Absolute Configurations of Secondary Alcohols. A Gas Chromatographic Modification of Horeau's Method

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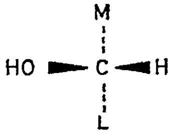
Summary Gas chromatographic determination of diastereoisomeric amides of (+)- and (−)-α-phenylbutyric acid permits the simple application of Horeau's method to small quantities (10 µmole) of chiral secondary alcohols.

THE determination of alcohol configurations *via* partial kinetic resolution of (±)-α-phenylbutyric anhydride[1,2] is a practical and useful method. The procedure is widely applicable, has high reliability, and is in some instances superior to chiroptical correlations.[3] A recent simplification of procedure has been described.[4] The use of optical rotation measurements for estimation has, however, required relatively large samples, typically 100 µmole, of alcohols. Guetté and Horeau[5] suggested that gas chromatographic estimation would allow the study of very small samples, but reported its application only to a large sample of partially-resolved α-phenylbutyric acid. We now describe a convenient procedure whereby Horeau's method can be applied to micromolar quantities of alcohols.



(I)

M = group of medium size
L = group of larger size

The method is based on the direct addition, to the acylation reaction mixture, of an amine which reacts rapidly with the excess of α-phenylbutyric anhydride. The resulting diastereoisomeric amides are then characterized and estimated by g.l.c. of a sample of the reaction mixture. The amine salts of the α-phenylbutyric acids do not interfere. Success is dependent upon rapid amide formation (without significant resolution of the anhydride by the amine)[6] and upon the degree of stability of the phenylbutyrates in the presence of the excess of amine. We have found that these conditions are met by the procedure outlined below.

TABLE

G.l.c. determination of (+)-*α-phenylethylamides of* (−)-(R)- *and* (+)-(S)-*α-phenylbutyric acid representing unreacted anhydride from Horeau reaction*

	Configuration	Peak increment (*R*-acid)[a]
(+)-Menthol	*S*	+5·6
(−)-Menthol	*R*	−6·4
(+)-Isomenthol	*S*	+2·7
(+)-Isoborneol	*S*	+2·2
(−)-Isoborneol	*R*	−4·0
Oestr-4-en-17β-ol	*S*	+5·3
5α-Androstan-17β-ol	*S*	+5·7
17α-Hydroxyandrost-4-en-3-one	*R*	−3·9
17β-Hydroxyandrost-4-en-3-one	*S*	+5·5
11α-Hydroxypregn-4-ene-3,20-dione	*R*	−2·5
3α,5-Cyclo-5α-cholestan-6β-ol	*R*	−4·7
Cholest-5-ene-3β,7α-diol 3-benzoate	*S*[b]	−3·3
Lanosterol	*S*	+3·2
Taraxerol	*S*	+1·0
Taraxasterol	*S*	+3·3
Oestra-1,3,5(10)-triene-3,17α-diol	17-*R*	−4·9
Oestra-1,3,5(10)-triene-3,17β-diol	17-*S*	+4·0
Pregn-5-ene-3β,20α-diol	20-*S*	+2·4
Pregn-5-ene-3β,20β-diol	20-*R*	−2·0
Betulin	3-*S*	+4·1

[a] The values cited (neglecting signs) represent half the uncorrected enantiomeric yields. [b] *S* because of precedence of olefinic bond according to the Sequence Rule.

The alcohol (10 µmole) in dry pyridine (7 µl) was treated with (±)-α-phenylbutyric anhydride (1·0 molar excess) and kept in a sealed vial at 40° for 1·5 h. In each case a parallel reaction was carried out with cyclohexanol. (+)-(*R*)-α-Phenylethylamine (6 μl) was added and mixed thoroughly by agitation ("Vortex" mixer). After 15 min the mixture was diluted with dry ethyl acetate (400 μl) and a sample was analysed by g.l.c. at 215° on a 3 m column packed with 1% OV-17 on Gas Chrom Q (Applied Science Laboratories, Inc., State College, Pa.). The relative proportions of the amides of (−)-(*R*)- and (+)-(*S*)-α-phenylbutyric acid were indicated by the areas of their respective peaks (retention indices 2390, 2420). The percentage area representing the (−)-(*R*)-acid was assessed. Subtraction of the corresponding value from the reaction with cyclohexanol gave the increments cited in the Table. The measured enantiomeric yields were mainly in the range 5—10%. After correction for the added excess of anhydride, and for the incompleteness of esterification, the following typical enantiomeric yields in the esterification process could be calculated: (+)-menthol, *ca.* 45; (−)-menthol, *ca.* 50%.

The twenty alcohols (including five diols) cited in the Table gave results fully consistent with their known configurations, in terms of Horeau's correlation. According to the latter rule, alcohols of configurational type (I) react preferentially with (*R*)-α-phenylbutyryl groups, causing the excess of anhydride to be relatively deficient in these forms. [In many instances, alcohols of type (I) represent *R* configurations: the Table includes one exception.]

We have also examined the use of α-phenylbutyryl chloride instead of the anhydride. Our observations suggest that the acid chloride is a less satisfactory reagent, as already concluded by Horeau.[1,7]

In the event of accidental coincidence of the chromatographic peaks of the esters and amides, α-phenylethylamine can be replaced by another amine to yield amides of different retention times.

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[1] A. Horeau, *Tetrahedron Letters*, 1961, 506.
[2] A. Horeau and H. B. Kagan, *Tetrahedron*, 1964, **20**, 2431.
[3] See, for example, D. Varech and J. Jacques, *Tetrahedron*, 1972, **28**, 5671.
[4] A. Horeau and A. Nouaille, *Tetrahedron Letters*, 1971, 1939.
[5] J. P. Guetté and A. Horeau, *Tetrahedron Letters*, 1965, 3049.
[6] H. Falk and K. Schlögl, *Monatsh.*, 1965, **96**, 276.
[7] A. Horeau, *Tetrahedron Letters*, 1962, 965.