If this mechanism is correct, the effectiveness of a nucleophile as a catalyst for the formation of the β-lactone dimer (2) depends upon its ability to coordinate with the carbonyl carbon of the ketene to give zwitterions **5** and **6**. Triphenyl phosphite is apparently too weak a nucleophile to form zwitterions of this type. At the other extreme, it appears that the phosphines (and tertiary amines) coordinate so strongly that ring closure to the β-lactone does not occur and **6** reacts instead with more dimethylketene, ultimately giving polymer.

Experimental Section

With the exceptions noted, the experiments listed in Table I were carried out according to the general procedure described below. The phosphorus compounds obtained from commercial sources were used without purification. Dimethylketene was generated by the pyrolysis of isobutyric anhydride[8] and was passed as the gas into the reaction vessel, where it was condensed and allowed to fall into the solution.

Five grams of triethyl phosphite was placed in a 1-l., three-necked flask which was fitted with a Dry Ice cooled reflux condenser, thermometer, inlet for dimethylketene, and magnetic stirrer. Stirring was started and dimethylketene was passed in. A strongly exothermic reaction occurred and the temperature rose spontaneously to between 90 and 100° and remained there until the dimethylketene stream was shut off. A total of approximately 300 g of product had collected. Gas chromatographic analysis of the crude product indicated that it contained 93% of 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone (**2**) and 4% of tetramethyl-1,3-cyclobutanedione (**1**). Distillation gave 235 ml of pure **2**, bp 78.5-79° (25 mm), $n^{20}\mathrm{D}$ 1.4380, the infrared spectrum and glpc retention time of which were identical with those of authentic material.

When this experiment was repeated with tributylphosphine as the catalyst, only a tough, horny, transparent polymer was obtained. The infrared spectrum of this polymer (KBr pellet) contained strong bands at 5.75, 5.85, 8.45, and 9.25 μ. This spectrum was identical with the spectrum of a polymer prepared as described by Staudinger.[5]

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(8) R. H. Hasek and E. U. Elam (to Eastman Kodak Co.), U. S. Patent 3,201,474 (1964).

Determination of the Absolute Configuration of Hydroxylated Sesquiterpene Lactones by Horeau's Method of Asymmetric Esterification[1]

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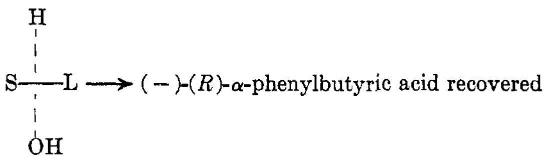
Horeau's method[4,5] for the determination of the absolute configuration of alcohols has been successfully applied to natural products such as terpenes,[4,5] caryophyllene derivatives,[6] steroids,[7] and the grayanotoxins.[8] Since esterification of an asymmetric alcohol, LCHOHS, where L is a bigger substituent than S in a steric sense,[9] by an excess of racemic α-phenylbutyric acid anhydride results in preferential combination with one of the antipodes of the acid, the excess of the acid which is recovered is optically active. Horeau[4,5,7] has empirically correlated in a great number of examples the sign of the recovered acid with the absolute configuration of the starting alcohol as follows.



$$\mathrm{S}\overset{\mathrm{H}}{\underset{\mathrm{OH}}{-\!\!\!-\!\!\!-}}\mathrm{L} \longrightarrow (-)\text{-}(R)\text{-}\alpha\text{-phenylbutyric acid recovered}$$

In order to test the applicability of the method in the sesquiterpene lactone series,[11] we applied it first to several hydroxylated sesquiterpene lactones previously studied by W. H., where the absolute configuration of the hydroxyl group had been established unequivocally by chemical or physical means. Chart I lists these compounds (**1**, **2**, and **3**) which are of the type $\mathrm{RCH_2}$-$\mathrm{CH(OH)CR_1R_2R_3}$[13-20] as well as three others of the same type (**4**, **5**, and **6**) where the configuration of the hydroxyl group was somewhat uncertain or completely unknown. The results of Horeau's method given in Chart I are in agreement with the previously known absolute configurations (**1**, **2**, and **3**) and, in the case of compound **4**, a derivative of pulchellin, in agreement with the configuration deduced[23] by the application of the Hudson–Klyne rule. For **5**[24] and **6**[24] we indicate

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(1) Work at Florida State University supported in part by grants from the National Science Foundation (GP-1962) and the U. S. Public Health Service (GM-05814).

(2) Florida State University.

(3) Collège de France.

(4) A. Horeau, *Tetrahedron Letters*, 506 (1961).

(5) A. Horeau, *ibid.*, 965 (1962).

(6) A. Horeau and J. K. Sutherland, *J. Chem. Soc.*, C247 (1966).

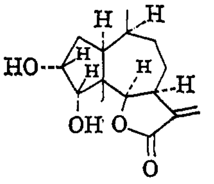
(7) A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964).

(8) H. Kakijawa, T. Kozima, M. Yanai, and K. Nakanishi, *ibid.*, **21**, 3091 (1965).

(9) S is $\mathrm{CH_2R}$ and L is a more heavily substituted carbon atom such as $\mathrm{CHR_1R_2}$. For a discussion of this classification, see ref 10.

(10) A. Marquet and A. Horeau, *Bull. Soc. Chim. France*, in press.

(11) H. B. K. has previously employed the method to determine the absolute configuration of the *cis*-glycol system of ambrosiol (i).[12]



i

(12) T. J. Mabry, W. Renold, H. E. Miller, and H. B. Kagan, *J. Org. Chem.*, **31**, 681 (1966).

(13) The equatorial orientation of the hydroxyl group of asperilin (**1**) was deduced[14] from the sodium borohydride reduction of dehydrotetrahydroasperilin which regenerated tetrahydroasperilin. The absolute configuration follows from correlation with alantolactone.

(14) W. Herz and N. Viswanathan, *J. Org. Chem.*, **29**, 1022 (1964).

(15) The relative and absolute configuration of **2** follows from its correlation[16] with helenalin,[17] the relative and absolute configuration of which has been established by X-ray analysis of a bromo derivative,[18] ORD data,[19] and correlation with isotenulin.[19]

(16) A. Romo de Vivar, L. Rodriguez-Hahn, J. Romo, M. V. Lakshmikantham, R. N. Mirrington, J. Kagan, and W. Herz, *Tetrahedron*, in press.

(17) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *J. Am. Chem. Soc.*, **85**, 19 (1963).

(18) M. T. Emerson, C. N. Caughlan, and W. Herz, *Tetrahedron Letters*, 621 (1961).

(19) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *Tetrahedron*, **19**, 1359 (1963).

(20) The relative and absolute configuration of **3** follows from its correlation with isotenulin,[21] the relative and absolute configuration of which have been established by X-ray analysis[22] and ORD data.[19]

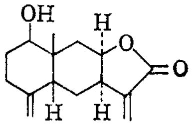
(21) W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman, and N. Viswanathan, *J. Am. Chem. Soc.*, **84**, 3857 (1962).

(22) D. Rogers and Mazhar-ul-Haque, *Proc. Chem. Soc.*, 92 (1963). See also W. Herz, Y. Kishida, and M. V. Lakshmikantham, *Tetrahedron*, **20**, 1986 (1964).

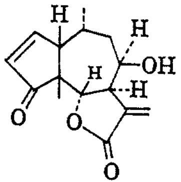
(23) W. Herz, K. Ueda, and S. Inayama, *ibid.*, **19**, 483 (1963).

(24) W. Herz, Y. Kishida, and M. V. Lakshmikantham, *ibid.*, **20**, 979 (1964).

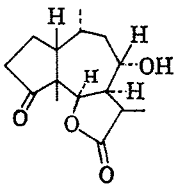
Chart I[a]



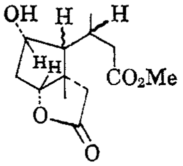
1, asperilin
optical yield, 44% (+)
configuration: predicted, *R*; found, *R*



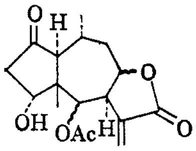
2, 1-epiallohelenalin
optical yield, 15% (+)
configuration: predicted, *R*; found, *R*



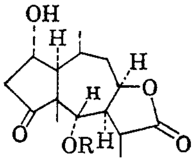
3, dihydrodesacetyl alloisotenulin
optical yield, 17% (−)
configuration: predicted, *S*; found, *S*



4, optical yield, 7% (−)
configuration: predicted, *S*, found, *S*



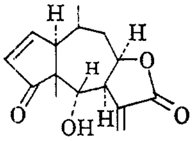
5, dehydroflexuosin A
optical yield, 7% (+)
configuration: predicted, ?; found, *R*



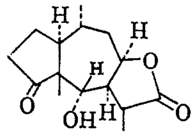
6, flexuosin B
optical yield, 15% (−)
configuration: predicted, ?; found, *S*

[a] Configurations refer to the alcohol carbon atom.

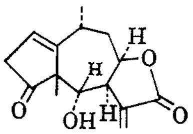
Chart II[a]



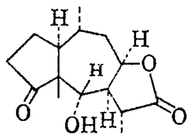
7, helenalin
optical yield, 39% (−)
configuration, *S*



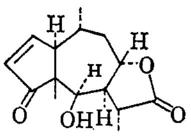
8, tetrahydrohelenalin
optical yield, 44% (−)
configuration, *S*



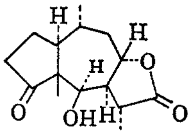
9, mexicanin A
optical yield, 11% (−)
configuration, *S*



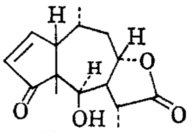
10, dihydromexicanin
optical yield, 66% (−)
configuration, *S*



11, desacetylisotenulin
optical yield, 1% (+)
configuration, *R*



12, desacetyldihydroisotenulin
optical yield, 6% (−)
configuration, *R*



13, 1-epidesacetylisotenulin
optical yield, 11% (+)
configuration, *R*

[a] Configurations refer to the alcohol carbon atom.

the previously unknown configuration given by the method.

In Chart II are listed several hydroxylated sesquiterpene lactones of known absolute configuration[16–19, 20–22, 25] which do not contain a methylene group α to the relevant asymmetric center. Horeau and co-workers have previously[26] discussed only two such compounds and proposed that the more heavily substituted α carbon be chosen as the large substituent, L. We have found that this rule gives correct results with the substances of known configuration used in this study if those examples are selected where the optical yield is higher than 10% (**7**, **8**, **9**, **10**, **13**). Empirically it seems safe to assign configuration at C-6 of pseudoguaianolides when the optical yield is high.[27] Nevertheless the large range of optical yields reported in Chart II is indicative of the strong influence of other structural factors and points out the necessity of taking into account the molecule as a whole.

Conclusion.—Horeau's method furnishes the correct absolute configuration for those sesquiterpene lactones where one methylene group is adjacent to the asymmetric carbon bearing the hydroxyl group. In 6-hydroxylated pseudoguaianolides a high optical yield can be empirically related to the configuration if it is assumed that C-5 is the large group L.

Experimental Section

The general procedure is described in the example given below. It differs slightly from the original procedure[7] since NaOH cannot be used to separate α-phenylbutyric acid and to determine the esterification yield, and has to be replaced by sodium bicarbonate. The purity of the α-phenylbutyric acid isolated from the esterification was checked either by thin layer chromatography or nmr spectroscopy. In all instances the esterification yield was estimated by nmr spectroscopy of the neutral extract and appeared to be practically quantitative except in the case of microcephalin which has an axial hydroxyl group. To calculate the data of Charts I and II, we took 100% as the esterification yield. Experiments were carried out on about 50 mg of alcohol, but it is possible to use 25 mg as was the case for **12**.

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[25] W. Herz, M. V. Lakshmikantham, and R. N. Mirrington, *Tetrahedron*, **22**, 1709 (1966).

[26] M. Harispe, D. Mea, A. Horeau, and J. Jacques, *Bull. Soc. Chim. France*, 972 (1963).

[27] In all compounds listed in Chart II a carbonyl group is present at C-4. We do not know whether the same conclusion could be reached if the ketone group were absent. For another possible limitation, see ref 10.

Calculations.—If a is the molecular ratio of α-phenylbutyric anhydride to the alcohol (the usual ratio was 2.5–3), fully stereoselective esterification will give an acid whose $[\alpha]_D = 96.5°/2a - 1$ since the specific rotation (benzene) of optically pure α-phenylbutyric acid is ±96.5°.[7] The optical yield is the ratio of the experimentally observed specific rotation to this theoretical value.

Example. Absolute Configuration of 1-Epiallohelenalin (2).—A solution of 207 mg of α-phenylbutyric anhydride (5.83×10^{-4} mole) and 59.4 mg of 2 (2.23×10^{-4} mole), in 2.5 ml of pyridine was allowed to stand overnight at room temperature. Excess anhydride was destroyed by adding 1 ml of water and allowing to stand for 6 hr at room temperature. The solution was extracted with ether (use of ethyl acetate is also feasible). The extract was washed with water, three 10-ml portions of 5% sodium bicarbonate solution, and again several times with water. The combined aqueous extracts were washed with chloroform and acidified with an excess of 1 *N* sulfuric acid solution. The acidified solution was extracted with chloroform and the chloroform extract was dried and evaporated. This afforded 90.0 mg (constant weight after drying *in vacuo*) of α-phenylbutyric acid (pure on tlc), α_D in 5 ml of benzene (1-dm tube) +0.061 ± 0.002°, $[\alpha]_D$ +3.4°, theoretical $[\alpha]_D = 95.6°/[2(2.61) - 1] = +22.8°$. The optical yield therefore was 3.4/22.8 = 14.9% (+).

The neutral fraction in ether was washed thoroughly with water, 1 *N* sulfuric acid, and again with water and evaporated. The residual ester (77.1 mg) contained no starting material, as demonstrated by nmr spectroscopy.

Acknowledgment.—H. B. K. thanks Professor T. J. Mabry for the opportunity to carry out part of this work in the Department of Botany, University of Texas, Austin, Texas, and acknowledges a NATO grant during 1965. We thank Professor A. Horeau for useful discussion and for private communication of unpublished results.

A Novel Condensation Reaction of α,β-Unsaturated Cyclic Ketones with Ammonium Thiocyanate

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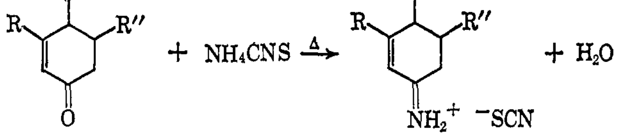
The reaction of ammonium thiocyanate with α,β-unsaturated aliphatic ketones (*e.g.*, mesityl oxide and styryl alkyl ketones) is little known in the literature.[2-4] The reaction products are substituted 2-mercaptodihydropyrimidines. In the present study, the condensation of 3-substituted 2-cyclohexen-1-ones with ammonium thiocyanate has been examined and the structure of the products has been established.

The condensations are conducted by heating 1 mole equiv of both the alicyclic unsaturated ketone and ammonium thiocyanate in a nonpolar solvent with azeotropic removal of the water formed. It was found that by carrying out the reaction in refluxing toluene, suitable reaction conditions are met. The products of the reaction are imine hydrothiocyanates.



The reaction is heterogeneous (ammonium thiocyanate and the imine hydrothiocyanates are insoluble in the hydrocarbon medium) and the addition of polar solvents reduces the yields considerably.

The formation of these alicyclic α,β-unsaturated imine hydrothiocyanates seems particularly influenced by the nature of the alicyclic ketone. Thus, whereas the ketones reported in Table I give the imines in very good yields, 2-cyclohexen-1-one and carvone only yield oily products, from which the corresponding pure imine hydrothiocyanate could not be isolated, and 2-phenyl-2-cyclohexen-1-one does not react at all with ammonium thiocyanate. Most probably, the α,β-unsaturated alicyclic imine hydrothiocyanates need a substituent on the 3 position for their stabilization. A bulky group on the 2 position hinders the reaction completely.

During the investigation of the condensation of isophorone with ammonium thiocyanate it was found that the reaction is favored by the addition of 1–3% by weight of sodium salts of phosphoric acid; *i.e.*, the yield of the condensation product increased from 60 to 85%. Sodium chloride and sodium sulfate show the same effect. Presumably, these inorganic salts stabilize the imine hydrothiocyanate as ammonium thiocyanate is stabilized by sodium phosphate.[5] Table I summarizes examples of the present study.

TABLE I
CONDENSATION OF α,β-UNSATURATED KETONES WITH AMMONIUM THIOCYANATE

	Imine hydrothiocyanates			
Ketone	Mp, °C	Yield, %	Pic,[a] mp, °C	Infrared, cm⁻¹ [b]
Isophorone	96–97	85	165–166	2040
3-Methyl-2-cyclohexen-1-one	87–88	86.5	168–169	2070
3,5-Dimethyl-2-cyclohexen-1-one	115–116	84.5	155–156	2065
3-Phenyl-2-cyclohexen-1-one	134–135	81.5	195–196	2075
10-Methyl-1(9)-octalone-2	115–116	82.0	154–155	2070

[a] Pic = picrate of the imine. [b] Infrared absorption band of the imine hydrothiocyanate group observed as a KBr disk.

These five imine hydrothiocyanates prepared here have an orange-yellow color and are characterized by three specific bands in the infrared spectrum (observed in a KBr disk) at 2050 ± 20, 1650 ± 10 (assigned to olefinic double bond), and 1610 ± 20 cm^{-1} (assigned to C═N stretching). The band at 2050 ± 20 cm^{-1} is a characteristic bond for ionic thiocyanates such as ammonium or sodium thiocyanates (2050 cm^{-1}), whereas organic thiocyanates (covalent) usually show bands at 2240 cm^{-1}. In agreement with their ionic property, they are all very soluble in polar solvents. Their aqueous or ethanolic solutions are stable at room temperature for several days but the addition of a base, such as sodium bicarbonate, to their aqueous solutions causes hydrolysis at room temperature yielding the corresponding α,β-unsaturated ketone. On the other hand, their stability toward acids is greater; thus an acidified solution (acetic acid) must be heated before

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[1] J. R. Geigy A. G., Basle, Switzerland.
[2] T. E. Robbins, U. S. Patent 2,539,480 (1951).
[3] W. H. Hill, British Patent 633,353 (1949).
[4] K. C. Robert and R. J. Moualim, British Patent 654,609 (1951).
[5] W. H. Hill and J. H. F. Veltman, U. S. Patent 2,440,717 (1948).