Oxidation of 2,6-di-*t*-butyl-4-*t*-butoxyphenol in the presence of oxygen gave the cream-colored, nicely crystalline peroxide IV, m.p. 115–116°, lit. 109–109.5°[7] and 115–116° dec.[11] A sample of peroxide IV (1×10^{-2} *M* benzene solution) was placed in the variable-temperature cavity of the dual-sample cavity and its signal was modulated at 400 c.p.s. In the other cavity, modulated at 100 kc.p.s., was placed a sample of the 2,6-di-*t*-butyl-4-*t*-butoxyphenoxy radical VII prepared by the same procedure as for V. The equivalence of the two spectra, shown in Fig. 6, leads us to conclude that peroxide IV also decomposes thermally by carbon–oxygen fission to give the 2,6-di-*t*-butyl-4-*t*-butoxyphenoxy radical VII; A_H (*meta* ring hydrogens) = 0.99 gauss, lit.[10] A_H (*meta* ring hydrogens) = 1.0 gauss.

In contrast, similar operation of the dual-sample cavity gave no correlation between the spectrum of the 2,4,6-tri-*t*-butylphenoxy radical and the spectrum resulting from thermal decomposition of peroxide II (1×10^{-2} *M* benzene solution at 100° (see Fig. 7).

The 2,4,6-tri-*t*-butylphenoxy radical VIII was prepared by the same procedure as for V and it gave, when modulated at 100 kc.p.s. in the multipurpose cavity, a 74-line spectrum with A_H (*meta* ring hydrogens) = 1.68 (1.77) gauss, A_H (*para t*-butyl hydrogens) = 0.36 (0.34) gauss, and A_H (*ortho t*-butyl hydrogens) = 0.07 (0.068) gauss. Splitting parameters found by Atherton, *et al.*,[12] are quoted in parenthesis.

A positive radical concentration from the decomposition of a sample of peroxide II prepared from freshly recrystallized II was detected only at temperatures in excess of 60°. Decomposition became rapid at temperatures in excess of 100° Samples prepared from II which were not recrystallized immediately prior to e.p.r. investigation, however, showed at room temperature an unsymmetrical, unidentified 25-line spectrum.

The symmetrical triplet resulting from the decomposition of peroxide II at 100° (see Fig. 7) was identified to arise from the production of the 2,6-di-*t*-butyl-4-*t*-butoxyphenoxy radical VII in agreement with Pokhodenko and Ganyuk.[3] Thus operation of the dual-sample cavity with peroxide II (1×10^{-2} *M* benzene solution, modulated at 400 c.p.s at 100°) gave a spectrum which corresponded with the spectrum of radical VII (approximately 1×10^{-4} *M* benzene solution modulated at 100 kc.p.s.). The traces obtained were almost identical with those produced by carbon–oxygen fission of peroxide IV to give radical VII, shown in Fig. 6. It is thus concluded that peroxide II decomposes thermally by homolytic oxygen–oxygen fission. Additional indirect evidence for oxygen–oxygen fission in peroxide II and carbon–oxygen fission in peroxide IV was obtained by examining previously decomposed samples of peroxides II and IV in the dual-sample cavity. Spectra identical with those shown in Fig. 6 were obtained.

The position of fission in peroxides I, II, III, and IV is suggested to depend chiefly upon how effectively the 1-substituent can stabilize by resonance the radicals that would result from carbon–oxygen fission. In peroxides I, III, and IV the 1-phenyl, 1-methoxy, and 1-*t*-butoxy groups can contribute to the resonance stabilization of the radicals V, VI, and VII, respectively. However, the 1-*t*-butyl group in peroxide II cannot resonance stabilize radical VIII. Thus, in peroxides I, III, and IV the stability of the product radicals V, VI, and VII would appear to lower the normally higher bond dissociation energy of the carbon–oxygen bond below that of the low dissociation energy of the oxygen–oxygen bond.[13] In peroxide II, this is not so, since by oxygen–oxygen fission, followed by or concerted with the cleavage and readdition of the 4-*t*-butyl group onto the exocyclic oxygen, the more stable radical VII can be formed.

Electron paramagnetic resonance identification of the radicals observed from the decompositions of peroxides I, II, III, and IV are consistent with carbon–oxygen fission in peroxides I, III, and IV and oxygen–oxygen fission in peroxide II. The position of fission in other symmetrical biscyclohexadien-4-one peroxides is currently being investigated with a view to correlating the position of fission with the resulting radical stability.

Experimental

The preparation of the phenols[2,4,7a] and peroxides[5,7] has been previously described. Spin resonance experiments were carried out with a Varian V-4502 e.p.r. spectrometer.

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(11) E. Muller, K. Ley, and W. Schmidhuber, *ibid.*, **89**, 1741 (1956).

(12) N. M. Atherton, E. J. Sand, and G. Porter, *Trans. Faraday Soc.*, **59**, 818 (1963).

(13) T. L. Cottrell, "The Strength of Chemical Bonds," Butterworth and Co. (Publishers) Ltd., London, 1958, pp. 275, 279.

The Preparation of N-Chloroformyl-N-phenylglycine and Its Use in Acylation

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In the direct phosgenation procedure for the preparation of N-carboxy-α-amino acid anhydrides or 2,5-oxazolidinediones,[1] an intermediate carbamyl chloride or N-chloroformyl derivative forms. In the preparation of 2,5-oxazolidinedione from glycine, Farthing[2] found that if the solvent were removed at 20° instead of 40°, N-chloroformylglycine resulted. This compound was identified by reaction with aniline to give N-phenylhydantoic acid. The phosgenation of N-*p*-anisylglycine resulted in the isolation of the N-chloroformyl derivative, which failed to cyclize to the anhydride at 40°.[6] In the reaction of L-proline with phosgene, N-chloroformyl-L-proline was formed and without isolation was cyclized by reaction with silver oxide in acetone[4] or

(1) (a) E. Katchalski and M. Sela, *Advan. Protein Chem.*, **13**, 243 (1958); (b) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2 John Wiley and Sons, Inc., New York, N. Y., 1961, p. 860 ff.

(2) A. C. Farthing, *J. Chem. Soc.*, 3213 (1950).

(3) E. Dyer, F. L. McCarthy, R. L. Johnson, and E. V. Nagle, *J. Org. Chem.*, **22**, 78 (1957).

(4) J. Kurtz, G. D. Fasman, A. Berger, and E. Katchalski, *J. Am. Chem. Soc.*, **80**, 393 (1958).

triethylamine in dioxane.[5] N-Chloroformyl-O-acetylhydroxy-L-proline and N-chloroformyl-O-*p*-toluenesulfonylhydroxy-L-proline were similarly cyclized with silver oxide.[4]

In Fuchs' original application of the direct phosgenation procedure,[6] N-phenylglycine formed the anhydride on treatment with phosgene in alkaline solution. We have found that, in dioxane, N-phenylglycine behaves as N-*p*-anisylglycine does, and good yields of N-chloroformyl-N-phenylglycine can be isolated. The N-chloroformyl structure is verified by cyclization to the anhydride (3-phenyl-2,5-oxazolidinedione) in dioxane containing triethylamine, in aqueous dioxane, or by heating.

In trying various acylating agents for preparing new penicillins, we have found that N-chloroformyl-N-phenylglycine and sodium 6-aminopenicillinate in an inert solvent form the penicillin, 6-(2-anilinoacetamido)-penicillanic acid.[7] In an aqueous system, essentially quantitative yields of the penicillin are obtained from the N-chloroformyl derivative as well as from the anhydride.[8]

Experimental

All melting points are corrected. Analyses and microbiological assays were by members of the Microanalytical and Bacteriology Departments of this laboratory, respectively. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer.

N-Chloroformyl-N-phenylglycine.—N-Phenylglycine (25.4 g.) was suspended in 600 ml. of dioxane (Fisher Scientific Co., D-111, certified grade) in a 2-l., three-necked flask fitted with a gas-inlet tube, thermometer, solid carbon dioxide condenser with drying tube, and magnetic stirrer. Phosgene was introduced *via* a safety flask at a rate which maintained the temperature at 40°. At the end of 2.5 hr., when complete solution had occurred, the solid carbon dioxide condenser was replaced with an air condenser, and dry nitrogen was passed through overnight. The dioxane solution was concentrated to an oil on a rotary evaporator. The oil was taken up in ethyl acetate and concentrated until crystallization occurred. The crystals were filtered off and washed with ethyl acetate, affording a first crop of 15.5 g. (43%), m.p. 124–125°. Further crops were obtained for a total yield of 68%. Material twice crystalized from ethyl acetate had a m.p. of 138–140°.

Anal. Calcd. for $C_9H_8ClNO_3$: C, 50.60; H, 3.77; Cl, 16.60; N, 6.56. Found: C, 50.65; H, 3.84; Cl, 16.4; N, 6.56.

Spectrum: λ_{max}^{KBr} broad carbonyl peak at 5.80 μ, unchanged after 7 weeks' storage over silica gel at room temperature.

In attempts to isolate more product from the original mother liquor, increasing amounts of the anhydride began to appear in successive crops.

Cyclization of N-Chloroformyl-N-phenylglycine. A. With Triethylamine.—N-Chloroformyl-N-phenylglycine (2.14 g., 0.01 mole) was dissolved in 10 ml. of dioxane. Triethylamine (1.39 ml., 0.01 mole) was added, and the solution was shaken for 30 min. The heavy precipitate of triethylamine hydrochloride (94% yield) that formed was filtered off and washed with dioxane. The filtrate and washings were concentrated *in vacuo*, and the oil was crystallized from ethyl acetate. The yield of 3-phenyl-2,5-oxasolidinedione was 1.30 g. (73%), m.p. 137–140° (lit.[9,10] m.p. 139° and 142°, respectively).

Anal. Calcd. for $C_9H_7NO_3$: C, 61.01; H, 3.96; N, 7.90. Found: C, 61.18; H, 3.95; N, 8.23.

TABLE I

CONCENTRATIONS OF POTASSIUM 6-(2-ANILINOACETAMIDO)PENICILLINATE INHIBITING GROWTH OF VARIOUS MICROORGANISMS ON AGAR

Organism	Strain no.	Concn., γ/ml.
Bacillus subtilis	ATCC 6633	0.061
	NRRL B-972	125
Lactobacillus casei	ATCC 7469	3.90
Staphylococcus aureus	ATCC 6538P	0.061
	53-180	250
	Wyeth CHP	31.3
Streptococcus faecalis	ATCC 8043	3.90
Pseudomonas aeruginosa	ATCC 10145	>250
Escherichia coli	ATCC 6880	125
	ATCC 11370	15.6
Brucella bronchiseptica	ATCC 4617	125
Salmonella paratyphi	ATCC 11737	62.5
Neisseria catarrhalis	ATCC 8193	3.90
Mycobacterium smegmatis	ATCC 10143	>250

Spectrum: λ_{max}^{KBr} characteristic absorption for anhydride group at 5.45 and 5.68 μ for carbon–oxygen stretching.

B. With Water.—N-Chloroformyl-N-phenylglycine (2.14 g.) in 50 ml. of dioxane was added to 150 ml. of water at 5° and stirred. A fine, white precipitate formed immediately. After 5 min., the mixture was extracted with 500 ml. of ethyl acetate. The extract was concentrated *in vacuo* to yield 3-phenyl-2,5-oxazolidinedione (0.65 g., 37%), m.p. 137–139°.

Anal. Calcd. for $C_9H_7NO_3$: C, 61.01; H, 3.96; N, 7.90. Found: C, 60.73; H, 3.80; N, 8.09; Cl, 0.4.

Infrared spectrum was the same as that given in A.

Further crops of the anhydride contained increasing amounts of the chloroformyl compound. Prolongation of the reaction time should improve the yield.

C. With Heat.—A small amount of N-chloroformyl-N-phenylglycine was heated at 100° in an Abderhalden dryer at atmospheric pressure for 4.5 hr. The weight of the product recovered was 96% of that expected from a conversion to 3-phenyl-2,5-oxazolidinedione, m.p. 135–137°. An infrared spectrum of this material further confirmed the identification.

Cyclization takes place during the melting point determination, since melting points of about 140° for the N-chloroformyl derivative and the anhydride must result from the cyclization of the former to the latter during the heating process in the melting point bath.

Potassium 6-(2-Anilinoacetamido)penicillinate. A.—N-Chloroformyl-N-phenylglycine (2.14 g., 0.01 mole) in 50 ml. of dioxane was added to a stirred solution prepared by adding 6-aminopenicillanic acid (1.08 g., 0.005 mole) to 100 ml. of water, adjusting pH to 6.0 with dilute sodium hydroxide, diluting to 150 ml., and cooling to 5°. After 20 min. at this temperature, the pH was adjusted to 7.0, and the solution was bioassayed and freeze dried to give 3.67 g. of product (384 γ of ampicillin equivalent/mg.).[11]

The crude product was purified by dissolving 2.00 g. in 6 ml. of water containing 1 g. of ammonium sulfate, adjusting the pH to 2.5–3.0 with 8% phosphoric acid, extracting the free acid with two 20-ml. portions of amyl acetate, and adding 3.2 ml. of 2 *M* potassium acetate in 90% isopropyl alcohol. Storage at −10° precipitated the purified potassium salt, which was collected, washed with 90% isopropyl alcohol, and dried *in vacuo*. The yield was 0.25 g. (825 γ of ampicillin equivalent/mg.).

Anal. Calcd. for $C_{16}H_{18}KN_3OS$: C, 49.63; H, 4.68; K, 10.10; N, 10.85; S, 8.28. Found: C, 49.16; H, 4.71; K, 9.84; N, 10.09; S, 8.5.

Spectrum: λ_{max}^{KBr} 3.01 (N–H), 5.62 (β-lactam C=O), 5.97 (amide C=O), 6.25 and 7.18 μ (—CO_2^-).

By calculation from the bioassay of the reaction mixture and the activity of the pure potassium salt, the penicillin yield was 97%. Substantiation was by paper chromatographic data. Bioautography of the reaction mixture chromatographed in the system butyl alcohol–*sec*-butyl alcohol–acetone–water (12:12:10:9, v./v.) by descending chromatography with Whatman No. 1

(5) A. A. Randall, *J. Chem. Soc.*, 374 (1962).

(6) F. Fuchs, *Ber.*, **55**, 2943 (1922).

(7) F. P. Doyle, J. H. C. Nayler, and H. Smith (to Beecham Research Laboratories Ltd.), British Patent 894,457 (April 18, 1962).

(8) N. H. Grant and H. E. Alburn, *J. Am. Chem. Soc.*, in press.

(9) W. Baird, E. G. Parry, and S. Robinson (Imperial Chemical Industries Ltd.), British Patent 646,033 (Nov. 15, 1960).

(10) (a) F. Wessely, *Z. Physiol. Chem.*, **146**, 72 (1925); (b) H. Leuchs and W. Manasse, *Ber.*, **40**, 3235 (1907).

(11) By disk bioassay against *Staphylococcus aureus* ATCC 6538P in terms of an ampicillin [6-(D-2-amino-2-phenylacetamido)penicillanic acid] standard.

paper impregnated with 0.1 *M* pH 6 potassium phosphate buffer showed only one round zone of activity against both *Staphylococcus aureus* and *Escherichia coli* plates at R_f 0.65–0.68.

The pure salt in tube serial dilution inhibited *Bacillus subtilis* ATCC 6633 and *Staphylococcus aureus* ATCC 6538P at 0.122 γ/ml. When it was tested against various microorganisms by agar serial dilution, the results shown in Table I were obtained.

B.—The penicillin could also be made in 38% yield by shaking equivalent amounts of N-chloroformyl-N-phenylglycine and sodium 6-aminopenicillinate in ethyl acetate for 5 min.

C.—3-Phenyl-2,5-oxazolidinedione (3.54 g., 0.02 mole) in 100 ml. of dioxane was added to a stirred solution of sodium 6-aminopenicillinate (2.38 g., 0.01 mole) in 300 ml. of water at 5°. After 2 hr. at 5° the reaction was stopped, and the crude penicillin was isolated as in A. The yield was 97%, R_f 0.68.

The Adduct of Triphenylphosphine and Maleic Anhydride

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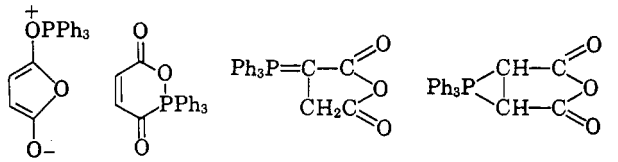
The reports of Chopard and Hudson[1] prompt us to report work which confirms their results. The reaction of triphenylphosphine with maleic anhydride in an inert solvent gave an adduct which, on recrystallization from benzene, agreed in melting point and analysis with earlier results.[2] Since the infrared spectrum did not conform to that expected for the proposed[2] structure I, other possibilities were considered (II–IV). Aksnes has proposed[3] III to be the correct formulation based on infrared evidence alone.



I II III IV

The adduct showed the following properties. Titration of a dioxane solution with aqueous base indicated a monobasic acid.[4] Decomposition at the melting point resulted in formation of triphenylphosphine. The P^{31} n.m.r. spectrum showed a peak at −13 p.p.m. relative to phosphoric acid. Compounds containing five groups attached to a phosphorus atom have been reported[5] to show a large positive shift. The proton magnetic resonance showed two nonvinylic protons[6] and 15 aromatic hydrogen atoms.

(1) (a) R. F. Hudson and P. A. Chopard, *Helv. Chim. Acta*, **46**, 2178 (1963); (b) P. A. Chopard and R. F. Hudson, *Z. Naturforsch.*, **18b**, 509 (1963).

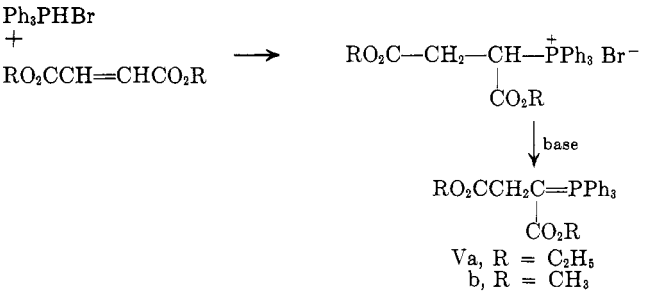
(2) A. Schonberg and A. F. A. Ismail, *J. Chem. Soc.*, 1374 (1940).

(3) G. Aksnes, *Acta Chem. Scand.*, **15**, 692 (1961).

(4) On the basis of III, this can be rationalized by assuming that the half-acid sodium salt ($Ph_3P{=}C(CO_2^-)-CH_2-CO_2H\ Na^+$ or $Ph_3P{=}C(CO_2H)-CH_2-CO_2^-\ Na^+$) can tautomerize to a stable zwitterion ($Ph_3P^+-CH(CO_2^-)-CH_2-CO_2^-\ Na^+$) which may exist as either an open chain as shown or as a cyclic lactone-type structure containing phosphorus in the ring.

(5) R. A. Y. Jones and A. R. Katritzky, *Angew. Chem., Intern. Ed.*, **1**, 32 (1962).

(6) The nonaromatic protons appear as a single peak. Closer investigation disclosed that a 0.8-c.p.s. coupling was present. This is in essential agreement with the report of Hudson and Chopard.[1a]



Since III was the only tenable structure remaining, the adduct was related to a known substance by the following route. The reaction of triphenylphosphine hydrobromide with diethyl fumarate followed by treatment with base has been reported[7] to give Va. When dimethyl fumarate was used, Vb was obtained in 69% yield. Treatment of the adduct III with methanol[8] followed by diazomethane also gave Vb in 82.5% yield. Furthermore, Vb has been previously prepared by an alternate route.[9,10]

We have also found that chloromaleic anhydride reacts with triphenylphosphine to give an adduct having the same characteristic infrared spectrum as the maleic anhydride adduct. Citraconic anhydride did not react in this fashion but gave, instead, an unidentified, red solid which contained only one carbonyl band in the infrared spectrum.

Experimental

Triphenylphosphine–Maleic Anhydride Adduct.—Equimolar amounts of triphenylphosphine and maleic anhydride solutions in benzene were mixed with stirring. The precipitated product was washed and dried to give a crude, orange, amorphous-looking powder in 92.8% yield. An analytical sample was obtained from benzene, m.p. 162.5–163.5° dec., lit.[2] m.p. 160° dec.

Anal. Calcd. for $C_{22}H_{17}O_3P$: C, 73.33; H, 4.75; P, 8.60; equiv. wt., 360 (monobasic), 180 (dibasic). Found: C, 73.58; H, 4.78; P, 8.39; equiv. wt., 366.

The infrared spectrum (mull in mineral oil) showed two strong carbonyl bands at 1682 and 1787 cm.$^{-1}$. In KBr these bands are reported[3] to appear at 1702 and 1805 cm.$^{-1}$.

Triphenylphosphinecarbomethoxymethylcarbomethoxymethylene (Vb).—Methanol (2 ml.) was added to 208 mg. of adduct III and the solution refluxed 15 min. After cooling, an ether solution of diazomethane was added until no further signs of reaction occurred and the mixture had a definite yellow color. The solvent was then removed under reduced pressure, and the resulting oil was triturated in ether to form a tan solid. One recrystallization from chloroform-*n*-hexane gave 193 mg. of product, m.p. 156–158° (lit.[9] m.p. 157–158°) alone and 163–165° when mixed with an authentic sample prepared as follows. To 721 mg. of dimethyl fumarate in 10 ml. of acetonitrile was added 1.716 g. of triphenylphosphine hydrobromide (prepared by bubbling HBr into an ether solution of triphenylphosphine), and the mixture refluxed 30 min. The mixture was diluted with water and extracted with ether; the aqueous layer was neutral-

(7) H. Hoffmann, *Chem. Ber.*, **94**, 1331 (1961).

(8) The resulting half-ester was not purified, but the crude material had the reported[1a] infrared spectrum. The proton n.m.r. spectrum of this crude material did not show the expected CH–CH_2 splitting required for the structure proposed by Hudson and Chopard.[1] Instead, a doublet (J = 15 c.p.s.) arising from the CH_2 group and split by PH coupling was observed at 2.86 p.p.m. (TMS = 0). The methyl group appeared at 3.3 p.p.m. as a sharp singlet. The H atom presumed to be on oxygen did not give a discernible peak.

(9) H. J. Bestmann and H. Schulz, *Chem. Ber.*, **95**, 2921 (1962).

(10) The proton n.m.r. spectrum of Vb showed a doublet (J = 17 c.p.s.) at 2.93 (2H), a sharp peak at 3.43 (3H), a broad band at 3.28 p.p.m. (3H), and the expected aromatic band (15H). We have no explanation for the anomalous behavior of one of the methyl groups of this diester nor for the absence of PH splitting in the anhydride III despite the apparent presence of such splitting in the mono- and diester. That the observed splitting in Vb (J = 17 c.p.s.) is due to PH coupling and not nonequivalent H's was confirmed by the fact that at 100 Mc. the coupling was unchanged (J = 17.3 c.p.s.).