Phosphorus Betaines Derived from Cycloheptene and Cyclooctene Oxides. Inversion of Cyclooctenes

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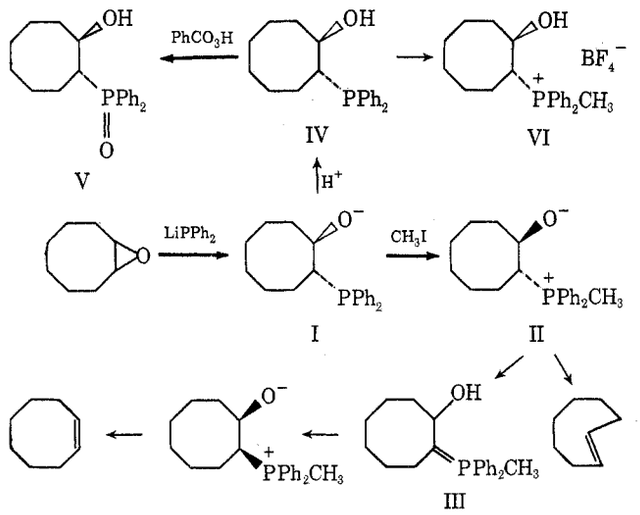
trans-Cyclooctene, *trans*-1-methylcyclooctene, *cis,trans*-1,4-cyclooctadiene, and *cis,trans*-1,5-cyclooctadiene can be prepared from the corresponding epoxides by treatment with lithium diphenylphosphide followed by methyl iodide. Similar treatment of cycloheptene oxide affords cycloheptenylmethyldiphenylphosphonium fluoroborate, but no *trans*-cycloheptene. Attempted deoxygenation of 1,2-dimethylcycloheptene oxide results in retro Wittig cleavage to the acyclic ketophosphonium salt XX instead of fragmentation to methyldiphenylphosphine oxide and 1,2-dimethyl-*trans*-cycloheptene. The "betaine" derived from cyclooctene oxide can be observed by ^{31}P nmr and is assigned the cyclic structure VII on the basis of its chemical shift of δ 62.8.

Deoxygenation of acyclic epoxides by treatment with lithium diphenylphosphide (LDP) followed by methyl iodide affords alkenes with overall inversion of stereochemistry.[3] Similar inversion in the case of cyclic epoxides would result in a simple route to strained *trans*-cycloalkenes; so we have studied the deoxygenation of several cyclooctene and cycloheptene oxides. The results of this study show that the relatively stable *trans*-cyclooctenes can be prepared, but that potential betaine precursors to *trans*-cycloheptenes readily find other reaction pathways when faced with the prospect of fragmentation to alkene and phosphine oxide.

Cyclooctene oxide reacts slowly with LDP at room temperature to form the expected SN2 product, the phosphine alkoxide I. Reaction of I with methyl iodide at 25° results in fragmentation to *trans*-cyclooctene (>90% yield, 70% isolated; >99.5% trans) provided that rigorously aprotic conditions are maintained throughout the experiment. Failure to dry the reagents has little effect on the overall yield, but the stereoselectivity drops from >99:1 to as low as 2:1 *trans*:*cis*-cyclooctene. Loss of stereochemistry under protic conditions is explained by formation of the hydroxy ylide III from the *trans*-betaine II followed by protonation to afford the *cis*-betaine.[4]



The first step in the sequence, cleavage of cyclooctene oxide by LDP, appears to be stereospecific and far less sensitive to reaction conditions than the betaine fragmentation step. Neutralization of the initial phosphine alkoxide I with acetic acid affords the phosphine alcohol IV, characterized as the oxide V or as the quaternary phosphonium fluoroborate VI. Within the limits of nmr or tlc analysis, other stereoisomers are not present. Treatment of the crystalline salt VI with *n*-butyllithium or diazabicycloundecene (DBU) in dry tetrahydrofuran affords *trans*-cyclooctene (80–85% yield, 99% trans). However, similar treatment of crude VI (at least 85% pure by nmr analysis) with DBU affords up to 30% *cis*-cyclooctene. Apparently, some minor side product from the epoxide cleavage step is able to catalyze interconversion of II and III under protic conditions with resulting loss of stereochemistry.

The reaction of VI with butyllithium can be followed conveniently by ^{31}P nmr spectroscopy. The ^{31}P resonance of VI occurs at δ −34.7 relative to external 85% phosphoric acid, as expected for a typical phosphonium salt.[5] Upon reaction of VI with butyllithium in tetrahydrofuran at −40°, a homogeneous solution is obtained which displays a single ^{31}P resonance at δ +62.8. This chemical shift is characteristic of pentavalent phosphorus[5] and is consistent with the cyclic structure VII but not with the betaine formulation II. Typical Wittig intermediates have not been studied previously by ^{31}P nmr, but the stable "betaine" produced by reaction between isopropylidenetriphenylphosphorane and diphenylketene appears to have considerable O–P bonding, as evidenced by the ^{31}P resonance at δ +36.[6] In other systems, pentavalent phosphorus structures have been distinguished from the isomeric betaines by ^{31}P chemical shifts of δ +35 to +67 for the former and *ca.* −7 for the latter.[7]

The broad ^{31}P resonance of VII begins to diminish perceptibly at 5° (rapidly at 20°) while a broadened quartet (J_{P-CH} = 13 Hz) appears at δ −33.8. The chemical shift and appearance of this signal can be duplicated precisely by a solution of authentic methyldiphenylphosphine oxide and lithium fluoroborate. Pure methyldiphenylphosphine oxide displays a broadened quartet at δ −25 (J_{P-CH} = 13 Hz) in tetrahydro-

(1) Alfred P. Sloan Fellow, 1971–1973.

(2) We thank the National Science Foundation for support of this work.

(3) E. Vedejs and P. L. Fuchs, *J. Amer. Chem. Soc.*, **94**, 822 (1972).

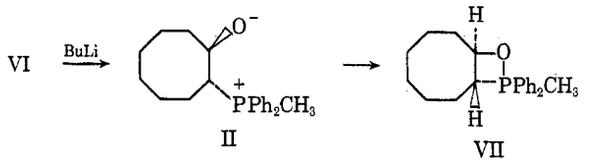
(4) Bissing and Speziale have suggested the formation of an analogous hydroxy ylide to explain partial loss of stereochemistry upon deoxygenation of 4-octene oxide with triphenylphosphine at 160°: D. E. Bissing and A. J. Speziale, *ibid.*, **87**, 2683 (1965).

(5) M. Grayson and E. J. Griffith, Ed., "Topics in Phosphorus Chemistry," Vol. 5, Interscience, New York, N. Y., 1967.

(6) G. Wittig and A. Haag, *Chem. Ber.*, **96**, 1535 (1963).

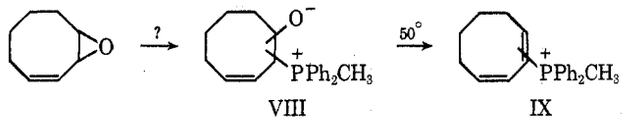
(7) I. Kawamoto, T. Hata, Y. Kishida, and C. Tamura, *Tetrahedron Lett.*, 2417 (1971); G. H. Birum and C. N. Matthews, *Chem. Commun.*, 137 (1967).

furan.[8] No other signals are observed in the temperature range −20 to 20°, indicating that the dipolar betaine structure II is unstable with respect to VII in tetrahydrofuran.



II VII

Deoxygenation of the monoepoxides of 1,4- or 1,5-cyclooctadienes under the usual conditions affords *cis,trans*-1,4-cyclooctadiene and *cis,trans*-1,5-cyclooctadiene in yields of 40 and 60%, respectively. Methyldiphenylphosphine oxide is isolated in >80% yield from both reactions; so it is likely that the low yield of cis,trans dienes is due to complications after betaine fragmentation. Addition of diphenylisobenzofuran along with the methyl iodide affords the expected Diels–Alder adducts from either *cis,trans*-1,5- or *cis,trans*-1,4-cyclooctadiene, but the yield of adducts is no higher than the yield of dienes in the absence of diphenylisobenzofuran. Attempted deoxygenation of 1,5-cyclooctadiene dioxide to the highly reactive *trans,trans*-cyclooctadiene affords only traces of hydrocarbon products. Treatment of the monoepoxide of 1,3-cyclooctadiene under the usual conditions also fails to form the hydrocarbon product. At 50° the presumed betaine VIII is converted into a phosphonium salt with a P–CH_3 doublet at δ 2.95 and olefinic hydrogens between δ 6 and 8, consistent with the cyclooctadienylphosphonium structure IX.



VIII IX

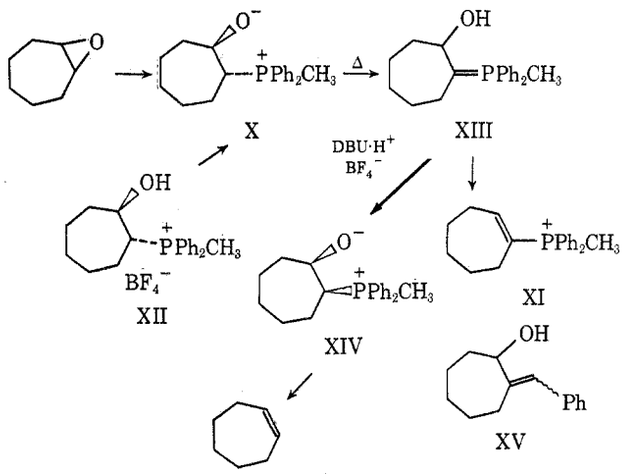
Reaction of 1-methylcyclooctene oxide with LDP followed by methyl iodide as usual affords a mixture of *cis*- and *trans*-1-methylcyclooctenes, even under scrupulously aprotic conditions. However, treatment of the corresponding crystalline hydroxyphosphonium salt with DBU in tetrahydrofuran affords only the trans isomer (70% isolated yield, 99% trans) characterized by exact mass, nmr, and formation of a diphenylisobenzofuran adduct. The factors causing loss of stereochemistry in the direct reaction have not been determined.

Cycloheptene oxide is converted into the betaine X under the usual conditions, but no evidence of fragmentation to *trans*-cycloheptene can be detected. In refluxing tetrahydrofuran, the betaine is converted into the methyldiphenylcycloheptenylphosphonium salt XI as the sole product observed by nmr. No trace of methyldiphenylphosphine oxide can be detected and addition of diphenylisobenzofuran does not result in the Diels–Alder adduct of *trans*-cycloheptene.[9] The structure of the salt XI is verified by independent synthesis from 1-lithiocycloheptene and chlorodiphenylphosphine followed by quaternization with methyl iodide.

(8) The $LiBF_4$ adduct of methyldiphenylphosphine oxide can be isolated if desired as a stable, crystalline, water-soluble substance.

(9) E. J. Corey, F. A. Carey, and R. Winter, *J. Amer. Chem. Soc.*, **87**, 934 (1965).

The crystalline hydroxyphosphonium salt XII can be prepared in the usual way, and treatment of XII with *n*-butyllithium followed by heating affords XI as before.[10] However, reaction of XII with DBU in refluxing tetrahydrofuran affords *cis*-cycloheptene and methyldiphenylphosphine oxide in addition to XI. Formation of *cis*-cycloheptene and XI is explained by conversion of X into the hydroxy ylide XIII. In the presence of the proton donor DBU·H⁺BF_4^-, XIII undergoes hydrogen transfer to form the *cis*-betaine XIV, which can fragment to *cis*-cycloheptene. Under aprotic conditions, XIII suffers elimination of hydroxide to form XI. Several other cases of vinylphosphonium salt formation from betaines have been reported recently.[11] The elimination of hydroxide is not reversible with or without added water, and cycloheptene is not formed from authentic XI under the DBU reaction conditions.

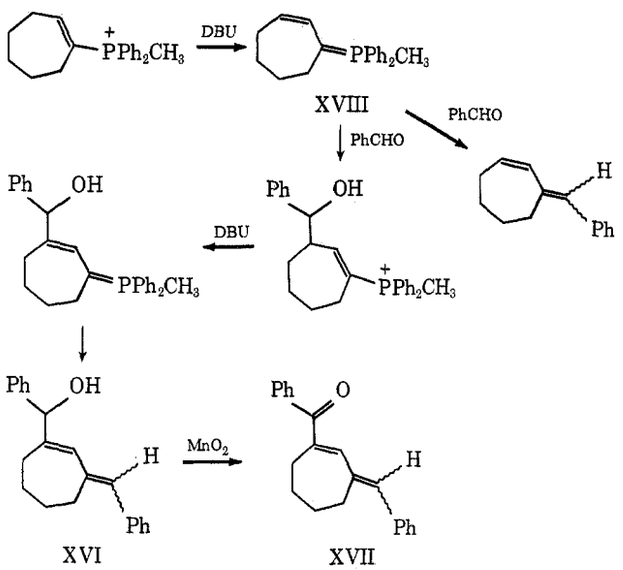


In an attempt to trap the hydroxy ylide XIII as the Wittig product, we have examined the reaction of XII with DBU in the presence of benzaldehyde. The simple product XV is not formed, however, and all of the new products are derived from further reactions of XI. In addition to cycloheptene, methyldiphenylphosphine oxide, and the obvious Wittig products styrene and benzylidenecycloheptene, the reaction mixture contains the dienol XVI ($C_{21}H_{22}O$) resulting from reaction of 2 mol of benzaldehyde with XI. Oxidation of XVI with active MnO_2 affords a cis,trans mixture of dienones, one of which has been isolated in pure form. The dienone is assigned the structure XVII on the basis of analysis, the nmr spectrum, and the ultraviolet chromophore (326 nm, ϵ 22,100; 255 nm, ϵ 15,000). Formation of the dienol XVI is explained by intial condensation of benzaldehyde at the γ position of the conjugated ylide XVIII followed by deprotonation and normal Wittig reaction. Benzyl-

(10) We have failed to detect X or its pentavalent phosphorane isomer by ^{31}P nmr under conditions which were successful in the analogous reaction of VI with butyllithium. The absence of ^{31}P signals at −20° is probably due to precipitation of the reaction intermediate(s). However, a homogeneous solution is obtained at *ca.* 0° which still has no observable ^{31}P signal even though an equally concentrated solution of XII displays an easily observed signal at δ −31.4. At present, we are inclined to suspect line broadening due to an equilibrium between two or more structures such as the betaine X, its $LiBF_4$ adduct, the cyclic phosphorane, etc., as the most plausible explanation.

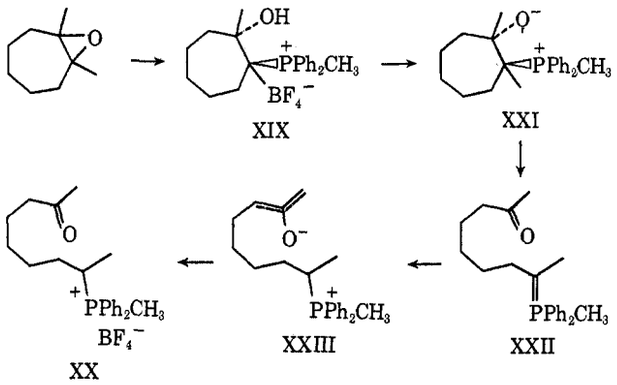
(11) (a) S. Trippett and B. S. Walker, *J. Chem. Soc. C*, 887 (1966); (b) E. E. Schweizer, T. Minami, and D. M. Crouse, *J. Org. Chem.*, **36**, 4028 (1971); (c) E. E. Schweitzer, D. M. Crouse, T. Minami, and A. T. Wehman, *Chem. Commun.*, 1000 (1971).

idenecycloheptene, styrene, and XVI are formed as expected from XI, benzaldehyde, and DBU. Although previous reports of γ attack on allyl ylides are rare,[12] we have found that the reaction is quite general and occurs to some extent with a variety of allyl ylides and aldehydes.[13]



From the above results, it is clear that highly strained *trans*-cycloalkenes cannot be generated by the betaine method unless the possibility of elimination to a vinylphosphonium salt is blocked. Elimination of hydroxide is not possible in the betaine derived from 1,2-dimethylcycloheptene oxide; so we have attempted to convert this precursor into 1,2-dimethyl-*trans*-cycloheptene. The tetrasubstituted epoxide reacts with LDP at 65°, but quaternization of the initial product with methyl iodide followed by aqueous work-up does not produce the expected hydroxyphosphonium salt XIX or any hydrocarbon products. Instead, an isomeric ketophosphonium salt XX is obtained (carbonyl infrared absorption at 5.86 μ). The nmr spectrum of XX has a methyl singlet at δ 2.05, a *P*-methyl doublet at 2.47 (J_{PCH} = 13 Hz), a broadened methylene triplet at 2.38 (J_{HCCH} = 6 Hz), and a methyl signal at 1.29 split into a doublet of doublets (J_{PCH} = 20 Hz, J_{HCCH} = 7 Hz). From the latter signal, it is clear that the *C*-methyl group next to phosphorus is attached to a carbon which also has one hydrogen substituent. These spectral features prove conclusively that XX is the ketophosphonium salt derived from retro Wittig cleavage of the betaine XXI.

The hydroxyphosphonium salt XIX can be isolated by treatment of 1,2-dimethylcycloheptene oxide with LDP, neutralization of the alkoxide with acetic acid, and quaternization of the resulting hydroxyphosphine with methyl iodide. The *C*-methyl signals of XIX are observed at δ 1.16 (singlet) and 1.60 (doublet, J_{PCH} = 20 Hz), and the ^{31}P nmr signal is observed at δ −28. Treatment of XIX with methanolic sodium carbonate or *n*-butyllithium in tetrahydrofuran followed by aqueous work-up affords XX as the only observable product.



Reaction of XIX with *n*-butyllithium in tetrahydrofuran at −70°, warming to 25°, and quenching with D_2O–DCl affords a sample of XX containing deuterium at both enolizable positions (pmr signals at δ 2.47 and 2.05). However, no change in coupling is observed in the doublet of doublets at δ 1.29 or in the intensity of the *P*-CH_3 doublet. Clearly, proton transfer to the ylide carbon in the initial retro Wittig product XXII occurs prior to D_2O–DCL work-up. On the basis of ^{31}P nmr evidence, we conclude that retro Wittig cleavage *and* proton transfer to form the enolates XXIII occur to some extent even at −20°. The only signal observed in the ^{31}P resonance spectrum of the solution obtained from XIX and butyllithium occurs at δ −26.5, and the signal is unchanged upon warming to 25°. The ^{31}P signal of the ylide XXII would be expected at higher field by δ 10–20 relative to the phosphonium salt.[14]

Neither methyldiphenylphosphine oxide nor 1,2-dimethyl-*cis*-cycloheptene is formed from XIX under any conditions examined. The absence of intra- or intermolecular Wittig products is somewhat surprising, since an equilibrium between XXIII and XXII might be anticipated from the comparable pK_a's of protons next to carbonyl or postive phosphorus.[15] Apparently, conversion of XXII to XXIII by proton transfer is rapid compared to Wittig condensation, and essentially irreversible in tetrahydrofuran solution.

The facile retro Wittig cleavage of XXI under aprotic conditions is an unusual example of such cleavage to a reactive ylide and a simple carbonyl fragment. Clearly established examples of betaine cleavage are limited to systems where the potential ylide is stabilized by carbonyl, phenyl, etc., systems where betaine fragmentation to olefin and phosphine oxide is retarded by electron-donating substituents at phosphorus,[16] or reactions which are conducted in hydroxylic solvents.[17]

Retro Wittig cleavage may also explain some of the nonstereoselectivity (formation of *cis*-cycloalkene) observed in decomposition of the betaines II and X under protic conditions. Although we cannot disprove this possibility rigorously, we doubt that internal Wittig reaction could account for the high material

(12) H. J. Bestmann and H. Schulz, *Angew. Chem.*, **73**, 27 (1961); H. J. Bestmann and H. Schulz, *Justus Liebigs Ann. Chem.*, **674**, 11 (1964); G. Buchi and H. Wuest, *Helv. Chim. Acta*, **54**, 1767 (1971).

(13) E. Vedejs, J. Bershas, and P. L. Fuchs, to be published.

(14) S. O. Grim, W. McFarlane, and T. J. Marks, *Chem. Commun.*, 1191 (1967); G. H. Birum and C. N. Matthews, *ibid.*, 137 (1967).

(15) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, Chapter 3.

(16) S. Trippett, *Pure Appl. Chem.*, **9**, 255 (1964); see also ref 4 and ref 15, Chapter 4; M. Schlosser and K. F. Christmann, *Justus Liebigs Ann. Chem.*, **708**, 1 (1967).

(17) M. E. Jones and S. Trippett, *J. Chem. Soc. C*, *1090 (1966)*; J. W. Rakshys, Jr., and S. V. McKinley, *Chem. Commun.*, 1336 (1971).

balance observed in these reactions, particularly in the experiments leading to cyclooctenes.

The betaine method holds considerable promise for synthesis of substituted *trans*-cyclooctenes, a subject which is under active investigation. However, the technique is not useful for preparation of more highly strained alkenes, since the intermediate betaines are readily converted into vinylphosphonium salts by elimination of hydroxide. Increased alkyl substitution at the epoxide carbons appears to facilitate retro Wittig cleavage; so it is unlikely that simple modifications of the technique will expand its scope to permit generation of *trans*-cycloheptenes.

Experimental Section

Epoxides were prepared by reaction of the appropriate alkenes with *m*-chloroperbenzoic acid in methylene chloride at 25°. The epoxides were worked up with sodium bisulfite and sodium carbonate and were distilled prior to use. Lithium diphenylphosphide (LDP) solution in tetrahydrofuran was prepared as described previously.[3] Hydrocarbon products were analyzed by glpc using a Varian Aerograph 90-P3 gas chromatograph. Proton nmr spectra were obtained using Varian A-60A and HA-100 spectrometers, and ^{31}P spectra were obtained using the Varian XL-100 system[18] with external water lock and without proton noise decoupling.

***trans*-Cyclooctene.**—LDP solution[3] (4.15 ml, 1.15 *M*, 0.00476 mol) was injected into a flame-dried three-neck flask under positive argon pressure. Cyclooctene oxide (0.63 g, 0.005 mol) in dry tetrahydrofuran (15 ml) was added at 25° over several minutes using a dropping funnel. The solution was allowed to stand for 30 hr at room temperature, at which time the ruby-red phosphide color had faded to a pale yellow. Freshly distilled methyl iodide was then added (1.03 g, 0.0072 mol) and the mixture was allowed to stand for 0.5 hr at 25° under positive argon pressure. Pentane (100 ml) was then added, and the mixture was filtered to remove precipitated salts and washed several times with water. The pentane layer was dried over sodium sulfate and analyzed by glpc (10 ft × 0.25 in., 20% TCEP/Chromosorb P at 50°) using toluene as internal standard, 90% yield of cyclooctene based on epoxide, <99% trans. For preparative purposes, the pentane layer was concentrated under a Vigreux column and the *trans*-cyclooctene was distilled using a short-path distillation head to yield 0.41 g (75%) of material boiling at 68–72° (100 mm), typically contaminated by *ca.* 3% tetrahydrofuran and 1–2% *cis*-cyclooctene.

(*trans*-2-Hydroxycyclooctyl)methyldiphenylphosphonium Fluoroborate (VI).—Cyclooctene oxide was allowed to react with LPD as before. After the usual reaction period at 25°, the solution was cooled in Dry Ice–acetone, treated with 1.1 equiv of acetic acid, and stirred for 15 min. The cooling bath was then removed, methyl iodide was added, and the mixture was allowed to warm to room temperature and stirred for 0.5 hr. Most of the solvent was removed under vacuum at room temperature and the salts were precipitated with hexane and washed well to remove unreacted epoxide and traces of cyclooctene. The viscous residue was then dissolved in methanol (5 ml/g of crude salt) and added to a vigorously stirred aqueous solution of sodium fluoroborate (*ca.* 250 equiv).

After stirring for 1 hr, the crude VI was extracted with chloroform and dried over sodium sulfate, and the chloroform was evaporated under vacuum at 30°. Residual chloroform was removed under high vacuum and the resulting foam was crystallized from tetrahydrofuran to afford VI: mp 77–78°; nmr ($CDCl_3$) δ 7.5–8.0 (10 H, br m), 3.4–4.2 (3 H, br m), 2.60 (3 H, d, J = 13 Hz), 1.2–2.2 (12 H, br m), and residual tetrahydrofuran signals at *ca.* 1.8 and 3.7. Extensive efforts to remove the last traces of tetrahydrofuran failed. The nmr spectrum of crude VI was identical except that tetrahydrofuran was not present, and a residual chloroform signal could not be removed completely.

Conversion of VI into *trans*-Cyclooctene. A. Using Diazabicycloundecene (DBU) as Base.—Crystalline VI (0.296 g, 0.00071 mol) was stirred with dry tetrahydrofuran (7 ml) and DBU (0.11 g, 0.000714 mol) under nitrogen for 2 hr at room temperature. Aqueous pentane work-up and glpc analysis as before indicated *trans*-cyclooctene, 80% yield, and <1% *cis*-cyclooctene. Under identical conditions, a noncrystalline sample of VI (containing traces of $CHCl_3$) afforded *trans*- and *cis*-cyclooctene in a ratio of 7:3.

B. Using *n*-Butyllithium.—Crystalline VI (0.30 g, 0.00072 mol) was stirred in dry tetrahydrofuran (30 ml) at −70°, and *n*-butyllithium in hexane (1.62 *N*, 0.46 ml) was added dropwise. The mixture was stirred for 15 min after addition and allowed to come to room temperature. After 30 min at 25°, the reaction was worked up as before, and glpc analysis indicated 82% *trans*-cyclooctene as the sole volatile product.

C. Conversion of VI into VII. ^{31}P Nmr Experiment.—The reaction of VI (0.51 g) and *n*-butyllithium (0.76 ml) was conducted as above except that 4 ml of tetrahydrofuran was used. The mixture was opaque after addition of butyllithium at −70°, but warming to −20° produced a clear solution. The solution was transferred into a 12-mm XL-100 nmr tube under argon pressure and spectra were recorded at 5° intervals between −20 and 25°. A single resonance was observed initially at δ +62.8 relative to external 85% H_3PO_4. At 5°, a new signal was detected at δ −33.8 and integration of the signals indicated a corresponding decrease in the δ 62.8 signal. At 25°, disappearance of the high-field signal was complete within 20 min. The usual work-up and glpc analysis of the nmr sample indicated stereospecific conversion into *trans*-cyclooctene.

(*trans*-2-Hydroxycyclooctyl)diphenylphosphine Oxide (V).—Cyclooctene oxide (0.94 g, 0.0075 mol) was cleaved with LPD as usual. The resulting tetrahydrofuran solution was then treated with 2% hydrogen peroxide (30 ml) at 10° and allowed to stand for 1 hr at 25° after the initial exothermic reaction. The product was extracted with chloroform, dried ($MgSO_4$), and evaporated under vacuum. The residual oil was crystallized from benzene to afford V (1.5 g, 62% isolated), mp 159–160°. *Anal.* Found: C, 73.28; H, 7.59; P, 9.43. Calcd: C, 73.15; H, 7.67; P, 9.43. By tlc or nmr analysis, the mother liquors contained no other phosphine oxides.

***cis,trans*-1,4-Cyclooctadiene.**—The same procedure was used as described for preparation of *trans*-cyclooctene, starting from the monoepoxide of *cis,cis*-1,4-cyclooctadiene. The product consisted of *cis,trans*-cyclooctadiene, 25% yield, and traces of the cis,cis isomer. The yield could be increased to 40% by adding the methyl iodide over 18 hr at 25°. After the usual pentane *vs.* water work-up, the aqueous phase was extracted with $CHCl_3$ to yield 85% of methyldiphenylphosphine oxide, mp 108° (lit.[19] mp 108–109°). The diene was isolated by preparative glpc of the concentrated pentane extracts and characterized by extract mass (calcd 108.0938 amu; found 108.0936 ± 0.001 amu): nmr ($CDCl_3$) δ 5.6–6.0 (4 H, m), 1.94–2.5 (8 H, m); ir ($CHCl_3$) 3.33, 3.40, 3.48, 6.94, 10.13 μ. The *cis,trans*-1,4-cyclooctadiene reacted with diphenylisobenzofuran at 25° to form an adduct in quantitative yield, mp 208–209° (recrystallized from $CHCl_3$–ether).

***cis,trans*-1,5-Cyclooctadiene.**—The same procedure was used as described for preparation of *trans*-cyclooctene. The known *cis,trans*-1,5-cyclooctadiene was formed in 60% yield (>99% cis,trans isomer) and was identified by spectral features[20] and formation of an adduct (mp 178–179°) with diphenylisobenzofuran.

(*trans*-2-Hydroxycycloheptyl)methyldiphenylphosphonium Fluoroborate (XII).—The same procedure was used as described for preparation of VI. The product XII crystallized from $CHCl_3$–CCl_4, 65% in two crops, mp 154–156°. The analytical sample was recrystallized from $CHCl_3$–CCl_4, mp 159–160°. *Anal.* Found: C, 60.06; H, 6.67; F, 18.86; P, 7.81. Calcd: C, 60.02; H, 6.55; F, 18.99; P, 7.74. Nmr ($CDCl_3$): δ 7.5–8.0 (10 H, m), 3.0–4.1 (3 H, br m), 2.51 (3 H, d, J = 13 Hz), 1.61 (br s, 10 H).

Attempted Inversion of Cycloheptene Oxide.—Cycloheptene oxide was treated with LDP followed by methyl iodide as usual. The usual work-up afforded no pentane-soluble products. Extraction of the aqueous phase and pentane-insoluble residues with $CHCl_3$ afforded a crude product having no trace of the *p*-

(18) Provided by the National Science Foundation.

(19) A. E. Arbuzov and and K. V. Nikonorov, *Zh. Obshch. Khim.*, **18**, 2008 (1948).

(20) A. C. Cope, C. F. Howell, J. Bowers, R. C. Lord, and G. M. Whitesides, *J. Amer. Chem. Soc.*, **89**, 4024 (1967).

methyl doublet of methyldiphenylphosphine oxide at δ 1.98. A *P*-methyl doublet was observed at δ 2.8, consistent with the presence of (*trans*-2-hydroxycycloheptyl)methyldiphenylphosphonium iodide.

The experiment was repeated as above, except that the solution obtained after addition of methyl iodide was refluxed for 12 hr. No pentane-soluble products were obtained. The chloroform-soluble fraction displayed a single *P*-methyl doublet at δ 2.88 and other signals characteristic of (1-cycloheptenyl)methyldiphenylphosphonium iodide (see below). The above experiment was repeated in the presence of diphenylisobenzofuran. No trace of the adduct of *trans*-cycloheptene could be detected by tlc analysis.

(1-Cycloheptenyl)methyldiphenylphosphonium Iodide (XI).—Chlorodiphenylphosphine (5.2 g, 0.0236 mol) was stirred in dry ether (100 ml) at −60°. A solution of 1-lithiocycloheptane[21] in ether (85 ml, 0.25 *M*) was added dropwise at a rate such that the temperature did not exceed −55°. After 30 min at −60°, methyl iodide (8.5 g, 0.063 mol) was added and the solution was allowed to come to 25°. After 30 min the mixture was diluted with water and extracted with chloroform, and the organic phase was dried over sodium sulfate and evaporated. The residual oil was taken up in methanol (100 ml) and stirred with excess sodium iodide to ensure a homogeneous counterion.

Chloroform *vs.* water work-up afforded a yellow oil which crystallized from chloroform–ethyl acetate to yield XI (5.5 g, 55%, mp 85–88°). Four recrystallizations afforded pure material, mp 89–90°. *Anal.* Found: C, 56.77; H, 5.96; I, 29.88; P, 7.16. Calcd: C, 56.98; H, 5.73; I, 30.05; P, 7.33. Nmr ($CDCl_3$): δ 7.5–8.0 (10 H, m), 6.88 (1 H, dt, J = 24, 6 Hz), 2.88 (3 H, d, J = 13 Hz), 2.2–2.8 (4 H, m), 1.4–2.0 (6 H, m).

Reaction of XII and DBU.—A suspension of XII (0.39 g, 0.00094 mol) in dry tetrahydrofuran (5 ml) and 1,5-diazabicyclo[5.4.0]undec-5-ene (Aldrich, 0.36 g, 0.0024 mol) was refluxed for 24 hr. The solution was analyzed directly by glpc and was found to contain *cis*-cycloheptene (45%). Water was added and the products were extracted with chloroform to yield 0.35 g of yellow oil. By nmr analysis, the oil consisted of XI (50% yield) and methyldiphenylphosphine oxide (45%).

Reaction of XII, DBU, and Benzaldehyde.—The above experiment was repeated using 0.22 g of XII, 0.087 g of DBU, and 0.29 g (5 equiv) of benzaldehyde. Analysis by glpc indicated the presence of *cis*-cycloheptene (30%) and styrene (15%). The chloroform extracts were separated by preparative layer chromatography over silica gel (three developments with $CHCl_3$) and three zones were collected: R_f 0.9, benzylidenecycloheptene (0.016 g, 20%); R_f 0.1, methyldiphenylphosphine oxide (0.092 g, 85%); R_f 0.3, 3-(α-hydroxybenzyl)benzylidenecycloheptene (XVI) (0.038 g, 30%), viscous oil [ir (neat) 2.80, 2.96, 3.30, 3.40, 3.50 μ; nmr ($CDCl_3$) δ 7.1–7.4 (10 H, m), 6.3–6.7 (2 H, m), 5.16 (1 H, s), 1.5–2.8 (9 H, m)].

XVI (0.2 g, 0.0065 mol) was stirred with active MnO_2 (4 g) in ethyl acetate (25 ml) at 45° for 12 hr, the mixture was filtered and evaporated, and the crude oil was taken up in hexane. The dienone XVII (stereochemistry unknown) crystallized slowly: mp 91–92.5°; uv (methanol) λ_{max} 226 nm (ε 20,500), 255 (15,000), 326 (22,100); ir ($CHCl_3$) 3.31, 3.40, 3.50, 6.12, 6.26 μ; nmr ($CDCl_3$) δ 7.4–7.9 (5 H, m), 7.33 (5 H, s), 7.92 (1 H, s), 7.57 (1 H, s), 2.6–2.9 (4 H, m), 1.8–2.1 (4 H, m); m/e 288 amu.

Attempted Inversion of 1,2-Dimethylcycloheptene Oxide.—1,2-Dimethylcycloheptene oxide was treated with LDP at reflux in tetrahydrofuran for 72 hr followed by methyl iodide at 25° as usual. Aqueous work-up afforded no pentane-soluble products, and the chloroform extract contained no methyldiphenylphosphine oxide by nmr or tlc analysis. The oily product was dissolved in methanol and added dropwise to a vigorously stirred solution of aqueous sodium fluoroborate, and the fluoroborate salt was recovered by $CHCl_3$ *vs.* water work-up. The nmr spectrum of the product was identical with the spectrum of XX prepared from pure XIX (see below).

(1,2-Dimethyl-2-hydroxycycloheptyl)methyldiphenylphosphonium Fluoroborate (XIX).—The product of reaction between 1,2-dimethylcycloheptene oxide and LDP was converted into XIX by the same method used to prepare VI. The oily product crystallized inefficiently from tetrahydrofuran to afford colorless crystals: mp 137–140°; nmr ($CDCl_3$) δ 7.5–8.2 (10 H, m), 3.7 (1 H, br s), 2.72 (3 H, d, J = 13 Hz), 1.2–2.4 (*ca.* 11 H, br m), 1.60 (3 H, d, J = 20 Hz), 1.16 (3 H, s). Traces of residual tetrahydrofuran were evident and could not be removed completely under vacuum.

Conversion of XIX into XX.—A suspension of XIX (0.44 g, 0.0011 mol) in dry tetrahydrofuran (4 ml) was cooled to −70° under argon. *n*-Butyllithium in hexane (0.68 ml, 0.0011 mol) was added dropwise *via* syringe with vigorous stirring. The resulting mixture was stirred for 0.5 hr at −70° and then warmed to −22°. The solution was transferred into an XL-100 nmr tube under argon pressure and spectra were recorded between −20 and 25°. A single resonance at δ −26.5 was observed throughout which increased slightly in intensity as the sample was warmed to 25°. The solution was treated with aqueous 5% HCl, the product was extracted with chloroform, and the crude product was treated with excess aqueous sodium fluoroborate as usual. After $CHCl_3$ *vs.* water work-up, XX was obtained as a pale yellow oil which could not be induced to crystallize: ir ($CHCl_3$) 5.86 μ; nmr ($CDCl_3$) δ 7.6–8.2 (10 H, m), 3.9 (1 H, br), 2.47 (3 H, d, J = 13 Hz), 2.38 (2 H, br t, J = 6 Hz), 2.05 (3 H, s), 1.1–2.0 with partially overlapping doublet of doublets at 1.29, J = 20 and 7 Hz (11 H combined).

The experiment was repeated using D_2O–DCl instead of H_2O–HCl. The tetrahydrofuran solution was stirred vigorously with the aqueous phase for *ca.* 10 min, and worked up as before. The nmr spectrum of the resulting XX showed no change in the relative height or appearance of the methyl signals at δ 2.47 or 1.29, but the signals at 2.05 and 2.38 were diminished in intensity. Integration indicated *ca.* 1.6 D/mol of XX.

***trans*-1-Methylcyclooctene.**—1-Methylcyclooctene oxide (0.4367 g, 0.003116 mol) in dry THF (4 ml, distilled from $LiAlH_4$) was added to a solution of lithium diphenylphosphide (0.00279 mol) in dry THF (*ca.* 5 ml) under positive argon pressure. The solution was stirred for 95 hr at 25°; the red color slowly faded to pale yellow. The reaction mixture was cooled to −78° and glacial acetic acid (0.1675 g, 0.00279 mol) was added under argon flow. After stirring for 1 hr, the solution was allowed to warm to −25° and methyl iodide (0.596 g, 0.00419 mol) was added under argon flow. After 2 hr at −25° the product was allowed to warm to 25° over *ca.* 1 hr, and was then diluted with water (100 ml) and extracted with pentane (2 × 30 ml) to remove unreacted epoxide. The aqueous layer and pentane-insoluble material were then extracted with chloroform (6 × 80 ml), the chloroform was dried over sodium sulfate and evaporated under the aspirator, and the last traces of chloroform were removed under high vacuum. The foamy residue (1.24 g) was crystallized from THF to yield (2-hydroxy-2-methylcyclooctyl)methyldiphenylphosphonium iodide, mp 208–211°, first crop 0.69 g (light sensitive).

Conversion of the above salt to 1-methyl-*trans*-cyclooctene was effected by treatment with 1 equiv of DBU in dry THF under a nitrogen atmosphere for 2 hr at 25°. The product was isolated by aqueous pentane work-up, the pentane was removed using a Vigreux column at atmospheric pressure, and the hydrocarbon was isolated by preparative glpc in 70% yield (10 ft × 0.25 in. 20% TCEP on Chromosorb P) as a colorless liquid with a characteristic unpleasant odor: nmr ($CDCl_3$) δ 5.35 (1 H, d × d × q, J = 11, 5, 1.5 Hz), 1.9–2.3 (4 H, m), 1.7 (3 H, d, J = 1.5 Hz), 0.5–1.9 (8 H, br m); ir (neat) 3.45, 3.52, 6.95, 11.45 μ; exact mass found and calculated, 124.125190. The olefin reacts with diphenylisobenzofuran (2 hr, refluxing $CHCl_3$) to form an adduct, mp 125.5–127°.

Registry No.—V, 38202-37-8; VI, 38213-74-0; XI, 34170-10-0; XII, 34215-20-8; XVI, 38202-39-0; XVII, 38202-40-3; XIX, 38229-25-3; XX, 38213-76-2; LDP, 15968-89-5; cyclooctene oxide, 286-62-4; methyl iodide, 74-88-4; *trans*-cyclooctene, 931-89-5; monoepoxide of 1,4-cyclooctadiene, 38202-42-5; *cis,trans*-1,4-cyclooctadiene, 34218-69-4; Diels–Alder adduct of 1,4-cyclooctadiene and 1,3-diphenylisobenzofuran, 38202-43-6; 1,5-cyclooctadiene monoepoxide, 637-90-1; *cis,trans*-1,5-cyclooctadiene, 5259-71-2; Diels–Alder adduct of 1,5-cyclooctadiene and 1,3-diphenylisobenzofuran, 38202-45-8; cycloheptene oxide, 286-45-3; 1-lithiocyclohep-

(21) E. A. Brande, W. F. Forbes, and E. A. Evans, *J. Chem. Soc.*, 2202 (1953).

tene, 38202-46-9; 1,2-dimethylcycloheptene oxide, 38202-47-0; 1-methylcyclooctene oxide, 16240-40-7; (2-hydroxy-2-methylcyclooctyl)methyldiphenylphosphonium iodide, 38202-49-2; *trans*-2-methylcyclooctene, 38229-26-4; adduct of diphenylisobenzofuran and *trans*-2-methylcyclooctene, 38215-60-0.

Preparation and Reactions of Nitrate Esters of *N*-Acylserine and -threonine Derivatives

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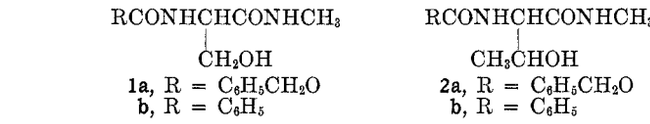
Nitrate esters of *N*-carbobenzoxyserinemethylamide, *N*-benzoylserinenmethylamide, *N*-carbobenzoxythreoninemethylamide, *N*-carbobenzoxyalanylserine methyl ester, *N*-benzoylallothreoninemethylamide, and *N*-carbobenzoxyglycylserylglycine ethyl ester were prepared from the corresponding amino acid derivatives and acetyl nitrate. Treatment of the first four compounds with ammonia causes an elimination of nitrate ion and formation of substituted acrylic acid and crotonic acid derivatives, respectively.

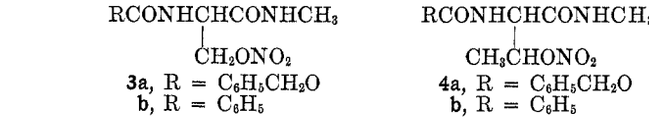
The reaction of acetyl nitrate with *N*-acylserine and -threonine derivatives has been studied to determine if the hydroxyl group present would cause the selective introduction of a nitro group on the amide nitrogen. Such a reaction would be important in the selective cleavage of peptides containing these amino acids. The resulting *N*-nitroamide bond would undergo cleavage with aqueous ammonia[2] more readily than the unmodified peptide bonds. The actual results obtained in the nitration were different from those expected and were considered important enough to report.

Treatment of *N*-acylserinemethylamide (**1**) and *N*-acylthreoninemethylamide (**2**) with fuming nitric acid



1a, R = $C_6H_5CH_2O$; **b**, R = C_6H_5 — **2a**, R = $C_6H_5CH_2O$; **b**, R = C_6H_5

and acetic anhydride in acetic acid gave exclusively the *O*-nitrate derivative (**3**, **4**) rather than the *N*-nitro derivatives. The use of fuming nitric acid and acetic anhydride alone gave lower yields of the nitrate ester. The behavior of a mixture of cupric nitrate and acetic anhydride[3] was not general and gave the *O*-nitro derivative with **1b** and the *O*-acetyl derivative with **1a**.

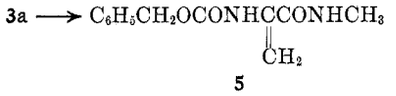


3a, R = $C_6H_5CH_2O$; **b**, R = C_6H_5 — **4a**, R = $C_6H_5CH_2O$; **b**, R = C_6H_5

Evidence for the location of the nitro group on the oxygen rather than on the nitrogens was based on nmr and infrared spectra. The nmr spectrum of **3a** showed broad absorptions for the two NH groups at δ 5.53 and 6.21. The former was a doublet and would correspond to the NHCH group. The infrared spectra for the nitrates showed frequencies for amide groups which were not markedly different from the *N*-acylamino acid derivatives. In contrast, the frequency for the carbonyl of the *N*-nitrobenzamide derivatives[3] was reported to be in the 5.85-μ region.

Nitration on nitrogen is apparently slow under the conditions employed, since *N*-carbobenzoxyalaninemethylamide was not affected.

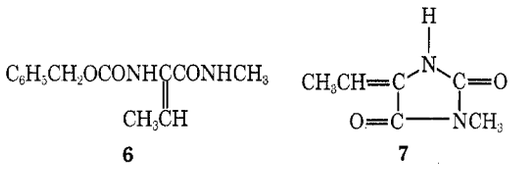
Treatment of **3a** with methanolic ammonia gave ammonium nitrate and α-*N*-carbobenzoxyaminoacrylmethylamide (**5**).



5

Proof for the structure of **5** was the spectra and chemical behavior. Treatment with dilute hydrochloric acid gave benzyl carbamate. The other hydrolysis product, *N*-methylpyruvamide, was difficult to isolate because of its high solubility in water. Catalytic hydrogenation gave alaninemethylamide. Oxidation with potassium dichromate gave *N*-carbobenzoxy-*N'*-methyloxamide, which on catalytic hydrogenation gave *N*-methyloxamide.

The reaction of alcoholic ammonia with **4a** gave ammonium nitrate, α-*N*-carbobenzoxyaminocrotonmethylamide (**6**), and 1-methyl-4-ethylidenehydantoin (**7**).



6 **7**

The structure of the hydantoin **7** was demonstrated by catalytic hydrogenation to 1-methyl-4-ethylhydantoin.

The hydantoin **7** is formed in this reaction by a base-catalyzed cyclization of the crotyl derivative **6**. The feasibility of such a reaction was demonstrated by cyclizing **6** with sodium hydroxide to **7**.

Changing the protecting group from carbobenzoxy to benzoyl did not change the course of the reaction with alcoholic ammonia but gave a more reactive species from **3b**; polymeric *N*-benzoylaminoacrylmethylamide was isolated. Substitution of sodium hydroxide in methanol for alcoholic ammonia in the reaction with **3b** gave *N*-benzoyl-*O*-methylserinemethylamide and benzamide.

The reaction of *N*-carbobenzoxyalanylserine methyl ester proceeded similarly and produced the *O*-nitrate,

(1) (a) Deceased. Inquiries should be addressed to S. Wawzonek. (b) Abstracted in part from the Ph.D. Thesis of F. E. B., Aug 1971.

(2) C. J. Peterson, Ph.D. Thesis, The University of Iowa, 1964.

(3) R. D. Campbell and C. J. Peterson, *J. Org. Chem.*, **28**, 2294 (1963).