

## ASYMMETRIC REACTIONS. XLII.\*

## ABSOLUTE CONFIGURATION OF ALKYLARYLMETHANOLS AND ALKYLARYLMETHYLAMINES

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The absolute configuration of some alkylarylmethanols *Ia–e* and alkylarylmethylaminomethanes (*Ila–i*) has been determined by asymmetric reduction with optically active lithium alkoxyhydridoaluminates and by the method of asymmetric transformation.

For the study of the relationships between the absolute configuration and optical rotatory dispersion and circular dichroism of substances containing an aromatic nucleus as the optically active chromophore in the molecule, it was necessary to prepare a series of optically active alkylarylmethanols and alkylarylmethylamines, and to check or determine their absolute configuration, if unknown<sup>1</sup>. In this study we prepared some optically active alcohols *Ia–e* and amines *Ila–j*, the absolute configuration of which is unknown, making use of asymmetric reduction with optically active lithium alkoxyhydridoaluminates and the method of asymmetric transformation.

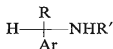
We prepared the starting ketones by Friedel–Crafts reaction; in some instances only we used Grignard's reaction with nitriles. On reduction of ketones with lithium tetrahydridoaluminate in the presence of (–)-quinine in ether we obtained dextrorotatory alcohols *Ia–e* exclusively, to which may be assigned the absolute configuration R on the basis of the empirical relationships<sup>2</sup> inferred earlier. The absolute configuration of alcohol *Ia* was determined by asymmetric reduction with the Grignard reagent prepared from (*S*)-(+)-1-chloro-2-methylbutane<sup>3</sup>, while that of alcohol *Ib*, by Prelog's method<sup>4</sup> and the asymmetric Meerwein–Ponndorf–Verley reduction<sup>5</sup>. The racemic alkylarylmethylamines *Ila–g* ( $R' = H$ ) were prepared by Wallach–Leuckart reaction from ketones. These were transformed to N-formyl derivatives *Ila–g* ( $R' = CHO$ ) under the effect of formyl acetate. The former were reduced to N-methyl derivatives *Ila–j* ( $R' = CH_3$ ) by lithium tetrahydridoaluminate. Only the N-formyl derivatives *Ilh–j* ( $R' = CHO$ ) were isolated directly from the Wallach–Leuckart reduction.

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*Ia*: R = C<sub>2</sub>H<sub>5</sub>, Ar = C<sub>6</sub>H<sub>5</sub>; *Ib*: R = CH<sub>3</sub>, Ar = 1-C<sub>10</sub>H<sub>7</sub>; *Ic*: R = CH<sub>3</sub>, Ar = *o*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>;  
*Id*: R = CH<sub>3</sub>, Ar = *m*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>; *Ie*: R = CH<sub>3</sub>, Ar = *p*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>.

For the determination of the absolute configuration of amines we used the method of asymmetric transformation<sup>6-8</sup>. In order to obtain unequivocal results we carried out our work with secondary amines and with (*S*)-(+)-hydratropic acid. The unreacted amines *Ia-i* (R' = CH<sub>3</sub>) isolated from the reaction were all levorotatory and of absolute configuration *S*. Presently the absolute configuration of amines<sup>9,10</sup> *Ila,c* and *Ilf* is known. It is not without interest that the empirically deduced rule,



*Ila*: R = C<sub>2</sub>H<sub>5</sub>, Ar = C<sub>6</sub>H<sub>5</sub>; *Ilb*: R = *i*-C<sub>3</sub>H<sub>7</sub>, Ar = C<sub>6</sub>H<sub>5</sub>; *Ilc*: R = *t*-C<sub>4</sub>H<sub>9</sub>, Ar = C<sub>6</sub>H<sub>5</sub>;  
*Ild*: R = CH<sub>3</sub>, Ar = *o*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>; *Ile*: R = CH<sub>3</sub>, Ar = *m*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>; *Ilf*: R = CH<sub>3</sub>,  
 Ar = *p*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>; *Ilg*: R = CH<sub>3</sub>, Ar = *p*-CH<sub>3</sub>O-C<sub>6</sub>H<sub>4</sub>; *Ilh*: R = C<sub>6</sub>H<sub>11</sub>, Ar = C<sub>6</sub>H<sub>5</sub>;  
*Ili*: R = C<sub>6</sub>H<sub>11</sub>, Ar = *o*-C<sub>6</sub>H<sub>4</sub>; *Ilj*: R = C<sub>6</sub>H<sub>11</sub>, Ar = 1-C<sub>10</sub>H<sub>7</sub>.

stating that all alkylarylmethanols of absolute *S*-configuration are levorotatory, is valid almost without exception<sup>11</sup>. In the UV spectra of both alcohols and amines we may see typical aromatic <sup>1</sup>L<sub>b</sub> bands with a fine structure between 250 and 270 nm. All alcohols and amines investigated of absolute *R*-configuration display in this region a negative Cotton effect, superimposed on the positive basic curve. In the case of the reversed configuration the opposite is true<sup>1</sup>.

## EXPERIMENTAL

The melting points and the boiling points are not corrected. Samples for analysis were dried *in vacuo* (oil pump) at room temperature for 8 hours. Optical rotations were measured using a polarimeter (±0.02° precision) the ORD curves on a Jasco UV 5 apparatus.

*p*-Methoxyacetophenone<sup>12</sup> b.p. 129°C/11 Torr, m.p. 36°C, 2,4,6-trimethylacetophenone<sup>12</sup> b.p. 107°C/10 Torr, propiophenone<sup>13</sup> b.p. 93°C/11 Torr, were prepared by Friedel-Crafts reaction from corresponding hydrocarbons. *Tert*-butyl phenyl ketone<sup>14</sup> b.p. 96°C/10 Torr, methyl *o*-tolyl ketone<sup>15</sup> b.p. 98°C/18 Torr, and methyl *m*-tolyl ketone<sup>16</sup> b.p. 94°C/11 Torr were obtained by Grignard reaction from nitriles.

### Asymmetric Reduction of Ketones

To 0.42 g (11 mmol) of lithium tetrahydridoaluminate in 300 ml of ether 3.56 g (11 mmol) of (-)-quinine were added and the mixture stirred for 10 minutes. Ketone (10 mmol) in 20 ml of ether was then added dropwise and the mixture refluxed for 4 hours. After cooling the mixture was decomposed with 10 ml of water and 100 ml of 20% H<sub>2</sub>SO<sub>4</sub>. The product was extracted with ether and the extract washed several times with dilute sulfuric acid and water, and dried over anhydrous sodium sulfate. The product was distilled *in vacuo*. The data concerning the obtained alcohols are in Table I.

TABLE I

Results of Asymmetric Reduction of Ketones with Lithium Tetrahydroaluminate in the Presence of (–)-Quinine in Ether

Alcohol	B.p. °C/Torr [ $\alpha$ ] <sub>D</sub> <sup>20</sup>	Formula (m.w.)	Calculated/Found	
			% C	% H
<i>Ia</i>	98.5/10	C <sub>9</sub> H <sub>12</sub> O (136.2)	79.37	8.88
	(+6.54)		78.96	9.00
<i>Ib</i>	162/9	C <sub>12</sub> H <sub>12</sub> O (172.2)	83.69	7.02
	(+2.57)		83.44	7.25
<i>Ic</i>	104.5/10	C <sub>9</sub> H <sub>12</sub> O (136.2)	79.37	8.88
	(+10.28)		79.39	9.03
<i>Id</i>	105/11	C <sub>9</sub> H <sub>12</sub> O (136.2)	79.37	8.88
	(+ 7.24)		79.27	8.98
<i>Ie</i>	101.5/10	C <sub>9</sub> H <sub>12</sub> O (136.2)	79.37	8.88
	(+12.45)		79.73	9.02

TABLE II

Racemic Alkylarylmethylamines, II (R' = H), Prepared by Wallach–Leuckart Reaction

Amine yield, %	B.p. °C/Torr (ref.)	Formula (m. w.)	Calculated/Found		
			% C	% H	% N
<i>Ila</i> (71)	85/12	C <sub>9</sub> H <sub>13</sub> N (135.2)	79.95	9.69	10.36
	99/16 (17)		79.82	9.73	10.12
<i>Ilb</i> (61)	86/9	C <sub>10</sub> H <sub>15</sub> N (149.2)	80.48	10.13	9.39
	95/14 (18)		80.58	10.25	9.61
<i>Ilc</i> (58)	111/20	C <sub>11</sub> H <sub>17</sub> N (163.3)	80.92	10.50	8.58
	115/22 (18)		80.99	10.72	8.82
<i>Ild</i> (55)	91/10	C <sub>9</sub> H <sub>13</sub> N (135.2)	79.95	9.69	10.36
	89/14 (19)		80.12	9.73	10.73
<i>Ile</i> (78)	83/10	C <sub>9</sub> H <sub>13</sub> N (135.2)	79.95	9.69	10.36
	204/205 (20)		80.22	10.08	9.99
<i>Ilf</i> (82)	85/11	C <sub>9</sub> H <sub>13</sub> N (135.2)	79.95	9.69	10.36
	205 (20)		80.01	9.88	10.12
<i>Ilg</i> (46)	126/20	C <sub>9</sub> H <sub>13</sub> NO (151.2)	71.49	8.67	9.26
	129/25 (20)		71.61	8.85	9.52

Preparation of Racemic Primary Amines *Ila-g* ( $R' = H$ ) from Ketones by Wallach-Leuckart Reduction

Formamide (45 g, 1 mol), formic acid (98%; 15.5 g; 0.35 mol), and 0.15 mol of the corresponding ketone were heated at 180°C for 40 hours. During this interval the reaction water and excess formic acid were distilled off. The ketone was returned. When the heating was terminated the reaction mixture was shaken with a double volume of water and the formyl derivative was extracted with ether. Formyl derivative was dissolved in 100 ml of concentrated hydrochloric acid and the mixture was refluxed for 2 hours. The cooled reaction mixture was extracted several times with benzene, in order to eliminate the unreacted ketone. The acid layer was alkalisied with a sodium hydroxide solution and the separated amine was extracted with ether. After drying the extract with solid potassium hydroxide the amine was distilled *in vacuo* (Table II).

TABLE III  
Racemic N-Formyl Derivatives *Ila-j* ( $R' = CHO$ )

Compound	M.p., °C (yield, %)	Formula (m.w.)	Calculated/Found		
			% C	% H	% N
<i>Ila</i>	49–50 <sup>a</sup> (58)	C <sub>10</sub> H <sub>13</sub> NO (163.2)	73.59	8.03	8.58
			73.47	8.23	8.53
<i>Ilb</i>	117–118/0.2 <sup>b</sup> (79)	C <sub>11</sub> H <sub>15</sub> NO (177.3)	74.54	8.53	7.90
			74.53	8.57	8.59
<i>Ilc</i>	66–67 <sup>a</sup> (58)	C <sub>12</sub> H <sub>17</sub> NO (191.3)	75.35	8.96	7.32
			79.49	9.26	7.15
<i>Ild</i>	55–56 <sup>a</sup> (58)	C <sub>10</sub> H <sub>13</sub> NO (163.2)	73.59	8.03	8.58
			73.43	8.25	8.57
<i>Ile</i>	125/0.06 <sup>b</sup> (82)	C <sub>10</sub> H <sub>13</sub> NO (163.2)	73.59	8.03	8.58
			73.55	8.29	8.87
<i>Ilf</i>	136/0.1 <sup>b</sup> (40)	C <sub>10</sub> H <sub>13</sub> NO (163.2)	73.59	8.03	8.58
			73.60	8.41	8.75
<i>Ilg</i>	145/0.05 <sup>b</sup> (67)	C <sub>10</sub> H <sub>13</sub> NO <sub>2</sub> (179.2)	67.02	7.32	7.82
			66.76	7.64	8.52
<i>Ilh</i>	127–128 <sup>a</sup> (75)	C <sub>14</sub> H <sub>19</sub> NO (217.3)	77.37	8.82	6.45
			77.49	8.94	6.38
<i>Ili</i>	116–118 <sup>a</sup> (38)	C <sub>15</sub> H <sub>21</sub> NO (231.3)	77.88	9.15	6.06
			77.90	9.39	5.70
<i>Ilj</i>	137–138 <sup>b</sup> (57)	C <sub>18</sub> H <sub>21</sub> NO (267.4)	80.86	7.92	5.24
			80.66	8.11	5.18

<sup>a</sup>Crystallised from light petroleum; <sup>b</sup>B.p. °C/Torr; <sup>c</sup>crystallised from ether.

## N-Formyl Derivatives of Racemic Amines

A solution of amine *Ila*-*j* ( $R' = H$ ) (0.1 mol) in 80 ml of benzene was mixed with 9.24 g (105 mmol) of formyl acetate<sup>21</sup>, under cooling with ice. After 24 hours standing benzene was distilled off and the residue dissolved in ether, washed with sodium hydrogen carbonate solution, and dried over sodium sulfate. After evaporation of ether the product was distilled or crystallised (Table III).

Secondary Amines *Ila*-*j* ( $R' = CH_3$ )

N-Formyl derivative of amine *Ila*-*j* ( $R' = CHO$ ) (50 mmol) was reduced with 3.8 g (100 mmol) of lithium tetrahydridoaluminate in 40 ml of ether. The mixture was boiled for 4 hours and decomposed gradually, after cooling, with 3.8 ml of water, 3.8 ml of 15% sodium hydroxide, and eventually 11.4 ml of water. The hydroxides were filtered off and the ethereal solution dried over anhydrous sodium sulfate (Table IV).

TABLE IV  
Racemic Secondary Amines *Ila*-*j* ( $R' = CH_3$ )

Amine	B.p., °C (yield, %)	Formula (m.w.)	Calculated/Found		
			% C	% H	% N
<i>Ila</i>	80/11 (88)	C <sub>10</sub> H <sub>15</sub> N (149.2)	80.48	10.13	9.39
			80.24	10.28	9.97
<i>Ilb</i>	56/0.7 (81)	C <sub>11</sub> H <sub>17</sub> N (163.3)	80.92	10.50	8.58
			80.80	10.67	8.48
<i>Ilc</i>	88-90/10 (75)	C <sub>12</sub> H <sub>19</sub> N (177.3)	81.30	10.80	7.90
			81.82	10.89	8.18
<i>Ild</i>	89/10 (93)	C <sub>10</sub> H <sub>15</sub> N (149.2)	80.48	10.13	9.39
			80.17	10.43	9.81
<i>Ile</i>	82/11 (68)	C <sub>10</sub> H <sub>15</sub> N (149.2)	80.48	10.13	9.39
			80.73	10.27	9.88
<i>Ilf</i>	112/32 (71)	C <sub>10</sub> H <sub>15</sub> N (149.2)	80.48	10.13	9.39
			80.42	10.14	9.85
<i>Ilg</i>	127-130/23 (86)	C <sub>10</sub> H <sub>15</sub> NO (165.2)	72.69	9.14	8.48
			72.43	9.25	8.55
<i>Ilh</i>	158/23 (83)	C <sub>14</sub> H <sub>21</sub> N (203.3)	82.70	10.41	6.89
			82.47	10.62	7.11
<i>Ili</i>	99-101/0.1 (81)	C <sub>15</sub> H <sub>23</sub> N (217.4)	82.89	10.67	6.44
			82.58	10.71	6.82
<i>Ilj</i>	162/0.13 (75)	C <sub>18</sub> H <sub>23</sub> N (253.4)	85.33	9.14	5.53
			85.24	9.42	6.55

Asymmetric Transformation of Amines *Ila*-*j* ( $R' = \text{CH}_3$ )

To 1 g (6.67 mol) of (*S*)-(+)-hydratropic acid,  $[\alpha]_{\text{D}}^{20} + 86.67^\circ$  (liquid) in 1.5 ml of tetrahydrofuran 1.4 g (6.67 mol) of dicyclohexylcarbodiimide in 4 ml tetrahydrofuran were added and the mixture allowed to stand for two hours. It was cooled to  $-10^\circ\text{C}$  and added with 10 mmol of amine *Ila*-*j* ( $R' = \text{CH}_3$ ) in 12 ml of tetrahydrofuran. The reaction mixture was allowed to stand at room temperature for 24 hours. The separated dicyclohexylurea was filtered off with suction and washed with ether. The unreacted amine was extracted several times with 2M acetic acid. The acid extract was extracted several times with ether and then alkalized with sodium hydroxide solution to liberate the base. The separated amine was extracted with ether, dried over solid potassium hydroxide, and distilled (Table V).

TABLE V

Results of Asymmetric Transformation of Amines *Ila*-*j* ( $R' = \text{CH}_3$ )

Amine	<i>Ila</i>	<i>Ilb</i>	<i>Ilc</i>	<i>Ild</i>	<i>Ile</i>	<i>Ilf</i>	<i>Ilg</i>	<i>Ilh</i>	<i>Ili</i>	<i>Ilj</i>
$[\alpha]_{\text{D}}^{20}$ (liquid)	-1.52	-0.44	-0.40	-11.60	-5.86	-6.88	-6.84	-1.40	-1.12	+6.44

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