been reported.[2] This paper describes the synthesis of this compound by a different route, which conveniently provides an intermediate which can be used in its resolution. The D and L isomers of cyclopentaneglycine are needed for use in the synthesis of peptides containing amino acid analogs.

Diethyl acetamidomalonate was allowed to react with cyclopentyl bromide in dimethylformamide to yield diethyl cyclopentylacetamidomalonate. The crude product, which proved difficult to crystallize, was refluxed with sodium carbonate and decarboxylated with acid[3] to obtain the resolvable intermediate, N-acetyl-DL-cyclopentaneglycine. Enzymatic resolution[4] with hog kidney acylase 1 (Sigma Chemical Co., St. Louis, Mo.) resulted in L-cyclopentaneglycine and N-acetyl-D-cyclopentaneglycine. The D isomer was obtained by acid hydrolysis of the N-acetyl-D-cyclopentaneglycine. N-Acetyl-L-cyclopentaneglycine was prepared by the method described by Sheehan and Bolhofer[5] and used for characterization.

Growth inhibition by cyclopentaneglycine in *E. coli* ATCC strain 9723 is apparently due to the L isomer. Complete growth inhibition occurred at a concentration of 30 μg./5 ml. with the L isomer; the D isomer had no inhibitory effect when added at a concentration of 300 μg./5 ml. Growth studies employed a salts–glucose medium in a previously described procedure.[6]

Experimental

Diethyl Cyclopentylacetamidomalonate.—In a 3-l. flask fitted with a drying tube, sodium hydride (12.5 g., 0.52 mole) was suspended in 1 l. of dimethylformamide,[8] and diethyl acetamidomalonate (108.5 g., 0.5 mole) was added in small portions; the exothermic reaction was controlled by cooling in an ice bath. After about 2 hr. the mixture was filtered through glass wool. The filtrate was added in one portion to 100 g. (0.66 mole) of dry cyclopentyl bromide (Eastman) contained in a 2-l. flask equipped with a magnetic stirring bar and drying tube. The solution was stirred at 60° for a period of 24 hr., whereupon an additional 25 g. of cyclopentyl bromide was added; stirring was then continued for 12 hr. The solvent was removed under reduced pressure at a temperature below 60°, and the residue was partitioned between water and ethyl acetate. The ethyl acetate solution was washed with three portions of a 5% solution of potassium bicarbonate and three portions of water and dried. Removal of the solvent left an oily residue which partially solidified after several days. This intermediate was used without further purification in the subsequent preparation.

N-Acetyl-DL-cyclopentaneglycine.—The total yield of diethyl cyclopentylacetamidomalonate was allowed to reflux for 36 hr. in a mixture of 900 ml. of 95% ethanol, 200 ml. of water, and 110 g. of Na_2CO_3. The solution was concentrated to a volume of about 500 ml. and adjusted to pH 3.5 with concentrated HCl while the temperature was maintained at about 50°. After decolorizing the solution with Darco G-60, the N-acetyl-DL-cyclopentaneglycine was extracted into ethyl acetate. Recrystallization of the product from hot ethanol–water resulted in a yield of 51 g. (55%), m.p. 173–175°.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.55. Found: C, 58.57; H, 8.11; N, 7.36.

L-Cyclopentaneglycine.—In 900 ml. of water were suspended 18.5 g. (0.1 mole) of N-acetyl-DL-cyclopentaneglycine, and the pH was adjusted to 7.6 with 4 *N* lithium hydroxide. The volume was increased to 1 l. with water, and hog kidney acylase 1 (100 mg.) was added. After 18 hr. of incubation at 37° hydrolysis was complete, as determined by titration of liberated amino acid.[9] The solution was carefully acidified to pH 5 and decolorized with Darco G-60 at a temperature of 50°. Removal of the solvent under reduced pressure at 40° resulted in a sirup which was taken up in a mixture 200 ml. of water and 800 ml. of ethanol. Upon cooling, L-cyclopentaneglycine crystallized. The crystals were harvested and washed successively with ethanol and ether. The filtrates were concentrated to 50 ml. and treated with 200 ml. of ethanol to obtain a second crop; total yield 5.9 g. (82%), m.p. 280–284° dec., $[\alpha]^{22}D$ +14.26° (*c* 2.0, 2 *N* HCl). The filtrate containing N-acetyl-D-cyclopentaneglycine was reserved for the following step.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.71; H, 9.14; N, 9.78. Found: C, 58.52; H, 9.06; N, 9.87.

N-Acetyl-D-cyclopentaneglycine.—The filtrate obtained after removal of L-cyclopentaneglycine was concentrated to a sirup, and the residue was dissolved in water. The pH of the solution was lowered to 2 with concentrated HCl, and the N-acetyl-D-cyclopentaneglycine was extracted into diethyl ether. The solution was taken to dryness, and the residue was recrystallized from hot ethanol–water to obtain 6.5 g. (70%) of N-acetyl-D-cyclopentaneglycine; m.p. 172–174°, $[\alpha]^{22}D$ +5.61° (*c* 2.0, 95% ethanol).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.55. Found: C, 58.17; H, 7.94; N, 7.38

D-Cyclopentaneglycine.—N-Acetyl-D-cyclopentaneglycine (1.0 g.) was hydrolyzed with 6 *N* HCl. Neutralization of the hydrochloride in ethanol with NH_4OH resulted in a yield of 0.45 g. (57%) of amino acid; m.p. 282–286° dec., $[\alpha]^{22}D$ −14.20° (*c* 2.0, 2 *N* HCl).

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.71; H, 9.14; N, 9.78. Found: C, 58.58; H, 8.99; N, 9.92

DL-Cyclopentaneglycine.—N-Acetyl-DL-cyclopentaneglycine (0.5 g.) was hydrolyzed by refluxing for 6 hr. in 10 ml. of 6 *N* HCl. The hydrochloride obtained was dissolved in ethanol and neutralized with NH_4OH. DL-Cyclopentaneglycine was recrystallized from hot ethanol–water; m.p. 284–286° dec. (lit.[1] m.p. 286–288°).

N-Acetyl-L-cyclopentaneglycine.—L-Cyclopentaneglycine (572 mg., 4.0 mmoles) was allowed to react with acetic anhydride (500 mg., 4.4 mmoles) in the presence of 8.0 mmoles of $NaHCO_3$ to obtain 425 mg. (75%) of N-acetyl-L-cyclopentaneglycine; m.p. 173–174°, $[\alpha]^{22}D$ −5.59° (*c* 2.0, 95% ethanol).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.55. Found: C, 57.80; H, 8.05; N, 7.50.

(2) W. M. Harding and W. Shive, *J. Biol. Chem.*, **206**, 1401 (1954).
(3) N. F. Albertson, *J. Am. Chem. Soc.*, **72**, 1396 (1950).
(4) V. E. Price, J. B. Gilbert, and J. P. Greenstein, *J. Biol. Chem.*, **179**, 1169 (1949).
(5) J. C. Sheehan and W. O. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2768 (1950).
(6) F. W. Dunn, J. M. Ravel, and W. Shive, *J. Biol. Chem.*, **219**, 809 (1956).
(7) All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.
(8) J. Shapira, R. Shapira, and K. Dittmer, *J. Am. Chem. Soc.*, **75**, 3655 (1953).
(9) W. Grassman and W. Heyde, *Z. Physiol. Chem.*, **183**, 32 (1929).

The Synthesis of Unsymmetrical Aliphatic Phosphine Oxides *via* Diphenyl Alkylphosphonates and Grignard Reagents

ROBERT G. LAUGHLIN

The Procter and Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

Received November 9, 1964

The preparation of unsymmetrical aryl-substituted phosphine oxides by reaction of diphenyl esters of phenyl-[1,2] and methylphosphonic[3] acids with Grignard reagents has been reported. The synthesis of purely aliphatic phosphine oxides of the type, $RP(O)R'_2$, *via* diphenyl alkylphosphonates has not been reported, al-

(1) K. D. Berlin and G. B. Butler, *J. Am. Chem. Soc.*, **82**, 2712 (1960).
(2) K. D. Berlin and M. Nagabhushanam, *Chem. Ind.* (London), 974 (1964).
(3) D. C. Morrison, *J. Am. Chem. Soc.*, **72**, 4820 (1950).

though the recent development of a convenient synthesis of these phosphonates makes them attractive intermediates.[2,4]

The synthesis of diallylphenylphosphine oxide from allyl Grignard reagent and diphenyl phenylphosphonate[1] was carried out in ether–benzene solvent under vigorous conditions (60–70°, 10:1 Grignard–ester mole ratio, 100-hr. reaction time). The reaction of other aliphatic Grignard reagents with the same ester and in the same solvent system under much milder conditions (60–70°, 3:1 mole ratio, 4-hr. reaction time) has been recently reported.[3]

We have found that dimethyl- and diethylalkylphosphine oxides (see Table I) can be conveniently synthesized from diphenyl alkylphosphonates[4] and the Grignard reagents from methyl or ethyl bromide in refluxing tetrahydrofuran (THF). Mole ratios of 4:1 Grignard–ester and 6–12-hr. reaction times were used. Isolated yields of the phosphine oxides were *ca.* 60%. Phenol was conveniently separated from the product by steam distillation,[5] after which the phosphine oxides could be isolated either by superheated steam distillation, by extraction and crystallization, or by vacuum distillation.

TABLE I

PHOSPHINE OXIDES, $RPOR'_2$

R	R′	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% P Calcd.	% P Found
$C_{12}H_{25}$	CH_3	84–85	68.3	68.0	12.6	12.8	12.6	12.1
$C_{12}H_{25}$	C_2H_5	48–48.5	70.1	69.8	12.8	12.8	11.3	10.9
$C_{14}H_{29}$	CH_3	89–90	70.1	69.8	12.8	12.7	11.3	11.0
$C_{14}H_{29}$	C_2H_5	56–57	71.5	71.3	12.9	13.0	10.3	10.1
$C_{16}H_{33}$	CH_3	93–94	71.5	71.3	12.9	12.8	10.3	10.0
$C_{16}H_{33}$	C_2H_5	62–63	72.7	72.6	13.0	12.8	9.4	9.0
$C_{18}H_{37}$	CH_3	94.5–96	72.7	72.5	13.0	13.0	9.4	9.1
$C_{18}H_{37}$	C_2H_5	65–67	...	...	...	...	8.6	8.3

The use of THF, rather than ether–benzene, is advantageous in that it provides a homogeneous rather than a heterogeneous reaction medium at comparable temperatures.[6] A much smaller excess of Grignard reagent and more reasonable reaction times were used than were originally employed in the reactions of the allyl Grignard reagent.[1] Our conditions are more comparable to those employed in the more recent report,[2] which appeared after our work had terminated.

Attempts were made to react diphenyl dodecylphosphonate with the Grignard reagent from isopropyl bromide in THF. However, the reaction was surprisingly slow; no apparent reaction had occurred after 24 hr. of reflux. This contrasts strikingly with the apparently facile reaction between the same Grignard reagent and diphenyl phenylphosphonate in ether–benzene.[2] From these results it appears either that THF is deactivating the Grignard reagent, relative to ether–benzene, or that diphenyl phenylphosphonate is much more reactive than diphenyl dodecylphosphonate. The former explanation seems more likely.[7]

Dodecyltrimethylphosphonium bromide was isolated from one reaction in *ca.* 5% yield. Its structure was firmly established by elemental analysis, spectral data, and comparison with an authentic sample (after conversion by ion exchange to the chloride). It was most likely formed by reaction of excess Grignard reagent with the phosphine oxide. Such a reaction has been

$$C_{12}H_{25}PO(CH_3)_2 + CH_3MgBr \longrightarrow C_{12}H_{25}\overset{+}{P}(CH_3)_3,\ Br^-$$

previously observed between phenyllithium and triphenylphosphine oxide,[8] but has not been observed in aliphatic systems.

Experimental

Dimethyldodecylphosphine Oxide.—The apparatus consisted of a 3-l. round-bottomed flask fitted with a 500-ml. pressure-equalizing addition funnel, stirrer, thermometer, and reflux condenser. After flaming and cooling, 665 ml. (2.00 moles) of 3 *M* ethereal methyl bromide Grignard reagent (Arapahoe Chemical Co.) was placed in the flask, and 1.33 l. of THF (digested over and then redistilled from $LiAlH_4$) was added carefully, using the addition funnel so as to control the vigorous heat evolution. The apparatus was then temporarily modified to permit distillation, and ether was distilled off until the liquid temperature reached 65–70°. The reflux condenser was replaced, the reaction was placed under a slight positive pressure of nitrogen, and 201 g. (0.500 mole) of diphenyl dodecylphosphonate[4] was added at a rate sufficient to maintain steady reflux. The reaction was then refluxed 12 hr., cooled in ice, and hydrolyzed with 500 ml. of water, keeping the temperature below 15°. To the heavy slurry of salts was added 174 ml. of concentrated hydrochloric acid. The pH of the aqueous layer measured *ca.* 3. The combined layers were heated on a steam bath to 60–80° and the upper layer was decanted. The lower aqueous layer was kept hot and thoroughly extracted, by decantation, with chloroform. The solvents were then removed.

The product was transferred to a two-neck flask immersed in a silicone fluid bath. The bath was heated by a 500-w. immersion heater that was regulated by a Therm-O-Watch (Instruments for Research and Industry, Cheltenham, Pa.) and by a hot plate. Steam was passed through a trap, then into a 10-turn, 0.25-in. copper coil which fit snugly around the periphery of the oil bath, and finally into the flask. An asbestos-wrapped Kjeldahl-type trap was mounted on the second neck and was connected to a high capacity condenser.

The bath was regulated at 115° (using only the immersion heater) and phenol was steam distilled from the reaction mixture until the distillate no longer gave a ferric chloride test. The crude product was extracted from the residue with chloroform (to separate from salts) and replaced in the flask, and the phosphine oxide was steam distilled with the bath at 225–240°. After extraction of the distillates ($CHCl_3$) and recrystallization from hexane or acetone, extremely pure salt-free product analyzing >99.5 % by gas chromatographic analysis was obtained. Yields were *ca.* 60%.

The crude product, after removal of phenol, could also be purified by recrystallization (see below) or by vacuum distillation. Steam distillation of homologs higher than tetradecyl was very slow.

The structure of dimethyldodecylphosphine oxide was firmly established by elemental analysis (Table I), spectra data, and comparison with a sample synthesized by oxidation of the tertiary phosphine.[9] The P^{31} n.m.r. chemical shift (−42.4 p.p.m., relative to 85% H_3PO_4 in $CHCl_3$) is compatible with a trialkylphosphine oxide structure.[10] (The chemical shift of the diethylalkyl compounds is −48.5 p.p.m.) The P–CH_3 doublet could be readily identified in the H^1 n.m.r. spectrum (τ 8.57, J = 14.5 c.p.s., $CDCl_3$) along with the *n*-alkyl signals at τ 8.73 and 9.19. The phosphoryl band in the infrared (mull) spectrum centered around 8.6 μ, and a sharp band for P–CH_3 (7.70 μ) was also ob-

(4) R. G. Laughlin, *J. Org. Chem.*, **27**, 3644 (1962).

(5) Separation of phenol from the product by base extraction[2] could not be utilized, at least with the dodecyl homolog, because the phosphine oxide is solubilized into the aqueous phase in the presence of sodium phenoxide.

(6) It would be expected that other ethers which would permit reaction temperatures of 60–70° (*e.g.*, dioxane, ethylene glycol dimethyl ether) could also be used.

(7) R. N. Lewis and J. R. Wright, *J. Am. Chem. Soc.*, **74**, 1253 (1952); E. I. Becker, *Trans. N. Y. Acad. Sci.*, [2] **25**(5), 513 (1963).

(8) G. Wittig and M. Rieber, *Ann.*, **562**, 187 (1949).

(9) R. G. Laughlin and J. T. Yoke (to Procter and Gamble Co.), French Patent 1,317,586 (March 13, 1962).

(10) R. A. Y. Jones and A. R. Katritzky, *Angew. Chem.*, **74**, 60 (1962).

served. The structures of the other compounds follow by analogy, and from their spectral and analytical data.

Dodecyltrimethylphosphonium Bromide.—After phenol was steam distilled from one preparation of dimethyldodecylphosphine oxide, the residue was extracted with hot benzene by decantation, the solvent was evaporated, and the residue was recrystallized from hexane. A hexane-insoluble product was observed, which was recrystallized from benzene–ethanol, and shown to be dodecyltrimethylphosphonium bromide. The yield was 5.5%.

Anal. Calcd. for $C_{15}H_{34}BrP$: C, 55.4; H, 10.5; Br, 24.5; P, 9.52. Found: C, 55.5; H, 10.5; Br, 24.5; P, 9.53.

The infrared spectrum (KBr pellet) showed P–CH_3 (7.70 μ) and strong P–C (10.0–10.3 μ) absorption, but no phosphoryl bands. The compound was readily soluble in water, titrated as a neutral compound towards both acid and base, and gave an immediate precipitate with silver nitrate reagent. A sample was converted to the chloride using Dowex 2-X8 ion-exchange resin. The infrared spectrum and powder X-ray diffraction pattern of the chloride were identical with those of an authentic sample, prepared by treating dimethyldodecylphosphine[9] with methyl chloride (16 hr. at 100° in ether in a sealed tube).

Acknowledgment.—The assistance of W. E. Ries in performing much of the experimental work is gratefully acknowledged.

The Mechanism and Stereochemistry of Formation and Cleavage of Epoxy Ethers.[1] II[2,3]

THEODORE B. ZALUCKY, SURESH MARATHE, LOUIS MALSPEIS, AND GILBERT HITE[4]

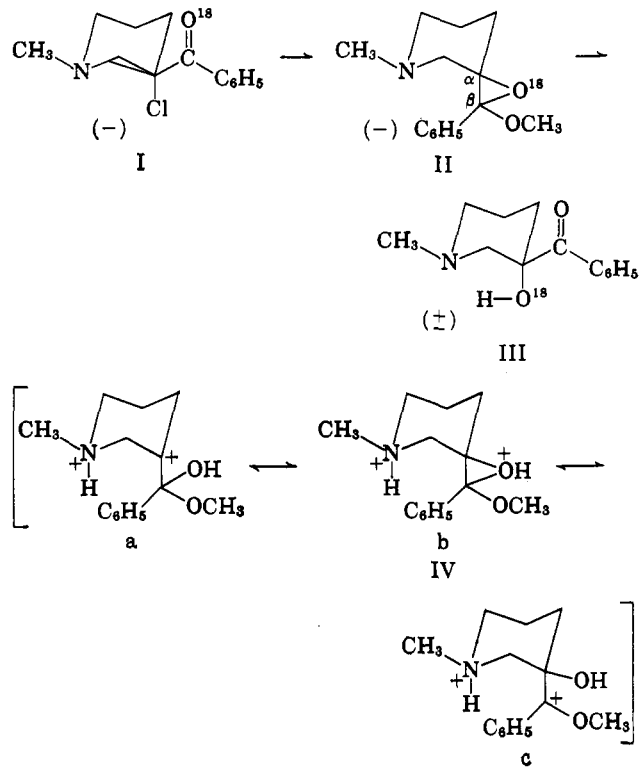
Departments of Pharmaceutical Chemistry, College of Pharmacy of the City of New York, Columbia University, New York, New York, and Howard University College of Pharmacy, Washington, D. C.

Received November 3, 1964

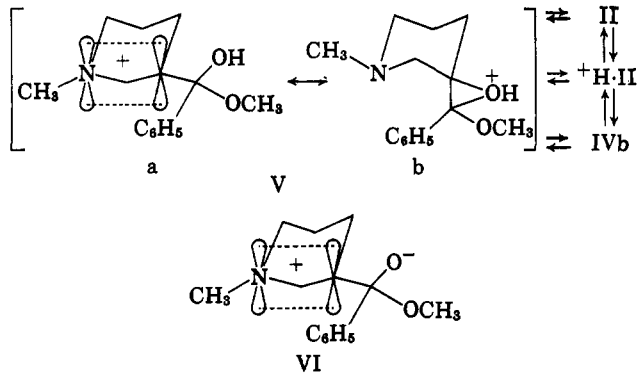
The mechanism of epoxy ether formation from α-halo ketones, proposed by Stevens and Weinheimer,[5] leads to inversion of the α-carbon. It has also been shown that epoxy ether cleavage proceeds by O–β-C scission which would result in retention of configuration at the α-carbon.[6]

However, while treatment of the β-amino α-halo ketone (−)-I with methanolic sodium methoxide or with a methanol-free slurry of sodium methoxide in xylene afforded optically active epoxy ethers, (−)-II or (+)-II, respectively, acidolysis of the epoxy ethers gave racemic α-hydroxy ketone III.[3]

It has been pointed out that inversion in the reaction (−)-I → (+)- or (−)-II must be followed by racemization through IV.[3] It may be argued that stabilization of IVa could be effected by N-deprotonation and participation (*cf.* V) as invoked in the corresponding conjugate base, VI, proposed, with some precedent,[3] as an intermediate in epoxy ether formation.



The more likely alternative involves asymmetric induction of the ketone carbon prior to or concurrent with α-carbon symmetrization[7] (*cf.* VI) in the former reaction, followed by epoxy ether cleavage through IVa and its SN2 counterpart and/or IVc and its SN2 counterpart.[3]



A reinvestigation of this sequence was initiated using isotopically (O^{18}) tagged α-halo ketone (−)-I in an attempt to detect participation of IVa, Va, and the SN2 counterpart.

A sample of (−)-1-methyl-3-benzoyl-3-chloropiperidine,[8] (−)-I, containing 3.04 atom % excess of O^{18} was treated with methanolic sodium methoxide and afforded the epoxy ether (−)-II, containing 1.52 atom % excess of O^{18}. The epoxy ether was subjected to acidolysis: method A, by refluxing in aqueous hydrochloric acid; or method B, by warming in glacial acetic acid followed by hydrolysis of the intermediate acetate ester (not isolated) in aqueous hydrochloric acid.

The racemic ketonic products (III) were freed of exchangeable (C=O^{18}) isotope before elemental and

(1) This investigation was supported by Public Health Service Research Grant B-3593 from the Institute of Neurological Diseases and Blindness, National Institutes of Health.

(2) Presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963.

(3) Paper I: T. B. Zalucky, L. Malspeis, and G. Hite, *J. Org. Chem.*, **29**, 3143 (1964).

(4) Author to whom inquiries should be addressed at Columbia University.

(5) C. L. Stevens and H. J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 4072 (1959).

(6) C. L. Stevens and S. J. Dykstra, *ibid.*, **75**, 5975 (1953); *cf.* C. L. Stevens and T. H. Coffield, *J. Org. Chem.*, **23**, 336 (1958).

(7) See ref. 3 for a definition of this term.

(8) (a) E. E. Smissman and G. Hite, *J. Am. Chem. Soc.*, **81**, 1201 (1959); (b) *ibid.*, **82**, 3375 (1960).