Dehydration of Secondary Alcohols by Hexamethylphosphoric Triamide

RICHARD S. MONSON* AND DEGGARY N. PRIEST

Department of Chemistry, California State College, Hayward, California 94542

Received May 10, 1971

The dehydration of secondary alcohols in refluxing hexamethylphosphoric triamide (HMPT) without added catalysts proceeds in good yield (70–98%) to afford unrearranged olefins.[1] We now report stereochemical studies which partly elucidate the mechanism of the reaction.

The following compounds were prepared by standard synthetic procedures (see Experimental Section): *cis*- and *trans*-2-phenylcyclohexanol, 1-phenylcyclohexanol, *cis*- and *trans*-2-*tert*-butylcyclohexanol, *trans*-1(e)-decalol, and *trans*-1(a)-decalol. The products of the HMPT-catalyzed dehydration of these compounds, as well as those of some commercially available alcohols, are shown in Table I.

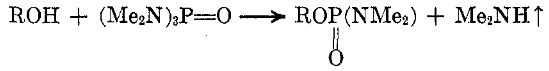
TABLE I

PRODUCTS OF THE HMPT-CATALYZED DEHYDRATION OF ALCOHOLS AT 215–230°

Alcohol	Reflux period, min	Relative amounts of volatile products: Products	%
trans-2-Phenylcyclohexanol	60	1-Phenylcyclohexene	54
		3-Phenylcyclohexene	46
cis-2-Phenylcyclohexanol[a]	65	1-Phenylcyclohexene	59
		3-Phenylcyclohexene	42
1-Phenylcyclohexanol	50	1-Phenylcyclohexene	100
trans-2-*tert*-Butylcyclohexanol	90	1-*tert*-Butylcyclohexene	56
		3-*tert*-Butylcyclohexene	44
cis-2-*tert*-Butylcyclohexanol	55	1-*tert*-Butylcyclohexene	95
		3-*tert*-Butylcyclohexene	5
trans-1(e)-Decalol	60	$\Delta^{1(9)}$-Octalin	61
		trans-Δ^1-Octalin	36
		Δ^9-Octalin	3
trans-1(a)-Decalol	55	$\Delta^{1(9)}$-Octalin	77
		trans-Δ^1-Octalin	14
		Δ^9-Octalin	9
2-Decalol (mixture of isomers)	*b*	Δ^1- and Δ^2-octalins (mixture of isomers) (98% yield)	100
1-Phenylethanol	*b*	Styrene (47% yield)	99
		1-Phenylethyldimethylamine	1

[a] Corrected for the presence of 28% trans isomer. [b] By distillation from the reaction mixture.

In all cases, olefin formation was accompanied by copious and rapid evolution of dimethylamine, and, in those cases in which the olefin was collected by distillation from the reaction mixture, the dimethylamine was observed to form prior to the distillation of the olefin. Moreover, the refluxing solvent, in the absence of a hydroxylic substrate, produces dimethylamine only very slowly and in small quantity. These observations, when considered in the light of the known chemistry of HMPT,[2,3] suggest prior formation of an alkyl tetramethylphosphorodiamidate (eq 1). Such compounds, which have been examined as flame retardants,[4] are heat sensitive, and distillation of ethyl tetraethylphosphorodiamidate at 150–160° may have given octaethylpyrophosphoramide.[5] The following discussion, then, will deal with the decomposition of this presumed intermediate under the reaction conditions.[6]



$$ROH + (Me_2N)_3P{=}O \longrightarrow RO\underset{\underset{O}{\|}}{P}(NMe_2) + Me_2NH\uparrow \qquad (1)$$

The three likely reaction pathways for the elimination are E1, E2, or Ei, requiring respectively the presence of carbonium ions, of trans elimination, or of cis elimination. The absence of carbonium ions in the reaction has definitely been established by the observation that 1- and 2-decalols undergo the elimination without the accompanying substantial rearrangement to Δ^9-octalin (see Table I). By contrast, phosphoric acid catalyzed dehydration of mixed 2-decalols gives mainly Δ^9-octalin,[7] and a similar dehydration of *trans*-1(a)-decalol in the present study gave 75% Δ^9-octalin, 20% $\Delta^{1(9)}$-octalin, and 4% *trans*-Δ^1-octalin.

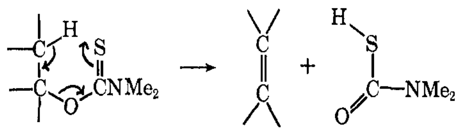
Rearrangement of the products, once formed, apparently does not occur. HMPT dehydration of *trans*-2-phenlcyclohexanol over a conversion range of 65 to 100% shows virtually the same product distribution (see Table II). In addition, 1-phenylcyclohexanol gives only 1-phenylcyclohexene under the reaction conditions.

TABLE II

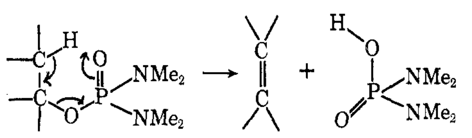
HMPT DEHYDRATION OF *trans*-2-PHENYLCYCLOHEXANOL

Reflux time, min	Conversion, %	Product distribution, %: 3-Phenylcyclohexene	1-Phenylcyclohexene
15	65.5	43	57
30	99	46	54
60	100	46	54
600	100	43	57

An Ei pathway has been proposed by Newman and Hetzel[8] for the pyrolysis of *O*-alkyl dimethylthiocarbamates (eq 2), and this reaction appears to be analogous to the decomposition of alkyl tetramethylphosphorodiamidates (eq 3). Cis elimination on *cis*-2-



(2)



(3)

---

[1] R. S. Monson, *Tetrahedron Lett.*, 567 (1971).

[2] H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).

[3] H. Normant, *Colloq. Int. Cent. Nat. Rech. Sci.*, No. 182, 207 (1970).

[4] Y. L. Gefter, "Organophosphorous Monomers and Polymers," Pergamon Press, New York, N. Y., 1962.

[5] B. Loev and J. T. Massengale, *J. Org. Chem.*, **22**, 1186 (1957).

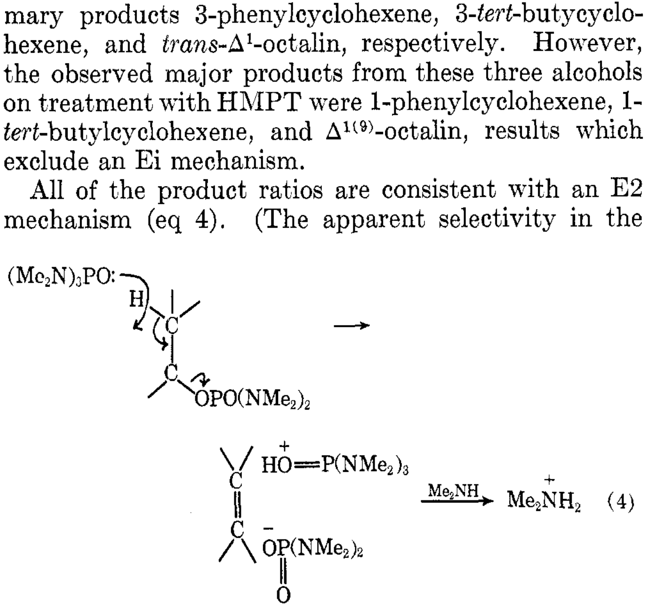
[6] Our original postulate (*cf.* ref 1) that the reactive intermediate was an alcohol–HMPT complex has been abandoned in the light of the experimental evidence presented herein.

[7] A. S. Hussey, J.-F. Sauvage, and R. H. Baker, *J. Org. Chem.*, **26**, 256 (1961).

[8] M. S. Newman and F. W. Hetzel, *ibid.*, **34**, 3604 (1969).

phenylcyclohexanol, *cis*-2-*tert*-butylcyclohexanol, and *trans*-1(a)-decalol would be expected to give as the primary products 3-phenylcyclohexene, 3-*tert*-butycyclohexene, and *trans*-Δ^1-octalin, respectively. However, the observed major products from these three alcohols on treatment with HMPT were 1-phenylcyclohexene, 1-*tert*-butylcyclohexene, and $\Delta^{1(9)}$-octalin, results which exclude an Ei mechanism.

All of the product ratios are consistent with an E2 mechanism (eq 4). (The apparent selectivity in the dehydration of *cis*-2-*tert*-butylcyclohexanol has been discussed in the literature and appears to be the result of special factors.[9]) An E2 pathway is also consistent with our earlier observation[10] that primary alkyl halides undergo HMPT-initiated dehydrohalogenation, a reaction which certainly proceeds by an E2 pathway. It thus appears reasonable that the solvent is capable of catalyzing E2 eliminations once a suitable leaving group has been formed.



The fate of the tetramethylphosphorodiamidate fragment has not been the subject of a thorough investigation. However, in those cases in which the molar excess of HMPT is not great (for example, a 3:1 ratio of HMPT to alcohol), a gummy, crystalline precipitate formed during the reaction. Spectral examination of the precipitate suggested the presence of pyrophosphate derivatives. After suitable purification, the mixture yielded bis(dimethylammonium) dihydrogen pyrophosphate, $(Me_2NH_2)_2H_2P_2O_7$. The formation of this substance can be explained by subsequent reactions of the phosphorus containing by-products of reaction 4. Moreover, the generation of the pyrophosphate linkage under related conditions[5] has been discussed above.

Experimental Section

Hexamethylphosphoric triamide and all other reagents not specifically described below were commercially available and were used without further purification. Melting points were determined on a Fisher–Johns apparatus and are uncorrected; boiling points are uncorrected. Gas chromatographic analyses were carried out on an Aerograph Model 600 HyFi with flame ionization detector, column FFAP on acid-washed Chromosorb, 80–100 mesh, 20 ft × 0.125 in. stainless steel with nitrogen as the carrier gas, flow rate 20 ml/min. The oven was operated at constant temperatures varying from 120 to 180 ± 2°. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Nmr spectra were taken on a Jeolco Model C-60 spectrometer with TMS as internal standard. Analyses were by Chemical Analytical Services, University of California, Berkeley, Calif.

Starting Materials.—The following compounds were prepared as described: *trans*-2-phenylcyclohexanol,[11] 1-phenylcyclohexanol,[12] *cis*-2-*tert*-butylcyclohexanol,[9] *trans*-2-*tert*-butylcyclohexanol,[9] *trans*-1(e)-decalol,[13] and *trans*-1(a)-decalol.[14,15] The fraction, bp 78–79° (0.05 mm), of a commerical mixture of *cis*- and *trans*-2-phenylcyclohexanol was taken up in pentane, cooled in a Dry Ice bath, and seeded with the pure trans isomer. After crystallization, the supernatant liquid was decanted. Two more repetitions of this procedure, followed by evaporation of the pentane, resulted in an oil which consisted of 72% cis isomer and 28% trans isomer by glpc analysis. The products obtained from HMPT dehydration of this mixture were corrected for the known product distribution obtained from the pure trans isomer.

Comparison Compounds.—Styrene and 1-phenylcyclohexene were the commercially available materials. 1-*tert*-Butylcyclohexene was prepared by dehydration of *cis*-2-*tert*-butylcyclohexanol in 85% phosphoric acid.[9] Δ^9-Octalin and $\Delta^{1(9)}$-octalin were prepared as a 4:1 mixture by the lithium–ethylenediamine reduction of tetralin.[16] The identities of other products were inferred from their relative retention times and infrared and nmr spectra.

Dehydrations in HMPT. A. Reflux Method.—The alcohol was dissolved in 5 to 30 times its weight of HMPT to give a convenient volume. The solution was refluxed (215–230°) for the indicated period. The evolution of dimethylamine could easily be followed by the formation of its deep blue amine complex with indicating Drierite. After cooling, the solution was taken up in pentane, washed three times with brine, dried, and subjected to glpc analysis.

B. Distillation Method.—The distillation technique of HMPT dehydration on a synthetic scale (0.1 mol of alcohol) has been described.[1]

Dehydration of *trans*-1(a)-Decalol in Phosphoric Acid.—The alcohol (0.1 g) was mixed with 4 ml of 85% phosphoric acid and heated at 130–155° for 100 min. The cooled reaction mixture was diluted with water and extracted with pentane. The pentane solution was washed once with 10% sodium carbonate solution, twice with brine, and dried. The resulting solution was subjected directly to glpc analysis.

Isolation of 1-Phenylethyldimethylamine.—The execution of HMPT dehydration on 0.1 mol of 1-phenylethanol resulted in a 47% yield of distilled styrene. The cooled reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed three times with brine and then extracted with 3 *N* hydrochloric acid. The aqueous acid extract was washed with ether and then made distinctly basic with 3 *N* sodium hydroxide solution. This aqueous mixture was now extracted with ether, the ethereal solution dried over potassium hydroxide pellets, and the ether vaporated affording the crude product in less than 1% yield. It was identified by conversion[17] to the picrate, which was recrystallized from methanol, mp 133–134° (lit.[18] mp 138–139°).

Isolation of Bis(dimethylammonium) Dihydrogen Pyrophosphate.—The reaction of 150 ml of HMPT with 0.3 mol of 1-phenylethanol gave, after a 60-min reflux period, a gummy, light yellow precipitate weighing 17.2 g. After decantation of the reaction mixture, the precipitate was transferred to a Soxhlet extractor and extracted overnight with isopropyl alcohol affording white crystals in the extraction flask. This material was further purified by dissolving in hot absolute ethanol and dilution with cold isopropyl alcohol. Repetition of this procedure gave 4.1 g of hygroscopic crystalline material, mp 178–180° dec. The presence of the pyrophosphate group was verified by treating an aqueous solution of the material with zinc acetate solution, which treatment afforded an immediate copious precipitate in-

---

(9) H. L. Goering, R. L. Reeves, and H. H. Espy, *J. Amer. Chem. Soc.*, **78**, 4926 (1956).

(10) R. S. Monson, *Chem. Commun.*, 113 (1971).

(11) C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Sinat, *J. Amer. Chem. Soc.*, **87**, 2421 (1965).

(12) L. F. Fieser and J. Szmuszkovicz, *ibid.*, **70**, 3352 (1948).

(13) R. S. Monson, D. Przybycien, and A. Baraze, *J. Org. Chem.*, **35**, 1700 (1970).

(14) W. Huckel, *et al.*, *Justus Liebigs Ann. Chem.*, **645**, 115 (1961).

(15) W. G. Dauben, R. C. Tweit, and C. Mannerskautz, *J. Amer. Chem. Soc.*, **76**, 4420 (1954).

(16) W. G. Dauben, E. C. Martin, and G. J. Fonken, *J. Org. Chem.*, **23**, 1205 (1958).

(17) R. L. Shriner, R. C. Fuson, and D. Y. Curten, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964.

(18) G. Wittig and D. Krauss, *Justus Liebigs Ann. Chem.*, **679**, 34 (1964).

dicative of the pyrophosphate group.[19] When the purified material was heated to its melting point, decomposition occurred, and dimethylamine could be detected by its characteristic odor: ir (film) 2.94 (NH), 7.83 (P=O), and 10.32 μ (POP).

Anal. Calcd for $C_4H_{18}N_2O_7P_2$: C, 18.0; H, 6.7; N, 10.5; P, 23.1. Found: C, 18.3; H, 6.5; N, 10.5; P, 23.4.

Registry No.—HMPT, 680-31-9; *trans*-2-phenylcyclohexanol, 2362-61-0; *trans*-1(a)-decalol, 31729-83-6; bis(dimethylammonium) dihydrogen pyrophosphate, 31729-84-7.

Ackowledgment.—The authors express their appreciation to the Research Foundation of California State College at Hayward for financial support.

[19] W. M. Latimer and J. H. Hildebrand, "Reference Book of Inorganic Chemistry," 3rd ed, Macmillan, New York, N. Y., 1951, p 232.

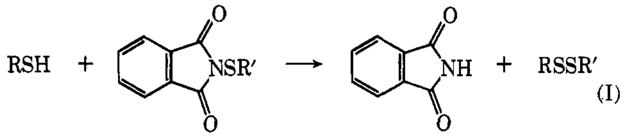
The Synthesis of Some New Cysteine-Containing Unsymmetrical Disulfides[1]

David N. Harpp* and Thomas G. Back

Department of Chemistry, McGill University,
Montreal, Canada

Received May 20, 1971

It was recently found[2] that a convenient route for the synthesis of dialkyl and aralkyl unsymmetrical disulfides is the thiolysis of the corresponding thiophthalimide as shown in eq I. Excellent yields, stable precursors, and minimal disulfide interchange are among the advantages offered by this method. Some of the disulfides prepared in this manner were the simple peptides, *S*-benzylthioglutathione and *S*-benzylthio-L-cysteine hydrochloride (R′ = benzyl in eq I).

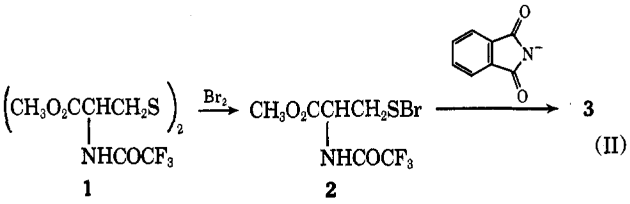


(I)

We now wish to report the synthesis of a cysteine-containing thiophthalimide, which has provided us with an excellent synthetic route *via* eq I to some new unsymmetrical disulfides, in two of which both R and R′ are cysteine or glutathione residues.

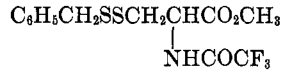
A 65% yield of *N*-trifluoroacetyl-*S*-phthalimido-L-cysteine methyl ester (**3**) (Table I) was obtained (eq II) by first brominating[3] disulfide[4] **1** at 0°, and then treating the resulting sulfenyl bromide **2** with the phthalimide anion.

Although **2** was used directly without isolation, evidence for its formation derives from nmr data. The methylene absorption of **2** in trifluoroacetic acid solution is shifted 0.3 ppm downfield relative to that of **1**. This appears reasonable, since the methylene absorption of the chlorine analog of **2** is found[5] 0.5 ppm downfield from that of **1**.



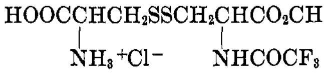
(II)

Thiolysis of **3** with benzyl mercaptan, cysteine hydrochloride monohydrate, and glutathione, according to eq I, gave excellent yields (92–99%) of the corresponding disulfides **4**, **5**, and **6**, respectively. Absence of the corresponding symmetrical disulfides in the products was established by tlc, except in the case of **6** where traces were found. The structures of compounds **3–6** were consistent with infrared, nmr, mass spectral, and elemental analyses. The mass spectrum of **3** shows an intense peak at *m/e* 148, likely due to formation of fragment a.



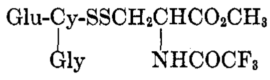
$$C_6H_5CH_2SSCH_2\underset{NHCOCF_3}{\underset{|}{C}}HCO_2CH_3$$

4



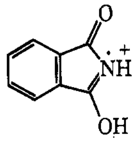
$$HOOC\underset{NH_3{}^+Cl^-}{\underset{|}{C}}HCH_2SSCH_2\underset{NHCOCF_3}{\underset{|}{C}}HCO_2CH_3$$

5



$$Glu\text{-}\underset{Gly}{\underset{|}{Cy}}\text{-}SSCH_2\underset{NHCOCF_3}{\underset{|}{C}}HCO_2CH_3$$

6



a

Major peaks reported[6] in the mass spectra of other thiophthalimides (at *m/e* 147, 130, 104, and 76) were also observed.

Disulfides **4–6** showed fragmentation similar to **1** as previously reported.[4] Cleavage of both the disulfide bond and the C–S bond on the side of the blocked cysteine residue was evident from intense peaks at *m/e* 230 and 198, respectively.

Attempts to selectively remove the trifluoroacetyl and methyl ester protective groups by mild alkaline hydrolysis of thiophthalimide **3** and disulfide **4** were unsuccessful, as both the S–N[7a] and S–S[7b] linkages proved too labile to withstand even the mild basic conditions[8] required to remove the trifluoroacetyl group. Treatment of **3** with 0.01 *N* NaOH at 5° for 0.5 hr gave 69% of phthalimide.[9] Reaction of **4** with 1 *N* NaOH under similar conditions gave 27% of benzyl disulfide.[9]

Thus it is clear that thiolysis of a cysteine thiophthalimide with an alkyl thiol, cysteine, or glutathione, provides a rapid, clean, and almost quantitative syn-

---

[1] Organic Sulfur Chemistry. XII. For part XI, see D. N. Harpp and D. K. Ash, *Int. J. Sulfur Chem.*, in press.

[2] (a) K. S. Boustany and A. B. Sullivan, *Tetrahedron Lett.*, 3547 (1970); (b) D. N. Harpp, D. K. Ash, T. G. Back, J. G. Gleason, B. A. Orwig, W. F. Van Horn, and J. P. Snyder, *ibid.*, 3551 (1970).

[3] The yield of sulfenyl bromide was considered to be quantitative; treatment of the corresponding sulfenyl chloride with the phthalimide anion resulted in the formation of significant amounts of phthalimide, thus indicating proton abstraction. No other identifiable products resulted.

[4] The yield of disulfide was 95%: D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **36**, 73 (1971).

[5] P. Mathiaparanam, Ph.D. Thesis, McGill University, 1971.

[6] B. A. Orwig, M.Sc. Thesis, McGill University, 1971.

[7] (a) J. E. Kerwood and M. Behforouz, *J. Org. Chem.*, **34**, 51 (1969); (b) A. Parker, and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

[8] It has been reported that the trifluoroacylamide bond is labile at pH greater than 10: E. Schallenberg and M. Calvin, *J. Amer. Chem. Soc.*, **77**, 2779 (1955).

[9] The remaining reaction mixture was not further investigated.