignard compound of this alkyl halide on hydrolysis yielded pure XIV (49%), b.p. 109–110°, n_D^{25} 1·3934, $[\alpha]_D^{25}$ +19·31° (lit.,[57] b.p. 109·429°, n_D^{25} 1·3929, d_4^{25} 0·6962).

Compound VI, $[\alpha]_D^{25}$ +11·77°, was reduced with H_2 and Raney Ni to (+)(5S)-2,5-dimethyl-1-heptanol (85%). The crude product (b.p. 103–104° (24 mm), n_D^{25} 1·4323–1·4329) with PBr_3 was converted to (+)(5S)-1-bromo-2,5-dimethylheptane (72%).

The product obtained boiled at 109–110° (33 mm), n_D^{25} 1·4528–31, $[\alpha]_D^{25}$ +7·83° (*c*, 6·257 in ethyl ether). (Found: C, 52·42; H, 9·30; Br, 38·69. $C_9H_{19}Br$ requires: C, 52·18; H, 9·24; Br, 38·57%.)

Hydrolysis of the corresponding Grignard reagent, yielded pure XV (55%), b.p. 136°, n_D^{25} 1·4019–20, $[\alpha]_D^{25}$ +9·65° (lit.,[58] b.p. 136°, n_D^{25} 1·4015, d_4^{25} 0·711).

Acknowledgment—The authors thank Prof. Piero Pino for helpful discussions during the present investigation.

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[56] P. A. Levene and R. E. Marker, *J. Biol. Chem.* **91**, 405 (1931); 111, 309 (1935).

[57] D. Rossini, K. S. Pitzer, R. L. Arnett, R. M. Braun and G. C. Pimentel, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds* p. 39, Carnegie Press, Pittsburgh (1953).

[58] See Ref. 57, p. 40.