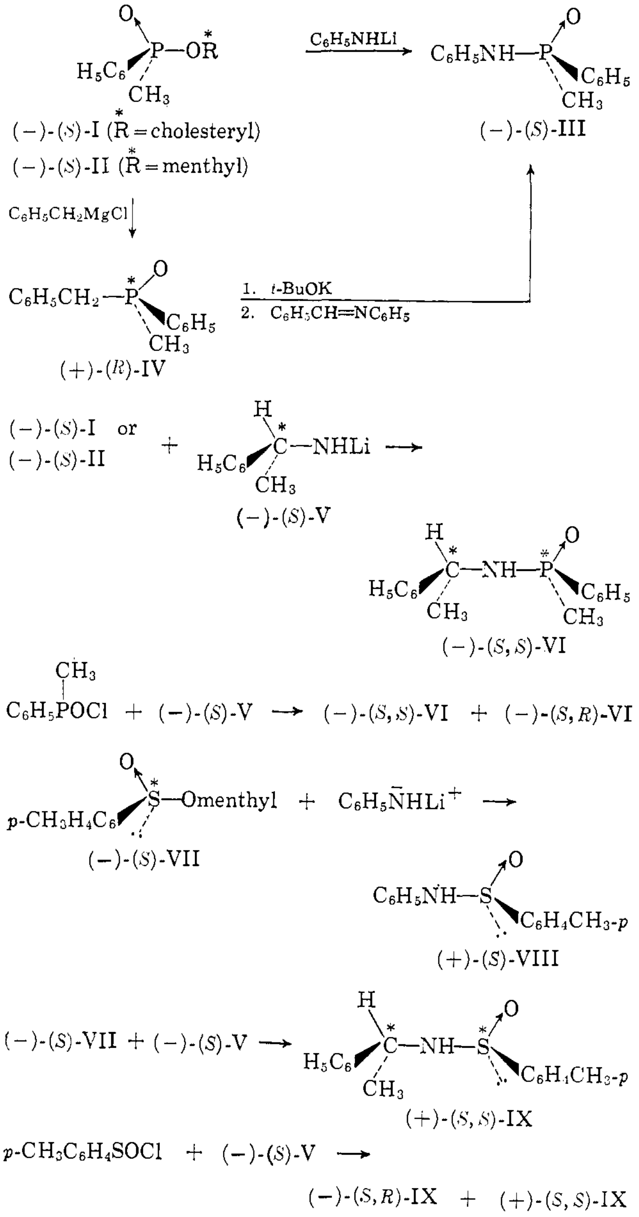
The Stereochemical Course of Ester–Amide Interchange Leading to Optically Active Phosphinic and Sulfinic Amides[1]

Sir:

In connection with our interest in the stereochemistry of substitution at sulfur[2] and phosphorus, we have examined for the first time the stereochemical course of ester–amide interchange leading to optically active phosphinic and sulfinic amides. Two examples of optically active phosphinic amides have been previously prepared by other approaches,[3] and one partially active sulfinic amide has been described.[4]

Chart I summarizes the reactions of substitution at asymmetric phosphorus that provide the conclusion that amide–ester interchange occurs with almost complete inversion of configuration. One of the diastereomers of the cholesteryl phosphinate (−)-(*S*)-I,[5] mp 134–134.5, $[\alpha]^{25}\text{D}$ −81.4° (*c* 4.53, chloroform), was obtained for the first time in 12% yield[5] by chromatography (12:1 silica gel–ester mixture; 3:2 ether–pentane eluent) of the mixture of diastereomeric esters produced by mixing equimolar amounts of methylphenylphosphinic chloride and cholesterol in pyridine at 25° for 10 hr. The menthyl ester was similarly prepared[6] in 10% yield, mp 80°, $[\alpha]^{25}\text{D}$ −93.8° (*c* 1.45, chloroform). Ester (−)-(*S*)-I when treated in ether with benzylmagnesium chloride gave phosphine oxide (+)-(*R*)-IV in 84% yield, mp 148–148.2°, $[\alpha]^{25}\text{D}$ +49.94° (*c* 1.64, methanol) (lit.[6] $[\alpha]^{25}\text{D}$ +50.9°). The correspondence of our and Korpium and Mislow's rotations coupled with these authors' establishment of the configuration of (+)-(*R*)-IV and the stereochemical course of the Grignard reaction (inversion) identifies the configuration at phosphorus of I and also demonstrates the diastereomeric purity of I. When either (−)-*S*-I or (−)-(*S*)-II was treated with a 10 molar excess of lithium anilide in dry refluxing benzene for 12 hr, (−)-(*S*)-III was produced: yield after chromatography and nonfractional crystallization from (−)-(*S*)-I, 35%; mp 161–163°; $[\alpha]^{25}\text{D}$ −26.2° (*c* 1.33, methanol) (lit.[3b] mp 164°; $[\alpha]^{25}\text{D}$ −25.8° (*c* 0.755, methanol)); yield from (−)-(*S*)-II after fractional crystallization from acetone–pentane to remove the menthol, 38%; mp 161–163°; $[\alpha]^{25}\text{D}$ −26.1° (*c* 0.83, methanol). Horner and Winkler[3b] established the relative configuration of (+)-IV and (−)-III and converted (+)-IV to (−)-III by a reaction that involved substitution with retention of configuration (Chart I). Our conversion of (−)-I or (−)-II to (−)-III and to (+)-IV completes a cycle of interconversions that indicates that the amide–ester interchange occurs with inversion at phosphorus. To determine the generality of this conclusion, a 10 molar excess of the lithium salt (−)-(*S*)-V of α-phenylethylamine ($[\alpha]^{25}\text{D}$ −40.1°, neat)[7] was mixed with either (−)-(*S*)-I or (−)-(*S*)-II in dry refluxing benzene for 12 hr. Chromatography of the product (silica gel, acetone–ether) and nonfractional crystallization gave only a single diastereomer (−)-(*S*)-VI, in 25% yield from (−)-(*S*)-I and 25% from (−)-(*S*)-II, mp 132–133.5, $[\alpha]^{25}\text{D}$ −63.0° (*c* 1.55, chloroform (both preparations)). Examination of the crude product by tlc chromatography (silica gel plates, acetone–methanol 9:1) showed the absence of the other diastereomer in the mixture. Control experiments with diastereomers (see below) demonstrated that as little as 1–2% could have been detected. These conversions demonstrate high stereospecificity in the substitution reaction at phosphorus. Both optically pure diastereomers configurationally identical at carbon were prepared by treating two parts of optically pure (−)-(*S*)-V[7] with 1 mole of methylphenylphosphinic chloride in dry ether at 25° for 1 hr. The diastereomers were separated by chromatography (silica gel, acetone–ether 4:1) to give (−)-(*S*,*R*)-VI[5] in 15% yield, mp 118.5–119.7°, $[\alpha]^{25}\text{D}$

Chart I



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[1] This investigation was supported by U. S. Public Health Service Research Grant No. GM 12640-04 from the Department of Health, Education, and Welfare.

[2] J. Day and D. J. Cram, *J. Am. Chem. Soc.*, **87**, 4398 (1965).

[3] (a) I. G. M. Campbell and J. K. Way, *J. Chem. Soc.*, 5034 (1960); (b) L. Horner and H. Winkler, *Tetrahedron Letters*, 3265 (1964).

[4] L. Sagramora, P. Koch, A. Garbesi, and A. Fava, *Chem. Commun.*, 985 (1967).

[5] Each new compound gave analytical results for at least two elements within 0.3% of theory. Yields were not maximized.

[6] O. Korpium and K. Mislow [*J. Am. Chem. Soc.*, **89**, 4784 (1967)] first prepared this ester and converted it to (+)-*R*-IV with benzylmagnesium chloride.

[7] (a) A. Ault, *J. Chem. Educ.*, **42**, 269 (1965); (b) W. Leithe, *Chem. Ber.*, **64**, 2827 (1931).

$-16.1°$ (c 1.38, chloroform), and (−)-(*S*,*S*)-VI[5] in 35% yield, mp 133–134°, $[\alpha]^{25}\text{D}$ −64.6° (c 1.96, chloroform). The nmr spectra of these diastereomers were distinctly different and were used to demonstrate the absence of less than 5% diastereomeric impurity in each sample.

Similar amide–ester interchanges were carried out that involved substitutions at sulfur (see Chart I). When (−)-(*S*)-VII ($[\alpha]^{25}\text{D}$ −197.3° (c 1.22, acetone) (lit.[8] $[\alpha]^{25}\text{D}$ −202°)) was treated with 1 mole of lithium anilide in ether at 0° (inverse addition), (+)-(*S*)-VIII[5] was produced in 41% yield after chromatography (silica gel, pentane–ether), mp 131–133° (nonfractionally crystallized), $[\alpha]^{25}\text{D}$ +216.9° (c 1.02, chloroform). After several recrystallizations of this material from ether, a maximum rotation of $[\alpha]^{25}\text{D}$ +224.4° (c 2.0, chloroform) was reached; mp 116–117°. This reaction appears to have been highly stereospecific. When carried out with excess lithium anilide by addition of ester to anilide salt, totally racemic VIII[9] was obtained, mp 133–135° (mixture melting point with (+)-(*S*)-VIII 106–125° dec). The two results provide strong evidence that the substitution reaction occurred essentially stereospecifically with inversion and that in the presence of excess anilide ion optically active sulfinanilide was converted to racemic material by multiple substitutions of anilide ion by anilide ion with inversion. Comparison of the ord curves of optically pure (+)-(*S*)-benzyl *p*-tolyl sulfoxide,[8] $\lambda_{\max}$ 277 mμ, $[\phi]$ $+27.8 \times 10^3$ (c 0.027, methanol), and that of (+)-(*S*)-VIII, $\lambda_{\max}$ 285 mμ, $[\phi]$ $+9.9 \times 10^3$ (c 0.016, methanol), provides direct evidence for the configuration of (+)-VIII since that of the sulfoxide has been established.[8] Others have demonstrated that Grignard reagents react with menthyl sulfinates stereospecifically[10a] and with inversion of configuration.[10b]

A second amide–ester interchange was performed with the more hindered lithium salt of (−)-(*S*)-V (see Chart I). When (−)-(*S*)-VII ($[\alpha]^{25}\text{D}$ −200.6 (c 1.22, acetone))[8] was added to 2 moles of optically pure (−)-(*S*)-V[7] in ether at 25°, (+)-(*S*,*S*)-IX was produced in 70% yield after chromatography (silica gel, pentane–ether): mp 116.5–119.5° (nonfractionally crystallized), $[\alpha]^{25}\text{D}$ +37.2° (c 3.89, chloroform). The nmr spectrum of this material demonstrated the absence of more than 5% of the other diastereomer (see below). Apparently the more hindered anion of V does not displace amide ion from (+)-(*S*,*S*)-IX to give (−)-(*S*,*R*)-IX once the former diastereomer formed, as did anilide anion under the same conditions. A mixture of optically pure diastereomers (−)-(*S*,*R*)-IX and (+)-(*S*,*S*)-IX was prepared by treating optically pure (−)-(*S*)-V[7] (2 moles) with *p*-toluenesulfinyl chloride (1 mole) in ether at 25° for 1 hr. The product was chromatographed (silica gel, pentane–ether 8:1) to give (+)-(*S*,*S*)-IX:[5] yield 5%; mp 119.5–120°; $[\alpha]^{25}\text{D}$ +41.2° (c 0.85, chloroform). A clear separation of diastereomers was not accomplished by chromatography, and the low isolated yield reflects this fact. The isomer (−)-(*S*,*R*)-IX was not obtained free of (+)-(*S*,*S*)-IX. However, a comparison of the nmr spectra of pure (+)-(*S*,*S*)-IX in deuteriochloroform (τ 8.42, d, 3 H, $J_{\text{H-H}} =$ 7 cps; 7.70, s, 3 H; 5.35, m, 2 H; 2.35–2.90, m, 9 H) and of the diastereomeric mixture ($[\alpha]^{25}\text{D}$ −40.5° (c 1.72, chloroform)) provided the spectrum of (−)-(*S*,*R*)-IX (τ 8.58, d, 3 H, $J_{\text{H-H}}$ = 7 cps; 7.66, s, 3 H; 2.35–2.90, m, 9 H). From integration of the methyl doublets of the two diastereomers present in the mixture and its rotation, the rotation of pure (−)-(*S*-*R*)-IX was estimated to be $[\alpha]^{25}\text{D}$ −95° (c ~2, chloroform).

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(8) C. J. M. Stirling, *J. Chem. Soc.*, 5741 (1963).

(9) J. von Braun and W. Kaiser, *Chem. Ber.*, **56**, 553 (1923).

(10) (a) K. K. Andersen, *Tetrahedron Letters*, **93** (1962); (b) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, Jr., *J. Am. Chem. Soc.*, **87**, 1958 (1965).

(11) This author wishes to acknowledge gratefully nonresident tuition grants from Dow Chemical Co. and U. S. Rubber Co.

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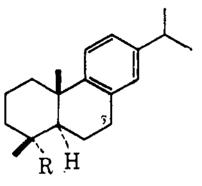
Received February 23, 1967

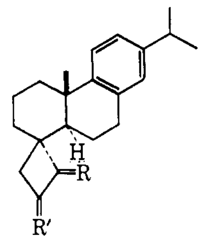
Anomalous Wolff Rearrangements

Sir:

Treatment of the diazomethyl ketone Ib, mp 99–101°, derived from dehydroabietic acid (Ia), with a suspension of silver oxide in methanol[1] has afforded methyl homodehydroabietate (Ic;[1] 55% yield), the liquid ketone Id [20%; infrared (neat): 5.82 μ (C=O, s); nmr ($CDCl_3$): two-proton singlet at δ 4.31 (ketomethylene), three-proton singlet at 3.38 (OMe)]—the exclusive product of the interaction of Ib with acidic methanol—and the ketone IIa [22%; mp 84–85°; infrared (Nujol): 5.65 μ (C=O, s); nmr ($CDCl_3$): three-proton singlet at δ 1.08 (C-10 methyl), six-proton doublet at 1.19 (J = 7.0 cps, isopropyl methyls)].[2–4] This observation invited an investigation of further examples of rearrangements of sterically compressed diazo ketones.



Ia, R = CO_2H
b, R = $COCHN_2$
c, R = CH_2CO_2Me
d, R = $COCH_2OMe$



IIa, R = O; R′ = H_2
b, R = O; R′ = CHC_6H_5
c, R = HOH; R′ = CHC_6H_5

Treatment of a methanolic solution of diazomethyl *t*-butyl ketone (IIIa)[5] with silver oxide yielded methyl homopivalate (IIIb;[6] 53%)—also the product of photolysis of a methanolic solution of IIIa—and two stereoisomers of IV, solids, mp 106° [13%; infrared (CCl_4):

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(1) For a previous study of this reaction, *cf.* G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **84**, 284 (1962).

(2) Satisfactory elemental analyses were obtained for all new compounds.

(3) Similar treatment of the diazomethyl ketone of 7-ketodehydroabietic acid produced the homoester 7-keto-Ic (61%; mp 90–90.5°), the methoxymethyl ketone 7-keto-Id (20%), and the cyclobutanone 7-keto-IIa (16%; mp 146°).

(4) The only previous example of cyclobutanone formation by intramolecular carbon–hydrogen bond insertion in an attempted Wolff rearrangement of a diazo ketone has been cited by H. O. House, S. G. Boots, and V. K. Jones, *J. Org. Chem.*, 30, 2519 (1965).

(5) K. B. Wiberg and T. W. Hutton, *J. Am. Chem. Soc.*, **76**, 5367 (1954).

(6) A. H. Homeyer, F. C. Whitmore, and V. H. Wallingford, *ibid.*, **55**, 4209 (1933).