

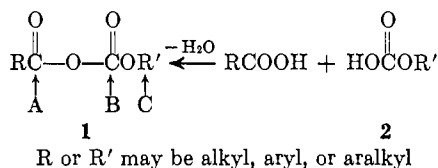
# The Carboxylic Carbonic Anhydrides and Related Compounds

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Received March 10, 1969

The carboxylic carbonic anhydrides **1** may be formally regarded as derived from a carboxylic acid, RCOOH, and a monoester of carbonic acid, **2**. A few isolated examples of these anhydrides have been known for a



long time, but thorough investigations of their preparation, isolation, synthetic properties, and mechanistic behavior have been reported only in recent years.

The anhydrides **1** are compounds of considerable theoretical and practical interest. They can be attacked by nucleophiles at the carboxyl carbonyl (A) or the carbonate carbonyl (B); their first synthetic usefulness was in the formation of peptide linkages, by the attack of the amino group of a protected amino acid at A.<sup>1</sup> The nucleophile can be a carbanion,<sup>2</sup> and the mixed anhydride **1** is particularly useful in cases where the acyl group contains structures that would be sensitive to reagents normally used to convert carboxylic acids to acid chlorides;<sup>3</sup> **1** may be prepared at low temperatures under practically neutral conditions.

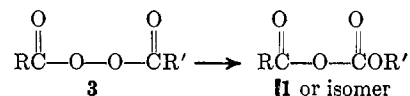
(1) The extensive applications of **1** in peptide synthesis are summarized by N. F. Albertson, *Org. Reactions*, **12**, 172 (1962), and by M. Bodansky and M. A. Ondetti, "Peptide Synthesis," Interscience Publishers, New York, N. Y., 1966, p 88 ff.

(2) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **21**, 144 (1956); **22**, 245 (1957); *Org. Syn.*, **37**, 20 (1957).

(3) Cf. J. H. Boothe, *et al.*, *J. Am. Chem. Soc.*, **81**, 1006 (1959).

The anhydrides have also been used to acylate inorganic azides, H<sub>2</sub>S, thiols, hydroxyl groups, and phosphates.

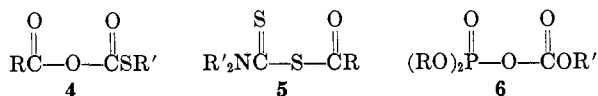
It is now known<sup>4</sup> that one of the important modes of decomposition of diacyl peroxides **3** is by the so-called carboxyl inversion reaction, to form the carboxylic carbonic anhydrides **1**, which may be isolated as such or converted to other products, depending on conditions. Denney<sup>4a</sup> has described conditions under which an acid, R'COOH, can be readily converted to the next



lower alcohol, R'OH, by the above process, followed by hydrolysis of the anhydride **1**.

From the mechanistic side, a study of the modes of decomposition of **1** as a function of structure, nucleophiles present, and solvent and Lewis acids has given much useful information about carbonyl reactivity, nucleophilic reactivity, and the behavior of ion pairs. By suitable substitution the cleavage of **1** can be made to occur at C (in **1**), *i.e.*, with alkyl-oxygen cleavage, depending on the solvent and presence of catalysts. The study of analogs of **1**, such as **4**, **5** and **6**, has given further synthetically and mechanistically useful information.

(4) For leading references, see (a) D. B. Denney and N. Sherman, *J. Org. Chem.*, **30**, 3760 (1965); (b) F. D. Greene, *et al.*, *J. Am. Chem. Soc.*, **86**, 2080 (1964); (c) P. D. Bartlett and F. D. Greene, *ibid.*, **76**, 1088 (1954); (d) J. E. Leffler, *ibid.*, **72**, 67 (1950); (e) C. Walling, *et al.*, *ibid.*, **87**, 518 (1965).



Our work on the anhydrides has involved the following points: (1) a demonstration that in general they are stable compounds which can be obtained analytically pure; (2) a study of the products and mechanism of their decomposition as a function of structure and conditions; (3) a study of O-R' bond cleavage in the decomposition, and a comparison with the analogous thiol compounds **4**; (4) preparation of types **4**, **5**, and **6**, and the study particularly of **6**, from the synthetic and mechanistic side; (5) the preparation and study of crystalline tricarbonates derived from *t*-butyl mercaptan, *t*-butyl alcohol, and analogous compounds (**21** and **22** below).

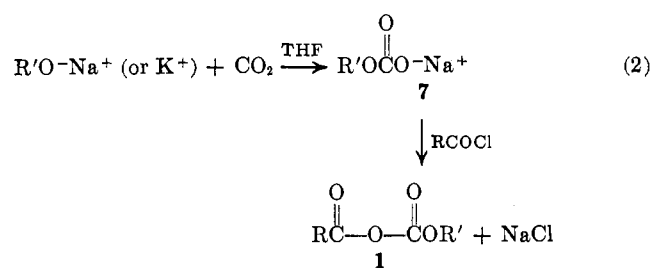
In our first isolation of a number of examples<sup>5</sup> of type **1**, they were prepared by eq 1, which has been the most common method of synthesis when the anhydrides were to be used *in situ*, with (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>N as the tertiary



amine. When R' is highly branched, and probably when R is also, it is advisable<sup>6</sup> to replace (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>N by an amine with smaller steric demand, such as N-methylpiperidine; presumably DABCO (diazabicyclo-[2.2.2]octane) would also be useful.

The carboxyl inversion reaction of diacyl peroxides (see above) is also available as a synthetic procedure, although it has not been much used to prepare carboxylic carbonic anhydrides as such.

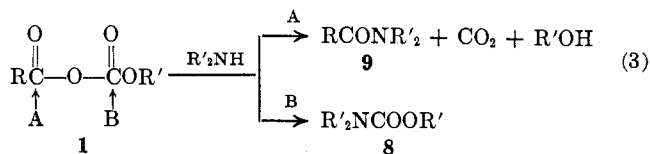
A very useful alternative procedure to eq 1 involves the carbonation of the alkoxide;<sup>7-13</sup> this is particularly



valuable when the corresponding chlorocarbonate is unstable, as with *t*-butyl alcohol<sup>7</sup> or *p*-methoxybenzyl alcohol.<sup>10</sup> It can be used with thiols<sup>9,12</sup> and with highly branched secondary alcohols.<sup>13</sup> The sodium

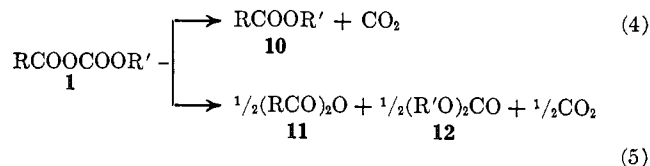
(or potassium) alkyl carbonates **7** can be converted to carbonic phosphoric anhydrides **6**.<sup>11,14</sup>

Turning to the action of nucleophiles on the anhydrides, it was found<sup>1,15</sup> that secondary amines could



form urethans **8** by attack at the carbonate carbonyl B, as well as amides **9** by attack at the carboxyl carbonyl A. Increasing the steric requirement around the amino nitrogen increased the ratio of urethan to amide.<sup>15</sup> If the amine was kept constant, increasing the branching in the R group increased the amount of urethan and decreased the amide.<sup>15</sup> Thus with the anhydride (CH<sub>3</sub>)<sub>3</sub>CCOOCOOC<sub>2</sub>H<sub>5</sub> and CH<sub>3</sub>NHC<sub>6</sub>H<sub>5</sub>, there was no amide formation, urethan being the sole product.<sup>15</sup>

It had been suggested,<sup>16</sup> although without any study



of pure compounds, that the carboxylic carbonic anhydrides could yield two types of transformation products: the ester **10** and CO<sub>2</sub> (eq 4), and the symmetrical acid anhydride **11** and the carbonate **12** (eq 5). Experiment has shown that both (4) and (5) do occur,<sup>6</sup> the relative proportions being found by isolation experiments and by determining the amount of CO<sub>2</sub> evolved; (4) requires 1 mol of CO<sub>2</sub>/mol of anhydride, and (5) requires 0.5 mol. In the absence of catalysts and accelerating solvents (such as dimethylformamide) the transformation requires temperatures around 150°, where R = C<sub>6</sub>H<sub>5</sub> or mesityl and R' = primary or secondary alkyl. Examination<sup>6</sup> of about ten such anhydrides showed that ester formation (eq 4) was favored when R' was secondary, or when R' was heavily substituted on the β carbon. Paths 4 and 5 occurred about equally when R' was a primary alkyl, such as methyl or ethyl.<sup>6</sup> With R' a benzyl or substituted benzyl group,<sup>10</sup> ester formation accounted for 80–90% of the material; similar results were obtained with the thiol anhydrides **4**, RCOOCOSR', when R = O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>-*p* and R' = *t*-butyl, benzyl, and isopropyl,<sup>17</sup> the main product here being the thiol ester RCOSR'.

It was found that when R was C<sub>6</sub>H<sub>5</sub> or mesityl, and R' was optically active *sec*-octyl, there was complete retention of configuration in both paths 4 and 5, even

(5) D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958).

(6) D. S. Tarbell and E. J. Longosz, *ibid.*, **24**, 774 (1959).

(7) C. J. Michejda and D. S. Tarbell, *ibid.*, **29**, 1168 (1964).

(8) Cf. L. A. Carpino, *J. Am. Chem. Soc.*, **82**, 2725 (1960).

(9) D. S. Tarbell and T. Parasaran, *J. Org. Chem.*, **29**, 2471 (1964).

(10) R. C. L. Chow and D. S. Tarbell, *ibid.*, **32**, 2188 (1967).

(11) D. S. Tarbell and M. A. Insalaco, *Proc. Natl. Acad. Sci. U. S. A.*, **57**, 235 (1967).

(12) A. Friederang and D. S. Tarbell, unpublished work, Vanderbilt University.

(13) S. Ebine and D. S. Tarbell, unpublished work, Vanderbilt University.

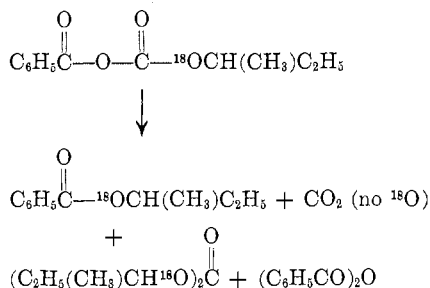
(14) A. A. Shamshurin, *et al.*, *Z. Obshch. Khim.*, **35**, 1877 (1965); *Chem. Abstr.*, **64**, 1945 (1966).

(15) N. A. Leister and D. S. Tarbell, *J. Org. Chem.*, **23**, 1152 (1958).

(16) A. Einhorn, *Ber.*, **42**, 2772 (1909); T. Wieland and H. Bernard, *Ann.*, **572**, 190 (1951).

(17) L. Wei and D. S. Tarbell, *J. Org. Chem.*, **33**, 1884 (1968).

when the reaction was carried out in boiling pyridine.<sup>6,18</sup> This strongly indicated, although it did not prove, that when R' was secondary alkyl there was no cleavage of the O-R' bond in the decomposition of the anhydride **1** via paths 4 and 5. The point was settled conclusively by an <sup>18</sup>O-labeling experiment as shown below.<sup>19</sup> All of the <sup>18</sup>O was found in the alcohol portion of the *sec*-butyl benzoate and the *sec*-butyl carbonate.



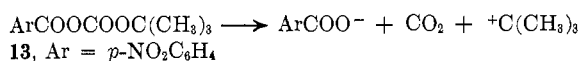
The *t*-butyl carbonic anhydride **13**, prepared best by the *t*-butyl carbonate procedure<sup>7</sup> (eq 2), was found to decompose rapidly at its melting point (*ca.* 100°) to give the products indicated in Table I. These products

Table I  
Products of Decomposition of ArCOOCOC(CH<sub>3</sub>)<sub>3</sub><sup>a,b</sup> at 100°

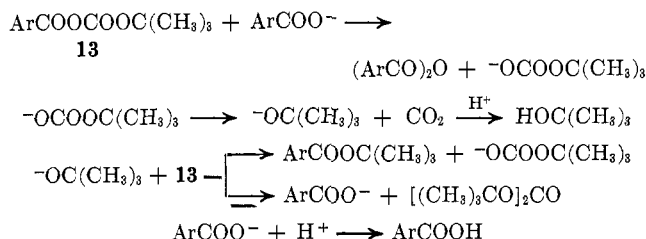
Product	Yield, %	Number of runs
CO <sub>2</sub>	90 ± 5	12
CH <sub>2</sub> =C(CH <sub>3</sub> ) <sub>2</sub>	61 ± 4	7
(ArCO) <sub>2</sub> O	52-84	4
ArCOOH	7-34	4
ArCOOC(CH <sub>3</sub> ) <sub>3</sub>	2-9	4
(CH <sub>3</sub> ) <sub>3</sub> COH	23-28	2
[(CH <sub>3</sub> ) <sub>3</sub> CO] <sub>2</sub> CO	6-12	2

<sup>a</sup> Ar = *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>. <sup>b</sup> This formula is incorrectly written in the table in ref 7.

are best explained by a cleavage to form a *t*-butyl carbonium ion, which loses a proton to form isobutylene. The *p*-nitrobenzoate ion can then react with the

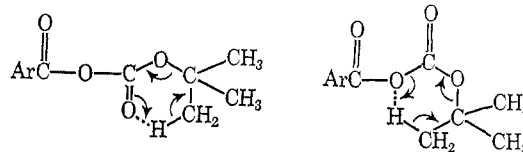


unchanged mixed anhydride, leading to the other products as shown below.

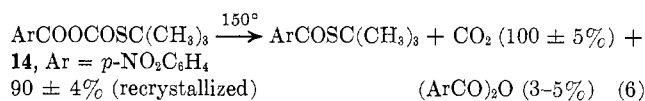


The yield of isobutylene indicates that the decomposition of the mixed anhydride **13** thus proceeds mainly by alkyl-oxygen cleavage. This mode of decomposition is probably the direct result of the stability of the *t*-butyl carbonium ion. The possibility that the alkyl-oxygen cleavage involves transition states such as those below cannot be excluded on the present

evidence; a kinetic study on this system has not yet been carried out.



The behavior of the thiol analog **14** is completely different from that of **13**; there is no measurable amount of sulfur-acyl cleavage, no COS can be detected by the mass spectrometer, and the conversion to the thiol ester requires a temperature of about 150°. This behavior emphasizes the complete failure of *t*-butyl thiol compounds to generate *t*-butyl carbonium ions, compared to their oxygen analogs; many examples of this are known.<sup>7,9</sup> A detailed ki-

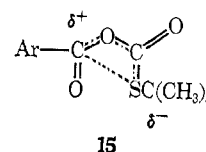


netic study of this reaction, which was readily followed by quantitative infrared measurements,<sup>20</sup> gave, among others, the following results: the rate of reaction 6 was increased by the presence of nucleophiles, such as halide ions and tertiary amines, but the yield of thiol ester and CO<sub>2</sub> was not appreciably affected. The effects of changes in solvent on the rate, and the activation parameters, are given in Table II.

Table II  
Decomposition of ArCOOCOSC(CH<sub>3</sub>)<sub>3</sub> (Eq 6) in Three Solvents

Solvent	Dielectric constant	Relative rate at 140.7°	ΔH <sup>‡</sup> , kcal/mol	ΔS <sup>‡</sup> , eu
Decalin	2.0	1	30.0 ± 0.5	-7.0 ± 0.9
<i>o</i> -Dichlorobenzene	9.9	2	30.3 ± 0.5	-5.1 ± 1.1
Benzonitrile	25.1	4	22.0 ± 0.5	-23.9 ± 1.1

The lack of a striking change in rate with increasing polarity of the solvent indicates that the decomposition does not involve a high degree of ion-pair formation in the transition state<sup>21</sup> and that the transition state may be represented as in **15**. In the more polar solvent



benzonitrile, the anhydride may exist in various solvated conformations quite different from the quasi ring from which the transition state **15** is derived; therefore, a relatively large loss of degrees of freedom would occur in going from the ground state to the transition state **15**. There is a notable change in activation parameters, which very nearly counteract each other, in going from decalin to benzonitrile.

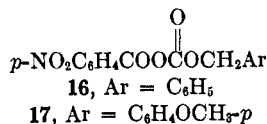
(18) E. J. Longosz and D. S. Tarbell, *J. Org. Chem.*, **26**, 2161 (1961).

(19) C. J. Michejda, D. S. Tarbell, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **84**, 4113 (1962).

(20) Cf. P. D. Bartlett and R. R. Hiatt, *ibid.*, **80**, 1398 (1958).

(21) Cf. D. J. Cram, *ibid.*, **75**, 332 (1953); K. B. Wiberg and T. B. Shryne, *ibid.*, **77**, 2774 (1955); and other papers cited in ref 17 above.

One might anticipate O-benzyl cleavage in benzyl-carbonic anhydrides such as **16**, due to the stabilization of a benzyl carbonium ion. Actually, an  $^{18}\text{O}$  study<sup>10</sup> showed that the benzylcarbonic anhydride **16** gave no O-benzyl cleavage under any conditions investigated; the *p*-methoxybenzyl compound **17** gave a high degree



of O-benzyl cleavage at higher temperatures, but only small amounts at room temperature, particularly in DMF or *o*-dichlorobenzene in the presence of DABCO, which is an active catalyst for the decomposition. The ester was the main product of decomposition. An experiment showed that there was no scrambling of the label by a dissociation-recombination<sup>22</sup> of the labeled anhydride **17**.

The *p*-methoxybenzylcarbonic anhydride **17** was suitable for a detailed kinetic study of ester formation,<sup>10</sup> the significant results of which are given in Table III. The rates gave linear first-order plots over

**Table III**  
Conversion of  $p\text{-NO}_2\text{C}_6\text{H}_4\text{COOCCH}_2\text{C}_6\text{H}_4\text{OCH}_3\text{-}p$  to  $p\text{-NO}_2\text{C}_6\text{H}_4\text{COOCH}_2\text{C}_6\text{H}_4\text{OCH}_3\text{-}p + \text{CO}_2$

A. Activation Parameters

Solvent	$\Delta H^\ddagger$ , kcal/mol	$\Delta S^\ddagger$ , eu
DMF	$15.0 \pm 0.3$	$-28.7 \pm 0.8$
<i>o</i> -Dichlorobenzene	$18.7 \pm 0.6$	$-24.7 \pm 1.7$

B. Effect of Added Nucleophiles in DMF at 32.0°

Additive	Mole %	Relative rate
None <sup>a</sup>		1.0
DABCO	0.4	2.5
	1.0	4.2
	2.0	9.0
	5.0	28.3
$\text{C}_6\text{H}_5\text{COONa}$	0.1	1.9
	0.5	3.5
	2.5	13.8
$\text{N}(\text{C}_2\text{H}_5)_3$	9.7	2.3
Imidazole	10	0.7
$\text{N}(\text{CH}_3)_4\text{Cl}$	1.5	1.5
	10	3.2
$\text{N}(\text{CH}_3)_4\text{Br}$	10	2.6
$\text{N}(\text{CH}_3)_4\text{I}$	10	2.2
LiCl	10	3.7

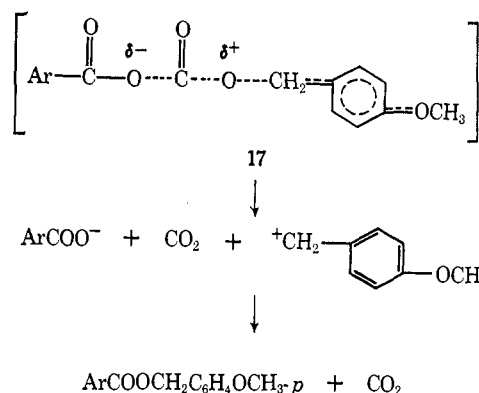
<sup>a</sup> Initial concentration of mixed anhydride was 0.07 M.

50–75% of the reaction course, the rate increasing at higher per cent of reaction. The yield of  $\text{CO}_2$  in DMF was similar to that in the absence of solvent ( $90 \pm 5\%$ ); the rate was reproducible, and the first-order rate constant was not changed by a twofold change in concentration. The  $^{18}\text{O}$ -labeling studies showed that in DMF at room temperature there was an average of 12% O-benzyl cleavage, and that in DMF + DABCO at room temperature there was 5% O-benzyl

cleavage. It should be mentioned that, as in an earlier kinetic study,<sup>18</sup> when a solution in which one decomposition had been run was used as solvent for a second run, the rate of the second decomposition was about twice that of the first. The product,  $p\text{-NO}_2\text{-C}_6\text{H}_4\text{COOCH}_2\text{C}_6\text{H}_4\text{OCH}_3\text{-}p$ , exhibited a slight positive catalytic effect on the rate, but not enough to account for the rate increase in the reused solution.

Pyrazine,  $\text{SbF}_3$ , HCl, and  $\text{LiClO}_4$  showed no catalytic effect on the rate, probably because the first three were too firmly bound to the DMF, and the  $\text{LiClO}_4$  has no nucleophilic properties. The differences in catalytic activity between the tetramethylammonium halides are not large, but are beyond experimental error and are in the order expected for nucleophilic activity in aprotic solvents.<sup>23</sup> The greater effectiveness of lithium chloride as compared to tetramethylammonium chloride is probably due to the more effective solvation of the lithium ion by DMF.<sup>24</sup>

The large negative  $\Delta S^\ddagger$  for the reaction in *o*-dichlorobenzene and the  $^{18}\text{O}$  results showing a high per cent of O-benzyl cleavage in this solvent indicate a mechanism in which the transition state shown below is involved. Such a mechanism is not applicable to the DMF reactions, where there is only little O-benzyl cleavage; the latter process must involve the ionic chain reactions discussed below.



It appears to be necessary to consider two general types of mechanism for the conversion of the carboxylic carbonic anhydrides to ester (eq 4) and to symmetrical anhydrides and carbonates (eq 5). The first mechanism is the cyclic transition state to form ester, of which **15** is one example. A similar four-membered transition state can be written for the oxygen analogs of **15**, and a six-ring transition state is also possible, particularly where alkyl-oxygen cleavage is observed. It has been shown that in the presence of strong Lewis acids, such as  $\text{BF}_3$ <sup>25</sup> or  $\text{SbCl}_5$ ,<sup>26</sup> high yields of ester are obtained in a very rapid reaction, which is best rationalized by a transition state such as **18**.

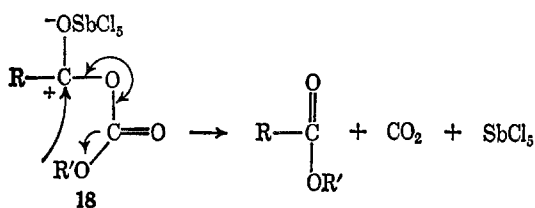
(23) Cf. A. J. Parker, *J. Chem. Soc.*, 1328 (1961); S. Winstein, *et al.*, *Tetrahedron Letters*, No. 9, 24 (1960).

(24) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Am. Chem. Soc.*, 82, 2895 (1960).

(25) T. B. Windholz, *J. Org. Chem.*, 25, 1703 (1960).

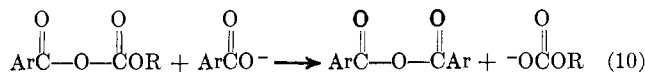
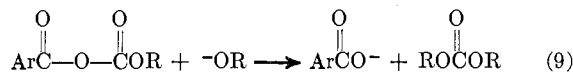
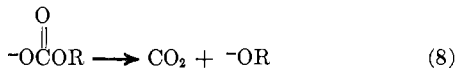
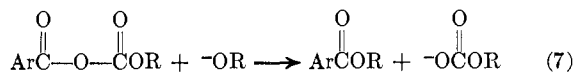
(26) D. Z. Denney, T. M. Valega, and D. B. Denney, *J. Am. Chem. Soc.*, 86, 46 (1964).

(22) Cf. H. L. Goering, M. M. Pombo, and K. D. McMichael, *J. Am. Chem. Soc.*, 85, 965 (1963), and earlier papers.



Observations<sup>18</sup> on the kinetics and product ratios from the decomposition of benzoic *n*-butylcarbonic anhydride, which gives 70–75% of CO<sub>2</sub> (40–50% of *n*-butyl benzoate) with the remainder going to dibutyl carbonate and benzoic anhydride (eq 4 and 5), require a different explanation, which probably also obtains in other cases of the mixed anhydride in eq 7, when R is primary or secondary alkyl. It was found that the product ratio was unchanged by dilution, by the presence of catalysts, and by changes in temperature and solvent, and that the molar amounts of dibutyl carbonate and benzoic anhydride were equal.

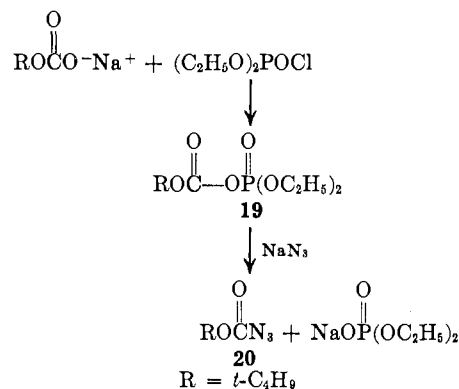
These results are in agreement with the suggestion<sup>18</sup> that the decomposition proceeds by an ionic chain reaction involving alkoxide ion (–OR) as the chain carrier; this could be generated by the action of a nucleophile on the mixed anhydride. The carboxylate ion, shown attacking the carboxyl carbonyl in eq 10,



can attack at the carbonate carbonyl, but this leads to no over-all change. The formation of ester is due to reaction 7, and the disproportionation reaction to form the dialkyl carbonate and the symmetrical anhydride is the result of eq 9, followed by eq 10. The alkylcarbonate anion generated in (10) decomposes according to (8).

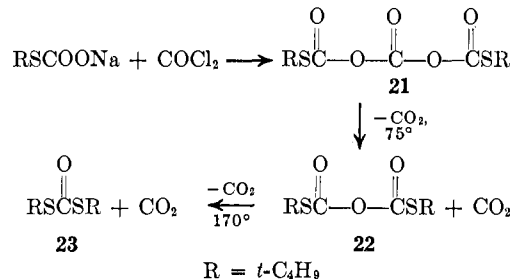
As mentioned briefly above, carbonic phosphoric anhydrides can be readily prepared by treatment of sodium alkyl carbonates with phosphochloridates.<sup>11–14</sup> The anhydride **19** reacts with nucleophiles mainly at the carbonate carbonyl and can be used to introduce the *t*-butoxycarbonyl group on amines;<sup>11</sup> treatment with sodium azide leads to a satisfactory synthesis of *t*-butoxycarbonyl azide<sup>27</sup> (**20**).

The thermal and photochemical behavior of car-

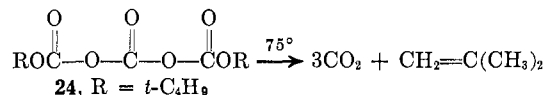


boxylic dithiocarbamic anhydrides **5** has been investigated.<sup>28</sup>

Recent studies in this laboratory have shown that sodium *t*-butyl thiolcarbonate is converted by phosgene to the crystalline tricarbonate<sup>29</sup> **21**; this decomposes with loss of CO<sub>2</sub> to the dicarbonate **22**, and this at a higher temperature loses CO<sub>2</sub> to form the carbonate **23**. By similar procedures, the tricarbonate **24** has been



obtained;<sup>30</sup> this has been found in quantitative experiments to yield, when heated above the melting point, the products shown below. The products must arise from the *t*-butyl carbonium ion, emphasizing again the



difference between O-*t*-C<sub>4</sub>H<sub>9</sub> and S-*t*-C<sub>4</sub>H<sub>9</sub> analogs.

There are numerous unsolved problems posed by the behavior of the mixed anhydrides such as **1**, **4**, **5**, **6**, and related types containing other hetero atoms which we hope to investigate more completely. The tricarbonates **21**, **24**, and related compounds offer a number of problems of mechanistic and preparative interest.

*I wish to express my appreciation to the National Science Foundation for support of research in this field, first at the University of Rochester and later at Vanderbilt University.*

(28) D. S. Tarbell and R. P. F. Scharrer, *J. Org. Chem.*, **27**, 1972 (1962); E. H. Hoffmeister and D. S. Tarbell, *Tetrahedron*, **21**, 35, 2857, 2865 (1965).

(29) A. W. Friederang and D. S. Tarbell, *Tetrahedron Letters*, 5535 (1968).

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*Additions and Corrections*

Volume 2, 1969

**D. Stanley Tarbell:** The Carboxylic Carbonic Anhydrides and Related Compounds.

Page 300. In the last equation, "+ ROH" should be added to the right-hand side.