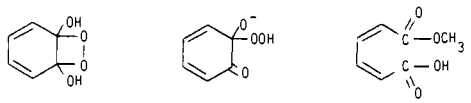
Acyclic Mechanism in the Cleavage of Benzils with Alkaline Hydrogen Peroxide

Yasuhiko Sawaki and Christopher S. Foote*

Contribution from the Department of Chemistry, University of California, Los Angeles, California 90024. *Received May 7, 1979*

Abstract: The reaction of benzil with alkaline hydrogen peroxide in aqueous methanol gives benzoic acid and methyl benzoate; the yield of ester increases to 69% when H_2O_2 is added gradually. The reaction in the presence of dimethyl sulfoxide gives the maximum yield (81%), close to that (87%) from the reaction of benzoic anhydride under the same conditions but in the absence of H_2O_2. These results rule out a dioxetane mechanism as the main pathway for the reaction of benzil but suggest that an anhydride is intermediate. ^{18}O-Labeled hydrogen peroxide could be conveniently prepared by the *t*-BuOK-catalyzed autoxidation of benzhydrol in the presence of $^{18}O_2$. The reaction of *p*-methoxy- and 2,4,6-trimethylbenzil with $H_2{}^{18}O_2$ showed that one oxygen atom is incorporated in the carboxylic acid product but none in the ester. These results clearly eliminate a proposed epoxide mechanism but support a Baeyer–Villiger-type acyclic mechanism involving the migration of an acyl group with formation of an intermediate anhydride. Some of the anhydride appears to react with H_2O_2 to form peroxy acid, which in turn oxidizes more benzil in a path which does not lead to ester. This reaction is blocked by the reduction of peracid by Me_2SO, which accounts for the high ester yields when Me_2SO is present.

Many biological C–C bond cleavages proceed by way of dioxygenase enzymes.[1] Mechanisms involving dioxetanes (e.g., **1**) are often written for these dioxygenase reactions, although they have been criticized on the basis that too much energy is required for dioxetane formation compared with a mechanism

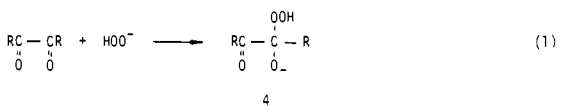


1 **2** **3**

involving an acyclic peroxide (e.g., **2**) which opens by a mechanism not involving **1**.[2]

A model reaction for pyrocatechase using copper complexes in methanol was reported to incorporate molecular oxygen, and the product, methyl muconate (**3**), was explained as resulting from attack of methoxide at the carbonyl of **2**.[3] However, the reaction has recently been shown to involve oxidative C–C fission by Cu^{II} alone, without the direct intervention of molecular oxygen.[4]

The facile cleavage of 1,2-diketones with peroxy acids or alkaline hydrogen peroxide is well known.[5] The few mechanistic studies[6-8] which have been carried out seem not to be conclusive. For the case of alkaline H_2O_2 oxidation, there appears to be no convincing evidence to differentiate among three mechanisms which have been suggested, all of which begin with addition of HO_2^- to a carbonyl to give intermediate **4** (reaction 1).

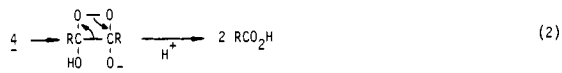


(1)

4

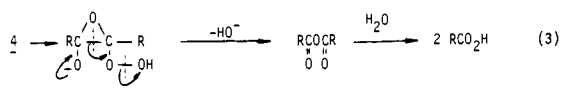
These three mechanisms are pictured below:

1. Dioxetane mechanism:



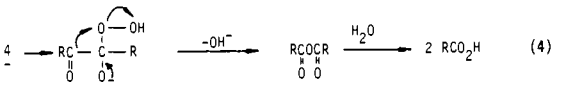
(2)

2. Epoxide mechanism:



(3)

3. Acyclic (Baeyer–Villiger) mechanism:



(4)

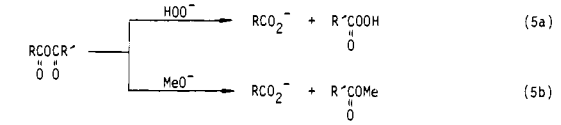
We were interested in this reaction because of its relationship to enzymatic C–C scission and to the oxidation of phenols or carbonyl compounds with O_2 or O_2^-.[1,9] We summarize here product and ^{18}O studies of this reaction which clearly rule out the first two mechanisms and are consistent with the third.

Results and Discussions

Formation of Esters. The reaction of benzil with alkaline H_2O_2 is fast, being complete within a few minutes. Products in aqueous MeOH are mixtures of benzoic acid and its methyl ester[10] (Table IA).

The amount of ester depends on the mixing procedure. The relatively low yield (13%) of methyl benzoate which results when all reagents are mixed at the start is dramatically increased to 69% by adding H_2O_2 dropwise. The maximum yield of ester is obtained when the reaction is carried out in the presence of dimethyl sulfoxide (run 4). The reaction of benzil and H_2O_2 under neutral conditions occurs slowly to afford a significant yield of ester (run 6).

Since acid anhydrides are sometimes isolated from the reaction of 1,2-diketones with peroxy acid in aprotic solvent,[5] the yield of ester from benzoic anhydride was also determined under conditions similar to that of the cleavage reaction. The yield of ester increases dramatically in the absence of HOO^- (runs 7 and 9) in analogy to the reaction of benzil. These variations in yield suggest that MeOH (or MeO^-) competes with H_2O_2 (or HOO^-) for the reaction of an intermediate anhydride:



(5a)

(5b)

Formation of methyl benzoate from 2,4,6-trimethyl- and 4-methoxybenzil is also observed; the mesitoate and *p*-anisoate esters are formed in zero and trace yields, respectively (Table IC). The relatively low yield of methyl benzoate for the *p*-MeO case probably reflects the slower reaction of the diketone with HOO^-, resulting in a higher concentration of HOO^- in the reaction system when H_2O_2 is added dropwise, and thus a larger proportion of path **5a**.

^{18}O-Tracer Study. Labeled hydrogen peroxide ($H_2{}^{18}O_2$) has been prepared by the reaction of $^{18}O_2$ and Na,[12] by an electric

0002-7863/79/1501-6292$01.00/0

Table I. Alkaline H_2O_2 Oxidation of Benzils

run no.	reagents, mmol: substrate	H_2O_2	NaOH	conditions[a]	reagent added	products, %[b]: $PhCO_2Me$	other
				A. Reaction of Benzil			
1	5	5	10		NaOH[c]	13	
2	5	5	10		H_2O_2[c]	69	
3	5	5	10	100% MeOH	H_2O_2[c]	77	
4	5	5	10	2 mL of Me_2SO	H_2O_2[c]	81	Me_2SO_2 (11%)[d]
5	5	10	12	60% acetone	NaOH[c]	0	$PhCO_2H$ (96%)[e]
6	2.5	10	none	98% MeOH, 5 days	*f*	28	
				B. Reaction of Benzoic Anhydride			
7	5	5	10		*f*	18	
8	5	5	none	2 mL of pyridine	*f*	39	
9	5	none	10		*f*	87	
				C. Reaction of Substituted Benzils			
10	1.0	1.2	2.0	90% MeOH	H_2O_2[c]	69	
11	1.0[g]	1.2	2.0	90% MeOH	H_2O_2[c]	60	no $MesCO_2Me$ detected
12	1.0[h]	1.2	2.0	90% MeOH	H_2O_2[c]	25	*p*-$MeOPhCO_2Me$ (trace)

[a] Ten minutes total reaction (5 min for dropping and 5 min stirring) in 75% MeOH (v/v) of total 40-mL volume at ca. 23 °C unless otherwise noted. Conversion of substrates was 100% except for run 4. [b] Products were determined by GLC for most runs. Benzoic acid was usually not determined. [c] Final dropwise addition of ~1 M H_2O_2 for 2 M NaOH for 5 min to solution of other reagents. [d] Conversion of benzil was 62%; yields based on consumed benzil. [e] Isolated yield. [f] All reagents were mixed at once. [g] 2,4,6-Trimethylbenzil. Mesitoic acid was isolated in 72% yield. [h] *p*-Methoxybenzil. In this case the reaction was slower, and reaction time was 20 min. *p*-Anisic acid was isolated in 65% yield.

discharge from $H_2{}^{18}O$,[13] and by the hydrolysis of labeled perbenzoic acid.[14] The former two reactions require specialized equipment and long reaction times, whereas the last method requires preparation of the labeled peroxy acid by autoxidation of benzaldehyde. The base-catalyzed autoxidation of benzhydrol[15] provides a convenient synthesis of $H_2{}^{18}O_2$ on a small scale.

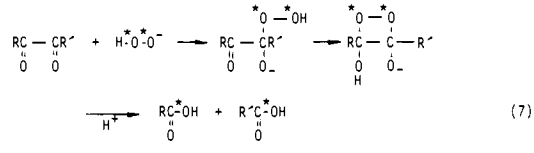
$$Ph_2CHOH + {}^{18}O_2 \xrightarrow[\text{benzene}]{\text{t-BuOK}} Ph_2C{=}O + H_2{}^{18}O_2 \qquad (6)$$

This reaction is complete within 40 min; extraction with water and neutralization affords $H_2{}^{18}O_2$ very conveniently and efficiently (>90% yield based on $^{18}O_2$). Mass spectral analysis indicates the doubly labeled $H_2{}^{18}O_2$ has the same isotopic content as the starting $^{18}O_2$. A very similar preparation of $K^{18}O_2$ was recently reported.[16]

The reaction of substituted benzils was conducted by using $H_2{}^{18}O_2$ (M + 2 = 16.4%, M + 4 = 8.4% excess). The results listed in Table II indicate that somewhat less than one atom of oxygen is incorporated into the acids from H_2O_2, but none in the esters. A control experiment with methyl *p*-anisoate showed 7.6% loss of ^{18}O under the same conditions, so that the absence of label in the ester is not due to exchange.

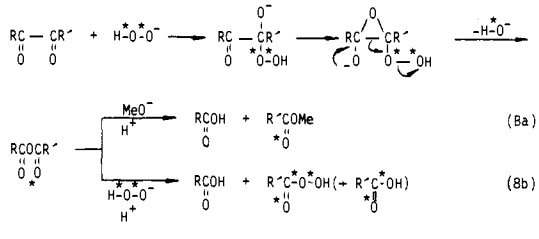
Mechanism. The three schemes for the reaction of α-diketone and alkaline $H_2{}^{18}O_2$ have the labeling consequences shown below:

(a) Dioxetane mechanism:



(7)

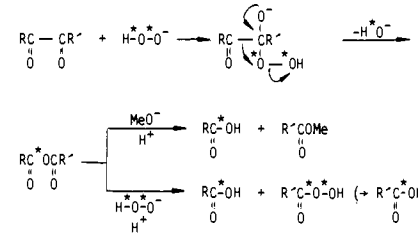
(b) Epoxide mechanism:[6]



(8a)

(8b)

(c) Acyclic (Baeyer–Villiger) mechanism:



(9a)

(9b)

In these schemes, R′ is the more electron-attracting group; the nucleophilic attack is assumed to occur preferentially on the R′ carbonyl. This assumption is confirmed by the finding that almost all the ester derives from this carbonyl in the unsymmetrical cases. The calculated ^{18}O % values in Table II were obtained according to these schemes. The calculated ^{18}O excess % for the incorporation of one oxygen is:

$$\left(\frac{M+2}{M}\right) \times 100 = \frac{\frac{16.4}{2} + 8.4}{100 + \frac{16.4}{2}} = 15.3\%$$

This is the expected incorporation in the labeled product for eq 7, 8a, 9a, and 9b. The case where a second ^{18}O is incorporated (as in $R'CO_2H$ in eq 8b) is somewhat more complicated. Since the mole fractions of M and M + 2 after the incorporation of one ^{18}O are 0.867 and 0.132, respectively, the calculation for

$$R'C(=\overset{*}{O})OH$$

is (M + 2)/M = 100 × 0.132 + 15.3 × 0.867 = 26.5.

Discussion

The dioxetane mechanism would seem to be attractive at a glance since the cyclic mechanism is actually operative, although as a minor reaction, in the decomposition of α-hydroperoxy ketones[17] and esters.[18] Although the incorporation of one oxygen from H_2O_2 in the acid (Table II) is consistent with the dioxetane mechanism, this mechanism cannot account for the high yield of ester under the alkaline conditions. Thus, the dioxetane mechanism cannot be a major pathway if it occurs at all under these conditions.

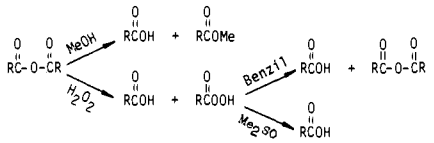
The observed high yield of methyl ester clearly suggests

Table II. ^{18}O-Tracer Study Using $H_2{}^{18}O_2$ (M + 2 = 16.4%, M + 4 = 8.4% excess)[a]

substrate	products (% yield)	obsd ^{18}O, excess %	calcd ^{18}O, excess % for mechanism: dioxetane	epoxide	acyclic
p-MeOPhCCPh ‖‖ OO	p-$MeOPhCO_2H$ (99%)	13.1 ± 0.6	15.3	0.0	15.3
	p-$MeOPhCO_2Me$ (trace)	0.08		15.3	0.0
	$PhCO_2H$ (75%)	12.3 ± 1.0	15.3	30.8	15.3
	$PhCO_2Me$ (25%)	nd		15.3	0.0
MesCCPh ‖‖ OO	$MesCO_2H$ (100%)	12.1 ± 0.9	15.3	0.0	15.3
	$PhCO_2H$ (40%)	12.3 ± 1.2	15.3	30.8	15.3
	$PhCO_2Me$ (60%)	0.12 ± 0.06		15.3	0.0
p-$MeOPhCO_2Me$[b]	p-$MeOPhCO_2Me$ (95%)	12.1 ± 0.6			

[a] The labeled $H_2{}^{18}O_2$ (1.25 mmol) was dropped into the stirred solution of diketone (1.25 mmol) and NaOH (2.5 mmol) in 75% aqueous MeOH at 23 °C. The ^{18}O % was determined four to seven times in each case. For the calculated value, see text. Mes, 2,4,6-trimethylphenyl. [b] Control experiment with the same initial concentration of unlabeled H_2O_2. The starting ester contained 13.1% excess of ^{18}O.

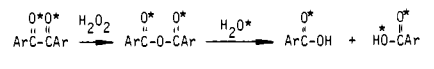
intervention of an anhydride. The second and third mechanisms involve acid anhydride and are consistent with the fact that anhydride is formed from 1,2-diketone and peroxy acid in aprotic solvent.[5] The effect of Me_2SO (run 4) suggests the formation of peroxy acid from anhydride and HOO^-. The peroxy acid would be reduced by Me_2SO[19] resulting in lower net conversion (62%) of benzil but a high yield of methyl benzoate as shown below.



The study using $H_2{}^{18}O_2$ easily discriminates between the epoxide[6] and acyclic mechanisms. According to the epoxide mechanism, label should be incorporated into ester and not into acid (RCO_2H), and benzoic acid should contain two ^{18}O atoms. The results in Table II show that this is not the case, and the epoxide mechanism can be clearly ruled out.

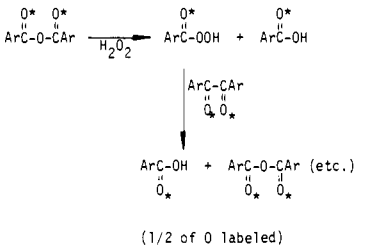
On the other hand, both the product and ^{18}O-tracer studies are completely consistent with the Baeyer–Villiger-type acyclic mechanism as suggested by Leffler.[20] This mechanism was discounted because of the very low migratory aptitude of the acyl group in carbon-to-carbon migrations.[7] However, a facile shift of acyl groups to peroxide oxygen has recently been established in the acid-catalyzed decomposition of α-hydroperoxy ketones.[21] The acyl shift to the peroxidic oxygen affords the ether-labeled anhydride, which should yield unlabeled methyl ester from the more reactive C=O, and labeled carboxylic acid from the less reactive side. The alternative attack of $H^{18}O^{18}O^-$ on the anhydride gives singly labeled carboxylic acid from both sides (see eq 9b).

An earlier study of this reaction has been carried out by using benzil which had been allowed to equilibrate its oxygens with solvent $H_2{}^{18}O$; when $H_2{}^{16}O_2$ was the oxidant, the benzoic acid retained 56% of the original isotopic content.[7] With *t*-BuOOH, the acid had 74%. The authors pointed out that a pure anhydride mechanism should have given 75% isotopic labeling,† as shown.



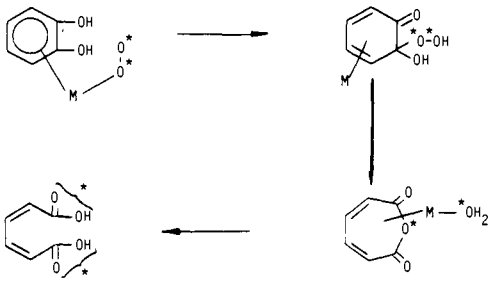
(3/4 of O labeled)

They rationalized the lower content by a more complex mechanism. However, the results are more simply explained by the anhydride mechanism, with some of the anhydride reacting with (unlabeled) H_2O_2 to give peroxy acid, as suggested above; the peroxy acid would in turn oxidize more benzil. In the limit, where H_2O_2 competes efficiently with H_2O_2, this mechanism gives benzoic acid with 50% labeling as shown below. With *t*-BuOOH, where this mechanism is not possible, 75% labeling would be expected, as was observed.



(1/2 of O labeled)

In conclusion, the product and ^{18}O tracer studies support the Baeyer–Villiger-type acyclic mechanism and clearly rule out the epoxide mechanism. The dioxetane mechanism cannot be a main reaction if it occurs at all. The present result is not consistent with the observed labeling in dioxygenase reactions, e.g., pyrocatechase-catalyzed oxidation of catechol, where incorporation of two oxygen atoms in the product muconic acid was shown.[22] Thus a simple anhydride mechanism of this type demonstrated here cannot be occurring. However, the enzymatic reaction involves a metal center (M) and might well involve reaction of water or hydroxide as a metal ligand with the anhydride, as shown below.



Experimental Section

Melting points are corrected. NMR spectra were obtained on a Varian Model T-60 spectrometer, and mass spectra on an AEI MS-9 (for organics) and on a Consolidated Electrodynamics 21-620 mass spectrometer (for oxygen gas). GLC analysis was performed on a HP Model 5920A, by using a 1.8-m column packed with 3% OV-275 on Anakrom Q at 80 °C. The internal standard used for ester determinations was 1,4-dimethoxybenzene.

Materials. *p*-Methoxybenzil was obtained by selenium dioxide oxidation of benzyl *p*-methoxyphenyl ketone in AcOH (1:1 mol ratio, reflux 2 h) and recrystallized from benzene–hexane in 37% yield, mp 62.0–62.5 °C (lit.[23] mp 61–62 °C). 2,4,6-Trimethylbenzil was synthesized similarly and recrystallized from benzene–methanol (62% yield), mp 135–136 °C (lit.[24] mp 134–136 °C).

† Apparent typographical errors in the paper have been corrected.

Table III. Example of Mass Spectral Data[a]

ionization conditions	height of peak, mm			(M + 2)/(M + 1) × 100
	M	M + 1	M + 2	
		(A) *p*-Anisic Acid (Authentic)		
70 eV, 100 °C	142 (100%)	11.5 (8.09%)	1.4 (0.98%)	12.2
	167 (100%)	10.4 (9.76%)	1.3 (1.22%)	12.5
	99.0 (100%)	9.5 (9.59%)	1.3 (1.31%)	13.7
14 eV, 100 °C	150 (10%)	13.3 (8.86%)	1.65 (1.11%)	12.4
	128 (100%)	12.3 (9.61%)	1.7 (1.41%)	13.8
mean	100%	9.18 ± 0.62%	1.21 ± 0.15%	12.9 ± 0.7
(lit.[26])	(100%)	(8.89%)	(0.95%)	10.6
		(B) Labeled *p*-Anisic Acid		
70 eV, 100 °C	off scale	17.4	27.2	156
		31.8	49.0	154
		21.8	31.4	147
		21.1	36.2	170
		14.0	22.0	157
14 eV, 100 °C	off scale	21.2	31.4	147
		14.0	22.0	157
		25.3	40.0	155
mean				155 ± 7

[a] Determined by an AEI MS-9 spectrometer. See the Experimental Section for calculation of (M = 2) excess %.

Oxygen gas of 51% ^{18}O excess, manufactured by Yeda R & D Co. Ltd., Rehovoth, Israel, was purchased from Research Products Division, Miles Lab. Inc., Ind. The ^{18}O-enriched gas was diluted with unlabeled O_2 to ca. 20% isotopic excess by volume, and the composition was determined by mass spectral analysis.

Preparation of Labeled Hydrogen Peroxide. In a 250-mL round-bottomed flask, fitted with a 100-mL dropping funnel and oxygen gas inlet bulb were placed *t*-BuOK (3.33 g, 30 mmol) and a magnetic stirrer, and, after evacuation, oxygen gas ($^{18}O_2$) was introduced and the cock was closed. Then, benzydrol (5.52 g, 30 mmol) in 80 mL of benzene was added dropwise with stirring. As $^{18}O_2$ gas was consumed by the autoxidation, the dropwise addition of the solution proceeded automatically and ceased within 5 min. Just when the dropping was complete, the cock of the dropping funnel was closed, and the other cock was opened to introduce $^{18}O_2$ gas. While the reaction mixture was stirred for 35 min, KOOH precipitated, which was filtered out, washed with benzene, and dissolved in 30 mL of 1 N HCl containing 1 mM EDTA. The aqueous solution was treated with a small amount of charcoal and filtered. The concentration of $H_2{}^{18}O_2$ was determined iodometrically to be 0.5 M, i.e., 50% yield based on benzhydrol, but over 90% based on $^{18}O_2$ consumed. Control experiments using unlabeled O_2 confirmed that the yield of H_2O_2 is in the range of 50–90% based on benzhydrol, but over 90% based on consumed O_2 gas.

It is known that no scrambling occurs during the ceric oxidation of $H_2{}^{18}O_2$.[12,25] After three freeze-pump-thaw cycles under high vacuum (< 1 μm Hg), 0.5 M $H_2{}^{18}O_2$ (0.2 mL, 0.1 mmol) was mixed with ceric sulfate (0.5 mmol) in 2.5 mL of 1 M H_2SO_4. The oxygen gas was purified by passing through a liquid N_2 trap. The results of mass spectral analysis were M + 2 = 16.4 ± 2.0% and M + 4 = 8.39 ± 0.04%. Here, M = 32 *m/e*. The ratio of (M + 2):(M + 4) is thus 100:51.2 for $^{18}O_2$ from $H_2{}^{18}O_2$, which is identical with that (100:50.7) of the starting $^{18}O_2$ gas. This confirms that no scrambling occurs during the autoxidation of benzhydrol and the ceric oxidation.

Reaction of Benzils with Alkaline $H_2{}^{18}O_2$. To a stirred solution of 2,4,6-trimethylbenzil (0.315 g, 1.25 mmol), 2 N NaOH (1.25 mL, 2.5 mmol) in 40 mL of MeOH, 0.5 M $H_2{}^{18}O_2$ (2.5 mL, 1.25 mmol) was slowly added dropwise (5 min). After 5 min of stirring, the reaction mixture was diluted with aqueous NaCl and extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4, and the evaporation of solvent under reduced pressure afforded methyl benzoate.

The aqueous layer was neutralized by 1 N HCl (2.5 mL) to precipitate mesitoic acid, mp 149–150 °C, 51 mg (25%). Extraction of the filtrate with ether and crystallization from CCl_4 gave a further 27% yield of mesitoic acid. After the evaporation of solvent from the filtrate, pure benzoic acid, 10 mg (8%), was obtained by sublimation at 85 °C. The three samples for mass spectral analysis were obtained in this way.

The corresponding products were obtained similarly from the reaction of *p*-methoxybenzil and $H_2{}^{18}O_2$, *p*-anisic and benzoic acids being isolated in 53 and 8% yields, respectively. A trace amount of methyl *p*-methoxybenzoate was obtained, but methyl benzoate was lost by evaporation with solvent in this case.

Mass Spectral Determination. All isotopic amounts given are presented as (M + 2)/M, corrected for natural abundance. Since all the products have a strong parent peak, it was easy to determine accurately (M + 1), (M + 2), and (M + 4) peak ratios. Mostly, (M + 2) was determined in comparison with the (M + 1) peak as a reference. This method can be justified by the fact that the observed M, M + 1, and M + 2 ratios of authentic samples (not containing excess ^{18}O) are identical with the calculated ratios,[26] as exemplified in Table IIIA. The (M + 2) value of 1.21% calculated by direct comparison to the parent peak (M = 152 *m/e*) is practically the same as that calculated by using the (M + 1) peak as a reference (1.18%). Thus, the excess (M + 2)%, (i.e., excess ^{18}O%) can be easily calculated as follows:

$$\frac{\text{excess (M + 2)}}{\text{M}}(\%) = \frac{\frac{\text{M + 2}}{\text{M + 1}}\text{labeled} - \frac{\text{M + 2}}{\text{M + 1}}\text{natural}}{\frac{\text{M}}{\text{M + 1}}\text{natural}}$$

$$= \frac{156 \pm 6 - 13.2}{100/9.18} = 13.1\%$$

Mass spectra for each sample were determined four to eight times and averaged. Errors given are σ.

It is known that carboxylate ion is not susceptible to oxygen exchange,[27] and we isolated the carboxylic acids immediately after neutralization. In the case of the ester, a control experiment with methyl *p*-anisoate showed that the exchange of ^{18}O was 8% under the experimental conditions (Table II). However, this control experiment was carried out at a higher effective alkali concentration because of the formation of carboxylic acid in the benzil oxidation, so that the oxygen exchange would be expected to be only 4% in the reaction of *p*-methoxybenzil with $H_2{}^{18}O_2$.

Acknowledgment. We are thankful to Drs. Kai Fang and David Hackney for mass spectra and helpful comments. This work was supported by Public Health Service Grant No. GM 20080 and National Science Foundation Grant No. CHE77-21560. MS9 was purchased with funds from National Science Foundation Grant No. GP3672.

References and Notes

(1) H. S. Mason, *Adv. Enzymol.*, **19**, 79 (1957); G. A. Hamilton, *ibid.*, **32**, 55 (1967); O. Hayaishi, in "Molecular Mechanisms of Oxygen Activation", O. Hayaishi, Ed., Academic Press, New York, 1974, p 1.
(2) G. A. Hamilton, in "Molecular Mechanisms of Oxygen Activation", O. Hayaishi, Ed., Academic Press, New York, 1974, p 136.
(3) (a) J. Tsuji and H. Takayanagi, *J. Am. Chem. Soc.*, **96**, 7349 (1974); (b)

Tetrahedron Lett., 1245 (1975).
(4) M. M. Rogic, T. R. Demmin, and W. B. Hammond, *J. Am. Chem. Soc.*, **98**, 7441 (1976).
(5) C. H. Hassall, *Org. React.*, 9, 73 (1957).
(6) H. Kwart and N. J. Wegemer, *J. Am. Chem. Soc.*, **83**, 2746 (1961).
(7) C. A. Bunton, in "Peroxide Reaction Mechanisms", J. O. Edwards, Ed., Interscience, New York, 1962, p 11.
(8) Y. Furuya and I. Urasaki, *Bull. Chem. Soc. Jpn.*, **41**, 660 (1968).
(9) Y. Moro-oka and C. S. Foote, *J. Am. Chem. Soc.*, **98**, 1510 (1967); T. Matsuura, *Tetrahedron*, **33**, 2869 (1977).
(10) Formation of ester from benzils and alkaline EtOOH has also been reported.[11] Unfortunately, it is not clear whether perester ($PhCO_3Et$) or methyl ester ($PhCO_2Me$) was formed.
(11) R. P. Beanes and R. E. Lewis, *J. Am. Chem. Soc.*, **58**, 947 (1936).
(12) M. Anbar, *J. Am. Chem. Soc.*, **83**, 2031 (1961).
(13) (a) R. E. Bail, J. O. Edwards, and P. Jones, *J. Org. Nucl. Chem.*, **28**, 2458 (1966); (b) P. A. Giguère, E. A. Secco, and R. S. Eaton, *Discuss. Faraday Soc.*, **14**, 104 (1953).
(14) K. Akiba and O. Simamura, *Tetrahedron*, **26**, 2527 (1970).
(15) A. Le Berre, *Bull. Soc. Chim. Fr.*, 1543 (1961); A. Le Berre and P. Goasguen, *ibid.*, 1682 (1962).
(16) I. Rosenthal, *J. Labelled Compd. Radiopharm.*, **12**, 317 (1976).
(17) Y. Sawaki and Y. Ogata, *J. Am. Chem. Soc.*, **99**, 5412 (1977), and references cited therein.
(18) Y. Sawaki and Y. Ogata, *J. Org. Chem.*, **42**, 40 (1977).
(19) It is known that $PhCO_3^-$ oxidizes sulfoxides but HOO^- does not in aqueous solvent; R. Curci and G. Modena, *Tetrahedron*, **22**, 1227, 1235 (1966). In aprotic solvent, on the contrary, hydroperoxide anion oxidizes sulfoxides to sulfones; Y. Ogata and S. Suyama, *J. Chem. Soc., Perkin Trans. 2*, 755 (1975); M. J. Gibian and T. Ungermann, *J. Org. Chem.*, **41**, 2500 (1976).
(20) J. E. Leffler, *J. Org. Chem.*, **16**, 1785 (1951).
(21) Y. Sawaki and T. Ogata, *J. Am. Chem. Soc.*, **100**, 856 (1978).
(22) O. Hayaishi and M. Katagiri, *J. Am. Chem. Soc.*, **77**, 5450 (1955); *J. Biol. Chem.*, **229**, 905 (1957).
(23) C. D. Shacklett and H. A. Smith, *J. Am. Chem. Soc.*, **75**, 2654 (1953).
(24) J. P. Freeman, *J. Am. Chem. Soc.*, **82**, 3869 (1960).
(25) E. Koubeck, M. L. Haggett, C. J. Battaglia, K. M. Ibne-Rasa, M. Y. Pyun, and J. O. Edwards, *J. Am. Chem. Soc.*, **85**, 2263 (2963).
(26) R. M. Silverstein, C. Bassler, and T. C. Morrill, "Spectrometric Identification of Organic Compounds", Wiley, New York, 1974, p 13.
(27) M. D. Kamen, "Isotope Tracers in Biology", Third Ed., Academic Press, New York, 1957, p 339.

The Penems, a New Class of β-Lactam Antibiotics. 2.[1] Total Synthesis of Racemic 6-Unsubstituted Representatives

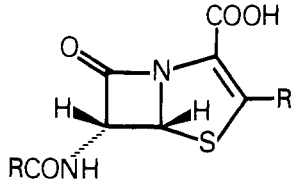
M. Lang, K. Prasad, W. Holick, J. Gosteli,* I. Ernest, and R. B. Woodward†

Contribution from the Woodward Research Institute, CH-4002 Basel, Switzerland.
Received April 16, 1979

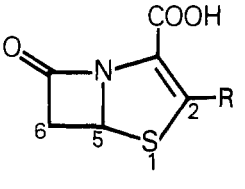
Abstract: Synthetic methods are described for the preparation of racemic compounds **1b**. The new substances differ from the previously described, penicillin-derived penems in their lack of an acylamino side chain. In striking contrast to penicillanic acid (**2**) and cephalosporanic acid (**3**), the new substances show antibiotic activity.

Recently we disclosed the preparation of compounds **1a** representing a new category of biologically active β-lactams. Structurally related to both the penicillins and the cephalosporins, these long-sought substances were obtained in optically active form by partial synthesis from penicillin V.[1] The antibiotic properties of these first members **1a** of the penem family justified the undertaking of a more extensive effort directed at elaborating synthetic routes to the penems. Besides widening the range of accessible structures and thereby giving insight into structure–activity relationships, such an endeavor was likely to produce synthetic methods applicable in related areas.

In this paper we present a first group of totally synthetic penems. At the outset we chose as the general target compounds represented by structure **1b**.

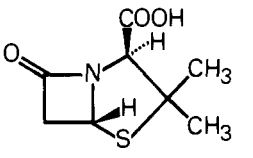


1a

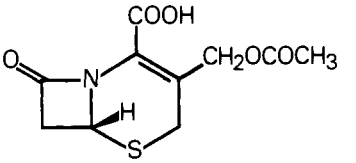


1b

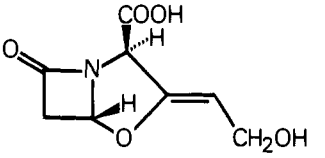
These differ from the substances described earlier in their lack of an acylamino side chain at position 6. Compounds containing a condensed β-lactam system unsubstituted in the 6 (or equivalent) position had been prepared by total and partial synthesis before.[2a,b] Our decision to construct the 6-unsubstituted members of the penem class rested on chemical rather than biological grounds; we felt that the fundamental chemistry of the new system could be best explored with these simple representatives. Further, we discerned the possibility, which in the event was realized, of preparing such substances relatively simply by total synthesis. Had we been guided by the biological activity of compounds such as **2** and **3** in our synthetic endeavors, the venture might have seemed fatuous, since both **2** and **3** are devoid of anitbiotic activity.[2b,3]



2



3



4

Clavulanic acid (**4**), a substance in some ways related to **1b**, which was isolated from natural sources by the Beecham group,[4] likewise carries no side chain at carbon 6. While this

† Deceased July 8, 1979.

0002-7863/79/1501-6296$01.00/0