Tetrahedron. Vol. 33, pp. 245 to 248 Pergamon Press 1977. Printed in Great Britain

EXPERIMENTAL DETERMINATION OF ENANTIOMERIC PURITY LOWER THAN 1% IN THE CASE OF CHIRAL SECONDARY ALCOHOLS

A. SCHOOFS and A. HOREAU*
Laboratoire de Chimie Organique des Hormones,† Collège de France, 11 place Marcelin Berthelot, 75231 Paris Cedex 05, France

(*Received in the UK* 23 *July* 1976; *Accepted for publication* 5 *August* 1976)

Résumé—Considérons un alcool secondaire, de pureté énantiomérique p, qui réagit sur un excès d'anhydride α-phénylbutyrique racémique. Il est possible de déterminer par titrage acidimétrique, le rapport N du nombre de molécules de cet anhydride mis en réaction, sur le nombre de molécules de carbinol estérifiées. De la proportion des esters diastéréoisomères formés, déterminée par GLC (ou RMN) on déduit la valeur de l'induction asymétrique Q de cette estérification. On mesure également la pureté optique de l'acide α-phénylbutyrique isolé, soit P. On établit facilement la relation $p = P(2N - 1)/Q$—reliant entre elles ces valeurs—qui permet le calcul de la pureté énantiomérique.

Cette méthode est appliquée, avec succès, au cas de très faibles puretés énantiomériques (< 1%).

Abstract—Consider a secondary alcohol, of unknown enantiomeric purity p which reacts with excess of racemic α-phenylbutyric anhydride in a solution of pyridine. The ratio N between the number of reacting anhydride molecules and the number of alcohol molecules esterified can be evaluated by acidimetric titration. The proportions of diastereomeric esters are measured by CPV (or NMR) and we obtain the asymmetric induction Q. The optical purity P of the α-phenylbutyric acid isolated is determined by a polarimetric reading.

We have established simply a relationship $p = P(2N - 1)/Q$ which allows the enantiomeric purity to be calculated. This method is used with success, in cases of very low enantiomeric purity (<1%).

The experimental results prove its efficiency.

The most general method of determining the enantiomeric purity of a chiral secondary alcohol consists of:

(a) Transforming the enantiomer mixture into diastereomeric esters with an optically pure chiral acid[1] and measuring their composition by NMR or gas chromatography.

(b) Engaging it by coordination with a chiral rare-earth complex[2] or, examining it in a chiral solvent.[3]

This method cannot be used in the cases of very low optical purity, for example below 1%.

The method proposed for the solution of this problem is based on the existence of "asymmetric induction", which can be manifested in the esterification of a racemic secondary alcohol DOH, LOH with a racemic acid dCO_2H, lCO_2H (used, e.g. in the form of the anhydride). The proportions of the two racemic diastereomeric esters dCO_2D, lCO_2L and dCO_2L, lCO_2D are easily measured, since in the hundreds of cases studied in the laboratory, they reach values that are normally between 20 and 60% when use is made of α-phenylbutyric anhydride.[4] Knowledge of this experimental fact combined with a polarimetric reading provides a method to determine very low enantiomeric purities.

Thus, consider an alcohol of unknown enantiomeric purity p, which reacts with *racemic* α-phenylbutyric anhydride $[C_6H_5CH(C_2H_5)CO]_2O$. To simplify the algebraic calculations, consider two molecules of the alcohol to be tested‡ and 2N molecules of the anhydride, in which the reaction in the first instance is assumed to be total. The reaction can be written out schematically as follows:

$$\begin{array}{c} \begin{array}{ccccc} LOH & + & DOH & + & dCOOCOl \\ 1+p & \Big\downarrow & 1-p & & 2N \end{array} \\ \overbrace{\begin{array}{ccccccccccccc} dCO_2D & + & lCO_2L & + & dCO_2L & + & lCO_2D & + & dCO_2H & + & lCO_2H & + & dCOOCOl \\ x & & x' & & y & & y' & & x'+y' & & x+y & & 2N-2 \end{array}} \end{array}$$

and after hydrolysis of the excess anhydride:

$$\overbrace{\begin{array}{ccccccccccc} dCO_2D & + & lCO_2L & + & dCO_2L & + & lCO_2D & + & dCO_2H & + & lCO_2H \\ x & & x' & & y & & y' & & x'+y'+2N-2 & & x+y+2N-2 \end{array}}$$

The esterification gives a pair of diastereomers, the first composed of x molecules of dCO_2D and x' molecules of its antipode lCO_2L and the second of y molecules of dCO_2L and y' molecules of lCO_2D. The amount of residual acid is:

$x' + y' + (2N - 2)$ for the dextrorotatory species dCO_2H

and

$x + y + (2N - 2)$ for the laevorotatory species lCO_2H.

---

†Groupe de recherche No. 20 du C.N.R.S.

‡1 molecule of laevorotatory alcohol of enantiomeric purity p consists of $(1 + p)/2$ molecule of LOH and $(1 - p)/2$ molecule of DOH.

The laevorotatory alcohol LOH is distributed after esterification between the two species $\mathrm{lCO_2L}$ and $\mathrm{dCO_2L}$ in such a way that we can write:

$$\text{(a)} \qquad 1 + p = x' + y$$

and, for the alcohol DOH:

$$\text{(b)} \qquad 1 - p = x + y'$$

From the values of x, x', y and y' the optical purity p as a function of the optical purity of α-phenylbutyric acid isolated P and "asymmetric induction" Q can be calculated.

Optical purity P of the residual acid

The optical purity of the isolated acid (which we suppose to be dextrorotatory) is equal to:

$$\frac{[d] - [l]}{[d] + [l]}$$

and if we recall that $x + x' + y + y' = 2$ (since we started from two molecules of the initial alcohol), we readily find that:

$$P = \frac{x' + y' - 1}{2N - 1}$$

Hence we can write the first equation:

$$\text{(1)} \qquad x' + y' = 1 + (2N - 1)P$$

and similarly:

$$\text{(2)} \qquad x + y = 1 - (2N - 1)P$$

Asymmetric induction Q

If we evaluate the "asymmetric induction" Q as the ratio $(S - S'/S + S')$, where S and S' are the areas on gas chromatography or NMR that correspond to the species $x + x'$ on the one hand and $y + y'$ on the other hand, we find the equation:

$$Q = \frac{S - S'}{S + S'} = x + x' - 1$$

from which we obtain:

$$\text{(3)} \qquad x + x' = 1 + Q$$

and similarly:

$$\text{(4)} \qquad y + y' = 1 - Q$$

We now have four equations and four unknowns, it might be supposed that from these four equations the values of x, x', y and y' can be obtained. In fact, however, one of these equations can be deduced from the three others, because we have already noted that $x + x' + y + y' = 2$. We must thus find yet another equation. This is achieved by the following considerations. The quantities of x, x' and y, y' formed as a function of time are proportional to the rates of reactions in which they are produced, i.e.:

$$\text{(c)} \qquad V_x = k_x[\mathrm{dCON^+C_5H_5}][\mathrm{DOH}]$$

$$\text{(d)} \qquad V_{x'} = k_{x'}[\mathrm{lCON^+C_5H_5}][\mathrm{LOH}]$$

$$\text{(e)} \qquad V_y = k_y[\mathrm{dCON^+C_5H_5}][\mathrm{LOH}]$$

$$\text{(f)} \qquad V_{y'} = k_{y'}[\mathrm{lCON^+C_5H_5}][\mathrm{DOH}].$$

The rate constants k_x and $k_{x'}$ in eqns (c) and (d) are equal, because one characterizes the esterification of $\mathrm{dCON^+C_5H_5}$ (resulting from the action of pyridine on the anhydride) by DOH and the other the esterification of $\mathrm{lCON^+C_5H_5}$ by LOH. Similarly, the rate constants k_y and $k_{y'}$ are equal. On the other hand, the concentrations of $\mathrm{dCON^+C_5H_5}$ and $\mathrm{lCON^+C_5H_5}$ are essentially equal even when the reaction is very advanced, since the optical purity of the α-phenylbutyric acid isolated is extremely low. As the optical purity of the alcohol tested does not vary, the ratio $(1 + p/1 - p)$ remains constant: the rates V_x and $V_{y'}$ are thus always proportional to $1 - p$, and the rates $V_{x'}$ and V_y to $1 + p$, and we can write:

$$\frac{x}{x'} = \frac{y'}{y} \quad \text{or} \quad \frac{x}{x + x'} = \frac{y'}{y + y'}$$

whence:

$$\text{(5)} \qquad \frac{x}{1 + Q} = \frac{y'}{1 - Q}$$

In a reaction in which the alcohol tested has a high enantiomeric purity this argument is only valid if the amount of the alcohol is small in comparison with the amount of the anhydride, or if the "asymmetric induction" Q is low. This restriction is irrevelant in the case studied and no detectable change is produced in the proportions of the enantiomers DOH and LOH at the end of the esterification.

It is then easy to solve the preceding system of equations and to obtain the values:

$$x = \frac{(1 + Q)[Q - (2N - 1)P]}{2Q}$$

$$x' = \frac{(1 + Q)[Q + (2N - 1)P]}{2Q}$$

$$y = \frac{(1 - Q)[Q + (2N - 1)P]}{2Q}$$

$$y' = \frac{(1 - Q)[Q - (2N - 1)P]}{2Q}$$

By using one of the formulae (a) or (b) we obtain the fundamental relationship:

$$\text{(6)} \qquad p = \frac{P(2N - 1)}{Q}.$$

In fact the reaction is not always total, and N is the ratio between the number of reacting anhydride molecules and the number of alcohol molecules esterified.

From an experimental point of view, it is convenient to dissolve in pyridine 1 mole of alcohol and 1 mole of anhydride and to stop the reaction when the degree of esterification is about 50%. N is then evaluated by determining the amount of anhydride consumed with the aid of acidimetric titration.

It can be verified *a priori* that this method is applicable to alcohols of enantiomeric purity as low as 1%. The value calculated from the optical purity of the isolated acid is

Table 1. Enantiomeric purities of chiral secondary alcohols

						α-Phenylbutyric acid recovered		Enantiomeric purity % of the alcohol tested	
	Alcohol	V ml [a]	v ml [b]	$2N-1=\frac{v}{V-v}$ [c]	Q	α_D^{22} liq. (l = 1 dm)	opt. · p %	calc.[d]	lit.
1	$CH_3CHOHC_6H_{13}$ (−)liq.	20.04	14.44	2.578	0.296[e]	+0.07	0.072	0.69	0.70[5]
2	$CH_3CHOHCH_2CH(CH_3)_2$ (+)liq.	19.72	15.0	3.178	0.230[e]	−0.048[g]	0.050	0.69	0.74[6]
3	$CH_3CHOHCH(CH_3)_2$ (+)liq.	19.53	15.3	3.617	0.40[f]	−0.074	0.077	0.69	0.72[7]
4	$CH_3CHOHC(CH_3)_3$ (+)liq.	19.61	15.95	4.358	0.69[f]	−0.145	0.150	0.95	1.04[8]
5a	menthol	20.08	13.9	2.249	0.556[e]	+0.213[g]	0.221	0.89	0.97[9]
b	(−)EtOH	20.49	14.55	2.449	0.558	+0.050	0.052	0.23	0.27
6a	$C_6H_5CHOHC_3H_7$[a]	19.77	14.00	2.426	0.617[e]	+0.125[g]	0.129	0.51	0.54[10]
b	(+)liq.	20.95	13.95	1.98	0.617	+0.047	0.049	0.16	0.16
7	$C_6H_5CHOHC_4H_9$ (+)liq.	19.63	13.6	2.255	0.575[e]	+0.138	0.143	0.56	0.57[11]

[a] Volume of sodium hydroxyde V used up by anhydride in the control test after hydrolysis.

[b] Volume of sodium hydroxyde v used up after esterification after hydrolysis.

[c] See the detailed example for calculation of 2N − 1.

[d] Calculated by formula (6).

[e] Properties of the esters measured by gas chromatography.

[f] Measurements by NMR in CCl_4 with the aid of $Eu(fod)_3$.

[g] Reading taken at 40° and referred to 22° using the factor 1.084.

obtained from the formula $P = (p \cdot Q/(2N-1))$. In the case where the yield of the reaction reaches 50% we have $N = 1/0.5 = 2$ and $(2N-1) = 3$, and if $Q = 30\%$ the optical purity P of the isolated acid is $(0.3 \times 0.01)/3 = 0.001$ or 0.1%, this corresponds to a reading of 0.100°, easily measurable for α-phenylbutyric acid. Table 1 gives the results obtained for seven different alcohols of enantiomeric purity equal to or lower than 1%, and we describe in detail a working procedure to illustrate this method which provides very satisfactory results.

The experimental error depends essentially on the value of the asymmetric induction Q, which is different for each carbinol, and on the observed rotation of the α-phenylbutyric acid isolated. In order to obtain significant results, the polarimetric measure of the acid should be at least ~0.050°. Thus, the enantiomeric purity, calculated with a precision of 10–15%, is 0.26% for Q = 60% and 0.78% for Q = 20%, for a 50% esterification. Table 1 shows good agreement between calculated and experimental values of p, generally better than 10%, except in the case **5b** for which it is about 15%.

We believe that the method described here for a particular case of esterification can be extended to other reactions in which asymmetric induction is sufficient.

EXPERIMENTAL

Example. Dextrorotatory methylisobutylcarbinol (1.024 g; 10 mmoles) of optical purity 0.74% (prepared by weighing from the racemic alcohol and an optically pure specimen) was added to 25 ml of a pyridine soln of α-phenylbutyric anhydride (about 10 mmoles). After 1.5 hr hydrolysis was carried out with water (5 ml) and the mixture was left to stand for 2 hr. α-Phenylbutyric acid was then determined by titration with 1N NaOH in the presence of phenolphthalein; the volume added was v = 15.0 ml. A control test was carried out by titrating 25 ml of the anhydride soln used with the same alkali. The volume added was V = 19.72 ml. We note that $N = [(V/2)/V - v]$, whence $2N - 1 = (v/V - v) = 3.178$.

The esterification yield was 48.3%.

Dilution with water (10 ml) was carried out and the esters formed were extracted with benzene and analysed by gas chromatography at 140° on a column of Carbowax 20 M.

Peak areas:

$$S = 615, \quad S' = 385$$

whence

$$Q = (S - S')/(S + S') = 0.23$$

The aqueous phase was acidified with excess 6N HCl and the α-phenylbutyric acid liberated was extracted with benzene. Distillation afforded 1.53 g of acid, b.p. 145–147°.

$$\alpha_D^{22} = -0.048° \text{ (liq., l = 1 dm)}†$$

The optical purity found is $p = (0.048/96.5) \times (3.178/0.23) = 0.0069 = 0.69\%$.

Note. The amount of alcohol used and the NaOH titre need not be known exactly, as the calculation is based on *relative* values of V and v.

---

†For very small polarimetric deviations it is preferable to measure the rotatory power at 436 nm and 40° to avoid possible crystallization of the supercooled acid. The ratio of rotations at wavelengths of 436 and 589 nm is 2.15.

REFERENCES

[1a] M. Raban and K. Mislow, *Tetrahedron Letters* 4249 (1965), *Ibid.* 3961 (1966); [b] J. Dale, D. Dull and H. S. Mosher, *J. Org. Chem.* **34**, 2543 (1969).

[2a] M. D. McCreary, D. W. Lewis, D. L. Wernick and G. M. Whitesides *J. Am. Chem. Soc.* **96**, 1038 (1974) and Refs. cited; [b] H. L. Goering, J. N. Eikenberry, G. S. Koermer and C. J. Lattimer, *Ibid.* **96**, 1493 (1974) and Refs. cited.

[3a] W. H. Pirkle, *Ibid.* **88**, 1837 (1966); [b] T. G. Burlingame and W. H. Pirkle, *Ibid*, **88**, 4294 (1966); [c] W. H. Pirkle and T. G. Burlingame, *Tetrahedron Letters* 4039 (1967); [d] W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.* **89**, 5485 (1967); [e] W. H. Pirkle, T. G. Burlingame and S. D. Beare, *Tetrahedron Letters* 5849 (1968).

[4a] I. A. Horeau, *Ibid.* 506 (1961) to XII. A. Schoofs, R. Weidmann, A. Collet and A. Horeau, *Bull. Soc. Chim. Fr.* in press; [b] A. Horeau, *Determination of the Configuration of Secondary*

Alcohols by Partial Resolution. Thieme–Verlag, Stuttgart, (1976) in press.

[5] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **99**, 45 (1911).

[6] J. Kenyon and H. E. Strauss, *Ibid.* 2153 (1949).

[7] R. H. Pickard and J. Kenyon, *Ibid.* **101**, 620 (1912).

[8] R. H. Pickard and J. Kenyon, *Ibid.* **105**, 1115 (1914). P. Newman, P. Rutkin and K. Mislow, *J. Am. Chem. Soc.* **80**, 465 (1958).

[9] A. W. Ingersoll, *Organic Reactions*, Vol. 2, p. 376. Wiley, New York (1944).

[10] K. Mislow and C. L. Hamermesh, *J. Am. Chem. Soc.* **77**, 1590 (1955). J. Keynon and S. M. Partridge, *J. Chem. Soc.* 128 (1936).

[11] A. Horeau, J. P. Guetté and R. Weidmann, *Bull. Soc. Chim. Fr.* 3513 (1966).