5-Acetyl-2-hexyl-1(*H*)-imidazole. A mixture of **5a** (25.0 g, 0.15 mol), heptanimidamide hydrochloride (32.9 g, 0.20 mol), and sodium acetate (28.7 g, 0.35 mol) was refluxed for 6 h in dioxane (500 mL). After cooling, the salts were removed by filtration and the filtrate was concentrated in vacuo to a red oil. This was taken up in ethyl acetate (500 mL) and extracted with 1 N hydrochloric acid (3 × 100 mL). The combined aqueous extracts were washed with ethyl acetate and then carefully basified with sodium carbonate (40 g). This solution was then extracted with chloroform (3 × 100 mL), and the combined extracts were dried over magnesium sulfate. Concentration of the filtered solution gave a light brown solid which was recrystallized from ethyl acetate/hexane to give 12.21 g (42%) light tan solid, mp 105–106 °C. Workup of the mother liquors gave 7.82 g (26%) of oily solid which was pure by TLC but which showed some minor imputities by NMR: mass spectrum, *m/e* 194 (M^+); ^1H NMR ($CDCl_3$) δ 0.8 (3 H, m), 1.3 (6 H, m), 1.7 (2 H, m), 2.52 (3 H, s), 2.8 (2 H, br t, *J* = 7 Hz), 7.72 (1 H, s).

Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 67.84; H, 9.00; N, 14.13.

5-Acetyl-2-phenyl-1(*H*)-imidazole. A mixture of **5a** (3.33 g, 20.0 mmole), benzamidine hydrochloride (4.70 g, 30.0 mmol), and sodium acetate (4.10 g, 50.0 mmol) was refluxed for 42 h in dioxane (100 mL). After workup as in the previous example, 3.23 g of crude product was obtained which was recrystallized from cyclohexane/toluene to give 2.33 g (60%) of fine yellow needles, mp 155–157 °C (lit.[13] mp 158–158.5 °C); mass spectrum, *m/e* 186 (M^+), 171 ($M^+ - Me$); ^1H NMR ($CDCl_3/Me_2SO$-d_6) δ 2.51 (3 H, s), 7.3 (3 H, m), 7.73 (1 H, s), 8.0 (2 H, m).

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.53; H, 5.43; N, 14.92.

(13) Paul, R.; Menschik, J. U.S. Patent 4 107 307, 15 Aug 1978.

Acknowledgment. I thank Professors D. S. Kemp, E. J. Corey, and S. L. Schreiber and my colleagues at Pfizer, especially Drs. J. L. LaMattina and C. A. Lipinski, for their helpful comments and suggestions during both the execution of this work and the preparation of this manuscript.

Registry No. **2a**, 91157-81-2; **2b**, 76511-78-9; **2c**, 91228-03-4; **2d**, 91157-82-3; **2e**, 91157-83-4; **2f**, 91157-85-6; **2g**, 91157-86-7; (*E*)-**2h**, 91157-90-3; (*Z*)-**2h**, 91157-92-5; **3a**, 91157-93-6; **3b**, 91157-94-7; **3c**, 91157-95-8; **3d**, 91157-96-9; **4**, 91157-97-0; **5a**, 91157-98-1; **5b**, 91157-99-2; **5c**, 91158-00-8; **5d**, 91158-01-9; **5e**, 91158-02-0; 1-(phenylsulfonyl)-2-propanone, 5000-44-2; dimethylformamide dimethyl acetal, 4637-24-5; 1-(phenylthio)-2-propanone, 5042-53-5; 1-(methylsulfonyl)-2-propanone, 5000-46-4; 1-(methylthio)-2-propanone, 14109-72-9; (*E*)-4-hydroxy-3-(methylthio)-3-buten-2-one, 91157-87-8; (*Z*)-4-hydroxy-3-(methylthio)-3-buten-2-one, 91157-88-9; trimethyloxonium tetrafluoroborate, 420-37-1; acetamidine acetate, 36896-17-0; acetamidine, 143-37-3; 1,2-dichloroethylene, 540-59-0; methyl mercaptan, 74-93-1; 2-methyl-2-propanethiol, 75-66-1; diethylamine, 109-89-7; 3-chloro-4,4-diethoxy-2-butanone, 77070-88-3; acetamidine hydrochloride, 124-42-5; 5-acetyl-2-methyl-1(*H*)-imidazole, 78210-66-9; 5-chloro-2,4-dimethylpyrimidine, 75712-73-1; 5-acetyl-2-hexyl-1(*H*)-imidazole, 91158-03-1; heptanimidamide hydrochloride, 57297-28-6; 5-acetyl-2-phenyl-1(*H*)-imidazole, 10045-68-8; benzamidine hydrochloride, 1670-14-0.

Mechanism of Copper-Catalyzed Oxygenation of Ketones

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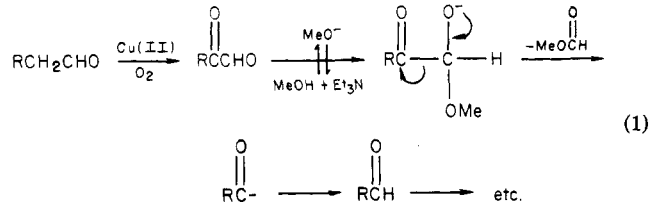
Deoxybenzoin (**1**) is converted by a Cu(II)–py–Et_3N–MeOH–O_2 (py = pyridine) system to a mixture of benzil (**2**), bidesyl (**3**), and the cleavage products PhCHO and PhCOOH. A product study comparing reactivities of **1** and **2** under identical conditions established (i) that the conversion of **1** to **3** is effected by Cu(II) alone, (ii) that PhCHO is generated only from **1**, in a reaction that requires both Cu(II) and O_2, and (iii) that **2** undergoes C–C cleavage only in the presence of H_2O, forming PhCOOH exclusively, in a reaction that requires Cu(II) but not O_2. α-Methyldeoxybenzoin (**5**) undergoes an exceptionally slow but similar reaction (giving the tertiary α-ketol **6** rather than diketone **2**). Mechanisms for these reactions are presented, and the significance of the results is discussed.

Copper ion catalysis of oxidation and oxygenation reactions is of recognized importance for carrying out selective transformations as well as in industrial applications.[1] There is also much current interest in the mechanisms of such reactions as they relate to model studies aimed at elucidating the biochemical roles of copper in a variety of oxidation and oxygenation cuproenzymes.[2]

On account of the mechanistic interest and possible synthetic utility, we have initiated a study of the copper-catalyzed oxygenation α to carbonyl groups. The conversion of aliphatic aldehydes to α-keto aldehydes was studied in the middle 1960's by Brackman and Volger, who observed that this conversion was accompanied by C–C bond cleavage, yielding an aldehyde of one less carbon atom, which then underwent further oxygenation and cleavage.[3] These reactions were conducted in MeOH with a cupric salt and excess triethylamine and pyridine. The rationale given for observed cleavage involved a nucleophilic displacement of a carbonyl anion by methoxide (eq 1). Brackman and Volger offered as precedent for such



(1)

displacement the base-promoted C–C cleavage that accompanies benzil–benzilic acid rearrangements. However,

(1) "Oxidation in Organic Chemistry", Part B; Trahanovsky, W. S., Ed.; Academic Press: New York, 1973.

(2) (a) "Copper Proteins"; Spiro, T. G., Ed.; Wiley: New York, 1981. (b) "Metal Ions in Biological Systems", Sigel, H., Ed.; Marcel Dekker: New York, 1981; Vol. 12 and 13. (c) "Copper Coordination Chemistry: Biochemical & Inorganic Perspectives"; Karlin, K. D., Zubieta, J., Eds.; Adenine Press: Guilderland, NY, 1983.

(3) (a) Volger, H. C.; Brackman, W.; Lemmers, J. W. F. M. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1203. (b) Brackman, W.; Gaasbeek, C. J.; Smit, P. J. *Ibid.* **1966**, *85*, 437. (c) Brackman, W.; Volger, H. C. *Ibid* **1966**, *85*, 446.

0022-3263/84/1949-3498$01.50/0

Table I. Nonvolatile Products Formed from 1 and 2[a]

condition/reagent	substrate: $PhCH_2COPh$ (1)	substrate: PhCOCOPh (2)
1. 5 mmol of Cu^{II} salt,[b] 50 mmol of Et_2N/py, O_2	PhCOOH (m), **2** (m), bidesyl[c] (m)	PhCOOH (l)
2. 0.4 mmol of Cu^{II} salt, 4 mmol of Et_3N/py, O_2	PhCOOH (m), **2** (m), bidesyl (l)	nr[d]
3. 0.4 mmol of Cu^{II} salt, 50 mmol of Et_3N/py, O_2	PhCOOH (m), **2** (m), bidesyl (l)	nr
4. 5 mmol of Cu^{I} salt, 50 mmol of Et_3N/py, N_2	bidesyl (h)	PhCOOH (l)
5. 0.4 mmol of Cu^{II} salt, 50 mmol of Et_3N/py, N_2	bidesyl (l)	nr
6. 50 mmol of Et_3N/py, O_2	nr	nr

[a] General conditions: 2 mmol of substrate in 30 mL MeOH, 18 h, 25 °C, 1 atm. h, m, and l indicate formed in high, medium, and low amounts, respectively. In all cases except conditions 1–3 for substrate 1, the starting material was at least partially recovered unchanged. [b] Cu^{II} salt = $Cu(NO_3)_2 \cdot 3H_2O$. [c] Bidesyl = $(PhC(O)CHPh)_2$, formed as a mixture of meso and *d,l* diastereomers. [d] nr = no reaction.

a careful scrutiny of the rearrangement literature reveals that the cleavage side reaction is rare and occurs only under strongly basic conditions.[4] Also, the species $PhC(=O)^-$ generated in this case is a much better leaving group than would be the conjugate bases of *aliphatic* aldehydes. We did not believe that the strongly basic $RC(=O)^-$ species would serve as leaving groups under the mild MeOH–Et_3N conditions used by Brackman and Volger.

In this report we provide evidence for an alternative mechanism leading to C–C bond cleavage which is independent from and competitive with the pathway leading to α-dicarbonyl compound. The ability to control reaction outcome may lead to a synthetically useful method for achieving oxygenation α to carbonyl groups. Such a transformation (in terms of electrophilic attack) is electronically disfavored, though it can be accomplished by the action of SeO_2. However, the copper-catalyzed reaction may display different regio- and stereochemical patterns than SeO_2. It is of note that the copper-catalyzed α-oxygenation of aldehydes contrasts the usual transition-metal-catalyzed autoxidation to the corresponding carboxylic acids.

We initially chose to study the ketone $PhCH_2C(=O)Ph$ (deoxybenzoin, 1) and the corresponding aldehyde $PhCH_2CHO$, on account of the advantages of enhanced reactivity and ease of characterization of products. This report is limited to the ketonic substrate, though the general mechanistic and reactivity patterns displayed appear to hold for aldehydes as well, studies of which will be described in a future report.

Results. Initial mechanistic information was obtained from parallel studies in which 1 and the supposed intermediate leading to C–C cleavage, PhCOCOPh (benzil, **2**), were identically subjected to a variety of reaction conditions. We initially used $Cu(NO_3)_2 \cdot 3H_2O$, one of the sources of copper used by Brackman and Volger. The series of experiments in Table I was conducted and the nonvolatile[5] product composition was determined qualitatively by TLC and IR. The following points are apparent from this data: (1) Under identical conditions *utilizing* O_2, more C–C cleavage (as diagnosed by the production of PhCOOH) resulted from the methylene substrate 1 than from the dicarbonyl substrate **2**. (2) Under identical conditions *utilizing* N_2, C–C cleavage occurred only for the dicarbonyl substrate **2**. (3) The yield of PhCOOH from **2** increased slightly upon changing the atmosphere from N_2 to O_2 but increased markedly in proportion to the amount of copper(II) salt utilized. (4) Oxidative coupling of 1, forming bidesyl (**3**), requires Cu^{II} but not O_2. (5) Under no condition was methyl benzoate[6] or benzilic acid[7] (or its methyl ester) observed as a product.

Table II. Quantitative Product Analysis for Reactions of 1 and 2 with Dioxygen[a]

substrate and experimental conditions	yield,[b] % **2**	PhCOOH	PhCHO	**3**	total recovery[c]
$PhCH_2COPh$, $Cu(NO_3)_2 \cdot 3H_2O$	44.7	39.6	17.8	23.9	97.3
$PhCH_2COPh$, $Cu(NO_3)_2py_2$	42.9	32.1	23.9	26.6	97.5
PhCOCOPh, $Cu(NO_3)_2 \cdot 3H_2O$	96.7	5.9	0.0	0.0	99.6
PhCOCOPh, $Cu(NO_3)_2py_2$	100.0	0.0	0.0	0.0	100.0

[a] Carried out with 6 mmol of substrate, 9 mmol of the Cu^{II} salt, 90 mmol each of Et_3N and pyridine in MeOH (120 mL) for 9 h at 25 °C, 1 atm of dioxygen. 1 was entirely transformed under these conditions. [b] Calculated per the stoichiometry: 1 → **2**, 1 → PhCOOH, 1 → PhCHO, and 2(1) → **3**; **2** → 2(PhCOOH). The numbers represent an average of three determinations. [c] Calculated on the basis of **2** + **3** + $^1/_2$(PhCOOH + PhCHO) for 1; **2** + PhCOOH for **2**.

The first point indicates that **2** is not an obligatory intermediate in the cleavage mechanism of 1. The second point indicates that a cleavage pathway exists for **2** which is independent from that followed by 1. The third point suggests that it is the water contained in the copper(II) salt that stimulates cleavage of **2** (Cu^{II} cannot be the limiting factor since it would be continuously regenerated in the case where O_2 was used).

In order to verify these hypotheses, we carried out a quantitative product study comparing 1 to **2**, utilizing both $Cu(NO_3)_2 \cdot 3H_2O$ and an anhydrous source of copper(II), $Cu(NO_3)_2py_2$. The data given in Table II include yields of benzaldehyde obtained by azeotropic removal during workup. The important observations are (i) the complete absence of PhCHO as a cleavage product from benzil (**2**) and (ii) the suppression of the cleavage reaction of **2** but not of 1 under anhydrous conditions. Control experiments established that benzaldehyde and bidesyl (**3**) are oxidized (to benzoic acid) only to a slight extent under the reaction conditions. This means that the product composition from reaction of deoxybenzoin (1) reflects the relative rates of competitive reaction pathways.

The formation of bidesyl (**3**) from 1 is rationalized by an anaerobic copper(II)-induced oxidative coupling, in analogy to previous reports using chromium(VI) and manganese(III) oxidants.[8] Bidesyl is the only product

(4) (a) Lachman, A. *J. Am. Chem. Soc.* **1923**, *45*, 1509. (b) Doering, W. v. E.; Urban, R. S. *Ibid.* **1956**, *78*, 5938. (c) Machell, G. *J. Chem. Soc.* **1960**, 683.

(5) Any PhCHO formed was azeotropically removed during the evaporation of solvent in vacuo and thus was not detected.

(6) In control experiments, methyl benzoate was shown to be stable to the reaction conditions and subsequent workup. It forms an azeotrope with MeOH–H_2O and can be determined quantitatively by treatment of the azeotrope with NaOH for 30 min, followed by acidification, extraction with ether, and weighing the PhCOOH obtained upon solvent evaporation.

(7) The possibility that any benzilic acid formed might undergo oxidative decarboxylation was also ruled out by the nonobservation of benzophenone in the product mixture.

Table III. Effect of Oxygen Pressure on Product Distributions for 1[a]

O_2 pressure, atm	yield,[b] % 3	2	PhCOOH	PhCHO	total recovery
air (0.2)	32.4	43.6	21.2	14.8	94.0
1	26.6	42.9	32.1	23.9	97.5
1.27	5.8	59.1	32.1	29.0	95.5
1.67	1.5	65.8	32.8	31.2	99.3
2.33	1.2	64.7	35.0	nd[c]	

[a] Reaction conditions: 6 mmol of 1, 9 mmol of $Cu(NO_3)_2py_2$, and 90 mmol each of Et_3N and pyridine in MeOH (120 mL) for 9 h at 25 °C. 1 was entirely converted in all cases. [b] Calculated according to notes b and c, Table II. The numbers represent an average of three determinations. [c] nd = not determined.

Table IV. Cleavage Reactivity of Benzil (2)

reaction conditions[a]	yield PhCOOH, %	recovered 2, %	total recovery, %
9 mmol of $Cu(NO_3)_2 \cdot 3H_2O$, 90 mmol Et_3N/py, O_2 (1 atm)	11.9	85.2	97.1
9 mmol of $Cu(NO_3)_2 \cdot 3H_2O$, 90 mmol of Et_3N/py, N_2 (1 atm)	6.1	91.6	97.7
27 mmol of H_2O, 90 mmol of Et_3N/py, O_2 (1 atm)	0.0	100.0	100.0
60 mmol of $Cu(NO_3)_2 \cdot 3H_2O$, 180 mmol of Et_3N/py, O_2 (1 atm)	46.7	44.4	91.1
60 mmol of $Cu(NO_3)_2 \cdot 3H_2O$, 180 mmol of Et_3N/py, N_2 (1 atm)	36.8	52.7	89.6

[a] General conditions: benzil (6 mmol) in methanol (120 mL for first three entries, 350 mL for last two), 18 h, 25 °C. The data represent an average of two experiments.

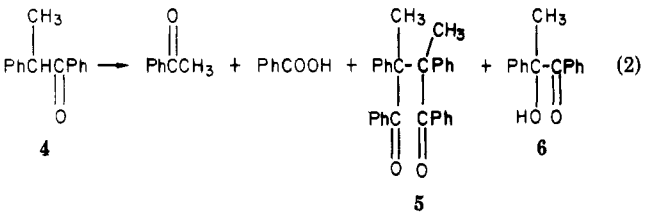
formed from 1 in the absence of O_2, and it follows that the yield of bidesyl should diminish upon stimulation of the dioxygen-derived reactions. Table III gives data that show the dependence of the product composition on the dioxygen concentration (as reflected by changing the O_2 pressure), using the anhydrous copper catalyst. It is seen that a relatively small increase in O_2 pressure resulted in a nearly complete suppression of bidesyl formation and compensatory increases in yield of the other three products. Benzil was produced at consistently about 4 times the level of benzoic acid.

Results of further experiments relevant to the production of PhCOOH from benzil under the influence of the hydrated copper catalyst are shown in Table IV. The data indicate (i) that the degree of cleavage is proportional to the amount of hydrated copper catalyst used (but that water alone is ineffective) and (ii) that the increase in yield of PhCOOH upon changing from N_2 to O_2 diminishes as the molar ratio of $Cu(NO_3)_2 \cdot 3H_2O$ to substrate increases. The latter point indicates that the stimulation of PhCOOH production by O_2 using low levels of copper salt is probably due to the Cu^I-to-Cu^{II} regenerating action of dioxygen.[9]

Table V

product (mmol)	oxidation with $Cu(NO_3)_2py_2$–O_2, MeOH, 25 °C, 9 h: 1 (2 mmol), $(p\text{-}MeC_6H_4CO)_2$ (1.4 mmol)	$p\text{-}MeC_6H_4CH_2COC_6H_4\text{-}p\text{-}Me$ (2 mmol), 2 (1.4 mmol)
2	1.31	1.30
$(p\text{-}MeC_6H_4CO)_2$	1.32	1.34
PhCHO	0.664	0.0
PhCOOH	0.721	0.125
$p\text{-}MeC_6H_4CHO$	0.0	0.533
$p\text{-}MeC_6H_4COOH$	0.015	0.548

In analogy to the production of PhCOOH and PhCHO from 1, we figured that a similar transformation would occur for the α-methyl compound 4 (α-phenylpropiophenone), with acetophenone being formed in place of benzaldehyde. Surprisingly, 4 was inert under the conditions (see Table II, note a) which resulted in complete conversion of 1. An extension of the reaction time (46 h) led to the trace production of $PhCOCH_3$, PhCOOH, the bidesyl-like dimer 5, and the α-hydroxy compound 6 (eq 2). Under more vigorous conditions (55 °C, 3 days) most



of 4 was transformed to the products shown above.[10] In a control study, we established that under these conditions, 6 was converted partially to $PhCOCH_3$ and PhCOOH but not nearly to the extent necessary to account for the yields of these products formed directly from 4. The production of 6 from 4 here is in contrast to the case of 1, where the analogous α-hydroxy compound PhCHOHCOPh (benzoin) was not observed as a final product. However, the formation of benzoin as an intermediate could not be excluded since it would be rapidly converted to benzil under the reaction conditions (as established by the appropriate control experiment).[11]

Discussion. Brackman and Volger reported a Cu(II)–Et_3N–pyridine-promoted oxygenation of aliphatic aldehydes in methanol that resulted in a stepwise degradation to lower homologues, the terminal carbons being removed as methyl formate:

$$RCH_2CH_2CHO \xrightarrow{-HCOOCH_3} RCH_2CHO \xrightarrow{-HCOOCH_3} RCHO \rightarrow \text{etc.}$$

These workers proposed the intermediate formation of α-keto aldehydes and the cleavage thereof by methoxide (eq 1). However, the involvement of strongly basic carbonyl anions as leaving groups in the C–C cleavage step seems unreasonable under the mild conditions employed. To test this point we conducted parallel studies on the deoxybenzoin (1)/benzil (2) pair as a model for aldehyde and corresponding α-keto aldehyde. The data we obtained elucidate two independent copper-catalyzed C–C bond-

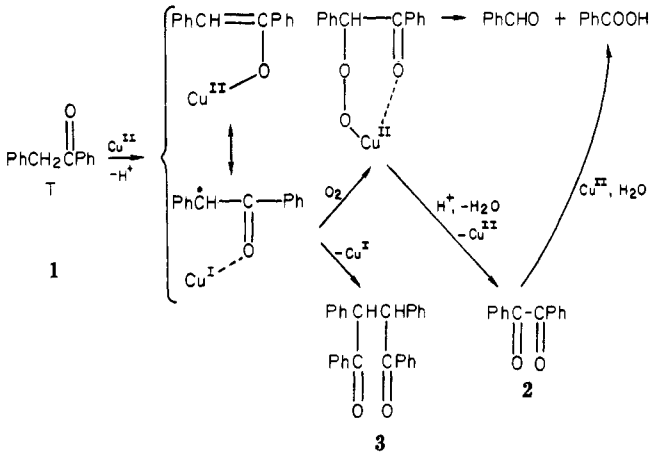
(8) (a) Wiberg, K. B.; Aniline, O.; Gatzke, A. *J. Org. Chem.* **1972**, *37*, 3229. (b) van Helden, R.; Kooyman, E. C. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 57.

(9) However, it has been shown that 1,2-diones can be cleaved to carboxylic acids by a copper peroxide species formed from Cu(I) and dioxygen in pyridine: Speier, G.; Tyelkar, Z. *J. Chem. Soc., Dalton Trans.* **1983**, 1995. We found that this reaction was not very effective in MeOH solvent but could account for the fact that the yield of PhCOOH remained greater in the presence of O_2 even when a large excess of Cu(II) was utilized.

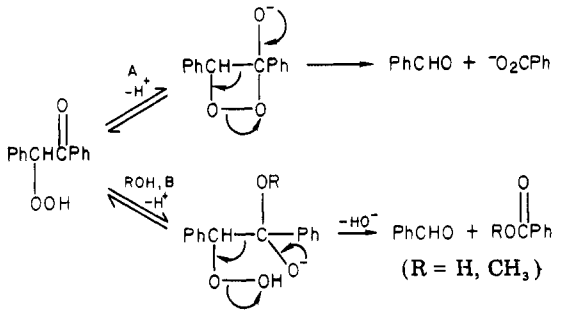
(10) As established by a separate control experiment, the yield of acetophenone was reduced partially by its further oxidation to PhCOOH.

(11) The facile oxidation of secondary α-ketols to 1,2-diketones by copper(II) and other oxidants is well-known: Connon, H. A.; Sheldon, B. G.; Harding, K. E.; Letterman, L. E.; Fulton, D. C.; Nigh, W. G. *J. Org. Chem.* **1973**, *38*, 2020 and references cited therein. See also: Russell, G. A. In "Aspects of Mechanism and Organometallic Chemistry"; Brewster, J. H., Ed.; Plenum Press: New York, 1978; p 59.

Scheme I



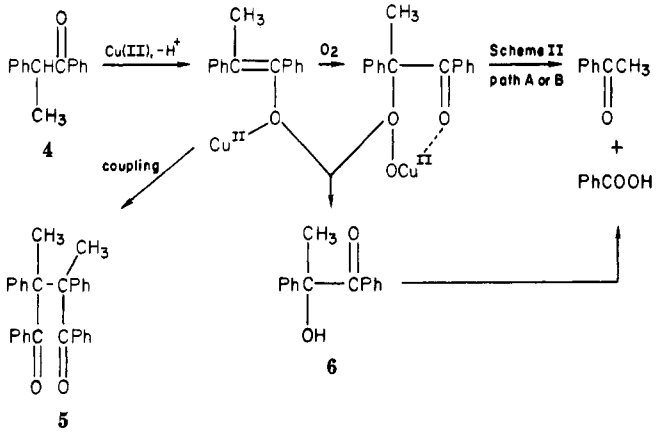
Scheme II



cleavage pathways. In one pathway the methylene compound 1 is converted to a "chain-shortened" aldehyde in an oxygen-consuming process as proposed by Brackman and Volger, but the *α-keto compound 2 is not an intermediate* since it is inert to this reaction.[12] The other cleavage reaction utilizes only 2 as a substrate, requires water and copper(II) *but not oxygen*, and *does not produce aldehyde*. A reaction scheme that accounts for all results is shown in Scheme I.

The first step is a Lewis acid promoted enolization. In the absence of oxygen, copper(II) effects an oxidative coupling of 1 to give bidesyl (3). This occurs stoichiometrically, or catalytically if O_2 is present to regenerate Cu^{II} from Cu^{I}. In the presence of dioxygen, coupling is competitive with oxygen incorporation, leading to an α-

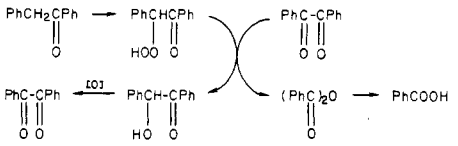
Scheme III



hydroperoxide equivalent (probably as the copper derivative shown). The α-hydroperoxide then undergoes competitive dehydration (giving diketone) and cleavage (giving aldehyde and acid/ester). Possible mechanisms for cleavage are shown in Scheme II.[13] Although we have no firm evidence for deciding between paths A and B, the fact that methyl benzoate is not a product of any of our experiments[6] leads us to favor path A. Interestingly, in contrast to our findings, Brackman obtained much more HCOOMe than HCOOH, and there has been a recent report that Fe(III)-catalyzed ketone autoxidations give esters when carried out in alcohol solvents.[14c] Also, esters predominate in certain *base-catalyzed* autoxidations of ketones but not in others.[15] Substantial precedent for the reactions shown in Schemes I and II exists in the chemical literature.[14-19]

Our observation of a copper(II)–water-promoted oxidative cleavage of benzil to benzoic acid is consistent with a previous finding of such by Kinoshita,[20] though his conditions were more strongly basic than ours. The mechanism he implied is shown in eq 3. The actual species undergoing redox may, however, be more like that

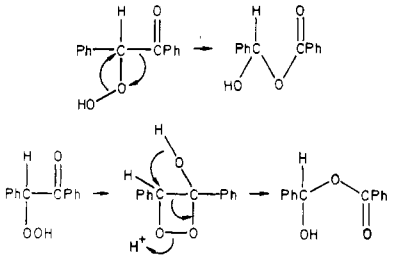
(12) A referee has suggested that the lack of observed oxidation of benzil (2) *alone* does not preclude the possibility of *cooxidation* of benzil formed in the deoxybenzoin (1) oxidations. One possibility for cooxidation would be a cleavage of benzil induced by the putative hydroperoxide formed from 1 (eq i). The occurrence of such a pathway would



(i)

mean that even under *anhydrous conditions* some of the PhCOOH product arises from 2 and not all from 1. In order to test for cooxidation, we examined the oxidation of deoxybenzoin in the presence of benzil labeled with *p*-methyl substituents, as well as the oxidation of labeled deoxybenzoin in the presence of unlabeled benzil. The results (average of three experiments) performed at 2.32 atm of O_2 (to minimize formation of bidesyl) are given in Table V. As can be seen, no cross-aldehydes are produced, but a low degree of cooxidation of the diketone to the acid does occur. Surprisingly, cooxidation of the unsubstituted benzil is much more extensive than of the *p*-methyl-substituted one. We interpret these results in terms of a substituent-sensitive, Cu(II)-induced cleavage of the benzils, which can proceed through consumption of the water generated upon dehydration of the deoxybenzoin-derived α-hydroperoxide.

(13) The mechanisms shown are intended in a formal sense only, and copper(I/II)-containing species are probably involved. Additional Baeyer–Villiger-like mechanisms have been postulated[14] (eq ii). Note that although the two mechanisms shown in (ii) produce the same intermediate (giving PhCHO and PhCOOH), they differ in terms of the fate of the original carbonyl oxygen atom.



(ii)

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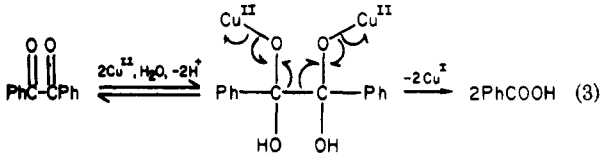
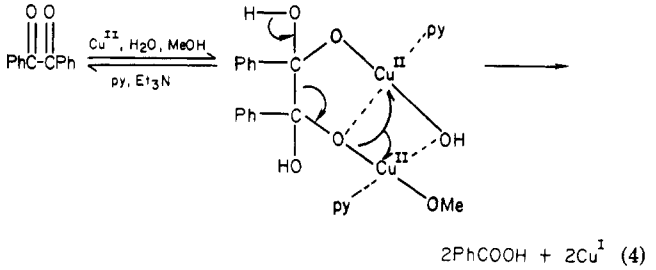
(18) Elkik, E. *Bull. Soc. Chim. Fr.* **1959**, 933.

(19) It should be noted that a very different pathway for copper-catalyzed autoxidation of aldehydes, involving the elimination of CO rather than HCOOH, has been reported: Van Rheenan, V. *Tetrahedron Lett.* **1969**, 985.

(20) Kinoshita, K. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 777, 783.

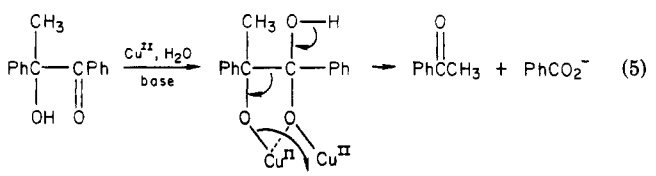


shown in eq 4. Rogić and co-workers have proposed that



concerted two-electron redox reactions via bridged binuclear species of the type shown may be a quite common phenomenon for copper.[21] The importance of this concept is that constrained binucleating ligand systems per se may not be necessary for observing two-electron copper-catalyzed redox reactions. Whatever mechanism is operating in our case must be consistent with the fact that PhCOOH is the exclusive product and that PhCOOMe is not formed even in the absence of H_2O.[6,22] In this respect, the oxidative cleavage we have observed clearly does not involve the action of H_2O_2 since this agent is known to effect a rapid conversion of benzil in basic MeOH to substantial quantities of PhCOOMe in addition to PhCOOH.[23]

For the slow-reaching α-methyl compound **4**, one can consider a similar reaction pathway (Scheme III) to that observed for **1**. Though dehydration of the corresponding α-hydroxyperoxide (or equivalent) is not possible, cleavage can still occur according to Scheme II. In addition, the hydroperoxide can effect oxygenation of the starting ketone (or Cu^{II} enolate) to give two molecules of alcohol **6**.[24] The alcohol was found to undergo a slow conversion to the same products formed more rapidly from **4** via the hypothesized hydroperoxide. Oxidative cleavage of **6** has been observed by Kinoshita under the same conditions that cleave benzil,[20] and the mechanism (eq 5) is thus probably analogous to that shown in eq 3 or 4, in which copper(II) alone is the oxidant and oxygen is required only to regenerate copper(II) from copper(I) when the metal is employed in catalytic quantities.



The extremely slow reaction of **4** compared to **1** has important mechanistic implications. The rate-retarding effect of branching is in contrast to the situation found for base-catalyzed autoxidations, wherein increased branching *accelerates* the rate of reaction (e.g., isobutyrophenone is attacked more rapidly than propiophenone,[17] and isobutyl methyl ketone is attacked only at the secondary α-carbon[18]). The slow disappearance of **4** indicates either that the initial copper(II)-promoted enolization is retarded and/or that *both* subsequent pathways (anaerobic oxidative coupling and oxygen incorporation) are slow. Steric effects are the probable cause.

Conclusion

We have studied the mechanism of oxygenation α to carbonyl groups which is achieved under mild conditions via copper catalysis. This catalysis takes advantage of the remarkable ability of copper to serve both a Lewis acid and redox catalytic role. In the absence of dioxygen, copper(II) effects oxidative coupling of benzylic ketones to give C^{α}–$C^{\alpha'}$-bonded dimers. In the presence of dioxygen, O_2 incorporation competes with coupling, and coupling can be eliminated by increasing the O_2 pressure. Under anhydrous conditions, dioxygen utilization results in a mixture of α-oxygenation and C–C cleavage products, which appear to arise from a common copper α-hydroperoxide intermediate. Controlled inhibition of the C–C cleavage pathway would provide a new synthetic method for achieving α-oxygenation, which may exhibit unique regio- or stereochemical features. We are currently investigating the possibility of controlling the partitioning of the α-hydroperoxide-like species by varying the temperature and the nature of copper complexation (e.g., the effects of ligands and solvent).

An additional C–C cleavage pathway was elucidated that converts benzil exclusively to benzoic acid and requires copper(II) and water but not dioxygen (see eq 3 and 4). This finding is in contrast to previous studies by Brackman, which proposed a methoxide-induced cleavage of α-keto aldehydes to the lower aldehyde homologues and methyl formate (eq 1). (A similar pathway was invoked for the conversion of methyl ethyl ketone to CH_3CHO and CH_3COOCH_3 via 2,3-butanedione). Our results suggest that aldehyde cleavage products arise directly from the starting carbonyl compounds and that the α-keto compounds (i) are produced simultaneously via a common intermediate, (ii) are not converted to aldehydes, and (iii) are further transformed only in the presence of water, in which case C–C cleavage results in the carboxylic oxidation state of *both* fragments.[12]

In contrast to our finding of the α-dicarbonyl compound benzil as an end product, α-keto aldehydes were not reported as end products in the oxidative degradation of aldehydes studied by Brackman and co-workers. However, it is unlikely that the observed absence of α-keto aldehydes is due to the MeOH–Et_3N induced cleavage proposed by these investigators, since the more reactive compound benzil is inert to these conditions. A more reasonable explanation is that the α-keto aldehyde is undergoing oxidative cleavage by Cu(II) utilizing the water generated during its formation.

Experimental Section

General Methods and Materials. ^1H NMR spectra were obtained at 60 MHz with a Varian A60-A or EM-360 spectrometer, using tetramethylsilane as internal standard and $CDCl_3$ as solvent. IR spectra were recorded on either a Beckman IR10 or Pye Unicam 3-100 spectrophotometer. Melting points were measured with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

$Cu(NO_3)_2py_2$ was obtained from $Cu(NO_3)_2 \cdot 3H_2O$ by azeotropic removal of water in refluxing pyridine–toluene, followed by solvent removal and evacuation at 50 °C for 24 h. The light blue powder was characterized as the dipyridine complex according to ref 25.

(21) Rogić, M. M.; Demmin, T. R. In "Aspects of Mechanism and Organometallic Chemistry"; Brewster, J. H., Ed.; Plenum Press: New York, 1978; p 141.

(22) The corresponding mechanism giving PhCOOMe may simply be too high in energy due to (i) the greater resonance stabilization of $PhCOO^-$ or (ii) the advantage of generating a product which maintains coordination to copper.

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(24) A copper(I)-promoted decomposition of the hydroperoxide would also give alcohol, but in the presence of oxygen any copper(I) formed would be reoxidized to copper (II).

α-Methyldeoxybenzoin (4) was prepared according to ref 26: NMR δ 1.58 (d, 3 H), 4.60 (q, 1 H).

α-Methylbenzoin (6) was prepared according to ref 27: NMR δ 1.87 (s, 3 H).

Bidesyl (3)[28] was characterized as the only product resulting from reaction of 1 under N_2 (IR, TLC). The NMR spectrum exhibited two singlets at δ 5.40 and 5.78 of nearly equal intensity, which together integrated to 1/10th of the aromatic signal. The two signals are believed to arise from the meso and *d,l* diastereomers, and no attempt was made to elucidate the correct assignment. The mp of the mixture (259–260 °C) corresponds closely to the 256–257 °C value reported in the literature for one of the diastereomers (the other melts at 158–159 °C).[29]

The dimethyl congener of bidesyl (5) was not characterized fully, although it does not appear to have been reported previously. It was obtained as the sole product (TLC) from reaction of 4 under N_2 and exhibited two singlets in the NMR (δ 1.70 and 3.20, together integrating as 3/10ths of the aromatic signal), believed to arise from the two possible diastereomers (meso and *d,l*).

4,4′-Dimethyldeoxybenzoin (see footnote 12) was prepared according to ref 30 and the 4,4′-dimethylbenzil used was that obtained as the neutral product of Cu(II)–O_2 oxidation of the corresponding deoxybenzoin.

All other materials were ACS reagent grade. The methanol used as solvent contained 0.1% water.

Reaction Procedure. Reactions were initiated by the addition of the organic substrate to the remaining ingredients, preequilibrated with and maintained under either N_2 or O_2. For reactions conducted at greater than 1 atm of O_2, a pressure bottle (Parr) was fitted with a one-hole neoprene stopper containing a copper tube insert and connected via a pressure gauge to the O_2 source. All reactions were worked up by addition of aqueous 3 N HCl to pH 1, evaporation of the methanol in vacuo, and extraction with 1:1 $CHCl_3$–CCl_4 (the use of CCl_4 effectively prevented the extraction of both py·HCl and Et_3N·HCl into the organic layer).

Quantitative Product Determination. The benzoic acid was removed from the $CHCl_3$–CCl_4 extract by extracting with aqueous $NaHCO_3$, reacidifying, and extracting into $CHCl_3$. Evaporation of the solvent in a preweighed flask gave the yield of benzoic acid (no contaminants could be detected by TLC, IR, or NMR). The initial organic extract was subsequently evaporated in vacuo in a preweighed flask, giving the combined weight of the remaining product(s): 2 or (2 + 3) in experiments with 1 (no other materials could be detected by TLC or NMR). Individual yields of 2 and 3 were determined from the integration of the aliphatic protons of 3 (two isomers) relative to that of the aromatic protons. For the quantitative determination of benzaldehyde, the removal of MeOH after the initial acidification was conducted in vacuo with a cold finger apparatus cooled with dry ice in 2-propanol. The condensate was treated with 2,4-dinitrophenylhydrazine, and the resulting hydrazone derivative was filtered, washed, dried, and weighed. It ran as a single spot on TLC and had mp 236–238 °C (lit.[31] mp 237 °C). A control study established that this sequence of azeotropic distillation followed by derivatization resulted in a 98% isolated yield.

Registry No. 1, 451-40-1; 2, 134-81-6; *meso*-3, 21072-57-1; (±)-3, 81176-44-5; 4, 2042-85-5; *meso*-5, 91112-28-6; (±)-5, 91112-29-7; 6, 5623-26-7; PhCHO, 100-52-7; $PhCO_2H$, 65-85-0; $PhCOCH_3$, 98-86-2; Cu^{2+}, 15158-11-9; Et_3N, 121-44-8; MeOH, 67-56-1; O_2, 7782-44-7; $Cu(NO_3)_2py_2$, 14842-51-4; *p*-$MeC_6H_4COCOC_6H_4$-*p*-Me, 3457-48-5; *p*-$MeC_6H_4CH_2COC_6H_4$-*p*-Me, 51490-06-3; *p*-MeC_6H_4CHO, 104-87-0; *p*-$MeC_6H_4CO_2H$, 99-94-5; $Cu(NO_3)_2$, 3251-23-8; py, 110-86-1.

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(26) Pomerantz, M.; Witherup, T. H. *J. Am. Chem. Soc.* **1973**, *95*, 5977.
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Total Synthesis of the Ionophore Antibiotic X-14547A (Indanomycin)

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The total synthesis of the ionophore antibiotic X-14547A (indanomycin) (1) is described by using a convergent strategy. 2-Ethylvalerolactone was converted into ethyl (*E,E,E*)-11-[[(β-methoxy)ethoxy]methoxy]-6-ethyl-2,7,9-undecatrienoate (8) in eight steps. Intramolecular Diels–Alder reaction of 8 at 110 °C followed by deprotection to give the racemic tricyclic lactone 7 proceeded with very high stereoselectivity (>90%) and in 38% overall yield from 2-ethylvalerolactone. The tricyclic lactone 7 was resolved via the diastereomeric amides 24 and 25 to provide the optically pure lactones 26 and 27. Reaction of 7 with 1-pyrrolylmagnesium bromide gave the pyrrolylcarbonyl derivative 28 whose structure was determined by X-ray crystallography. Alternatively, the optically pure lactone 26 was reacted with 2-lithio-1-[[(β-trimethylsilyl)ethoxy]methyl]pyrrole to give the corresponding *N*-SEM protected pyrrolylcarbonyl 32. Elaboration of 32 afforded the phenylsulfone 34 which constituted an appropriate right-hand fragment suitable for later coupling. Synthesis of the left-hand tetrahydropyranyl α,β-unsaturated aldehyde 3 was achieved by using levoglucosan (1,6-anhydro-β-D-glucopyranose) as the starting material. Coupling of 3 with the lithio anion from 34 followed by trapping with benzoyl chloride gave the benzoyloxy phenyl sulfones 57. Reduction of these with sodium amalgam stereoselectively afforded the *E,E*-diene 58. The synthesis was completed by deprotection and hydrolysis to afford the antibiotic X-14547A (indanomycin).

Naturally occurring ionophore antibiotics, with their wide range of structural and stereochemical features, continue to provide challenging synthetic targets. As a result of the complexity of these molecules structural determinations have been slow, and total syntheses have only recently been achieved.[1] In 1978 a new polyether iono-

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