lated as described for the earlier kinetic runs.[2] From each experiment an aliquot derived from 5.0 mg of tosylate was removed, freed of solvent as before,[2] and analyzed in the ir by measuring its absorbances at 813, 781, and 687 cm^{-1}. Mean tosylate fractions remaining after 10 and 20 min were calculated and are given in Table II. The remainders of each sample were processed as follows.

A. 10-Min Run.—A solution in 0.5 ml of acetone was applied to a column (110 × 10 mm) of silica gel which was packed as a suspension in the upper phase of ligroin (bp 88–90°), methanol, and water (10:9:1). The silica gel used had been thoroughly washed with water, dried to constant weight by exposure to air, and then hydrated (silica–water, 3:1).[35] Elution with the same upper phase was completed within 30 min. Fraction 4 (1 ml) was 6.0 mg. Fractions 5 (1 ml, 4.7 mg) and 6 (5 ml, 4.4 mg), which were essentially tosylate, were combined and recrystallized until N_2/N_1 of crystals (0.559) and last mother liquor agreed (Δ 1%). Fraction 4 was diluted with 8.2 mg of unlabeled tosylate and recrystallized to give N_2/N_1 0.553 (Δ 0.5%).

B. 20-Min Run.—As the data presented under A showed that even samples high in product could be recrystallized to give pure tosylate, the material remaining from B (15.6 mg) was mixed with 25 mg of unlabeled tosylate and recrystallized until $\Delta N_2/N_1$ was 0.7%.

C. 212-Min Run.—No tosylate remained as even the tritiated component had formolyzed for >10 half lives. This sample (N_2/N_1 0.693 as compared to 0.694 for the starting material) was, therefore, fractionated as described for the products of **9c**. To avoid any possible fractionation of the two radioactive components of any compound by chromatography, incompletely separated fractions were mixed with cold carriers and again subjected to the separation procedure. The 5α-pregn-20-en-3β-ol needed for this purpose was prepared by the method of Barton.[36] The chromatographically separated olefins were recrystallized as the 3β-ols, and the formates were recrystallized as such, hydrolyzed, recrystallized, acetylated, and recrystallized. The percentage differences in N_2/N_1 between final crystals and their mother liquors are given in Table I.

Dynamic State of 17β-Methyl-18-nor-5α,17α-pregn-13-en-3β-yl Acetate (2b) in Formolysis Medium.—A mixture of 0.66 ml of tritiated water (66 mCi) with 110 ml of dry formic acid was used to prepare solutions as follows: (a) 3β-acetoxy-5α-pregnan-20α-yl tosylate (**1b**), 25 mg in 0.6 ml of benzene and 50 ml of formic acid-^3H; (b) (*Z*)-5α-pregn-17-en-3β-yl acetate (**8b**), 12 mg in 0.3 ml of benzene, 6.0 mg of *p*-toluenesulfonic acid monohydrate, and 36 ml of formic acid-^3H; (c) 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (**2b**) in the same medium and in the same concentration as b. All stood for 150 min at 25.0°. The 3β-hydroxy-Δ^{13} olefin was isolated from all runs by the usual procedures (except that chromatography was omitted from run b). The recrystallized products (mp 130–132°) had in channel 1 the following cpm/mg; (a) 2520, (b) 4210, and (c) 2870. In run a the fraction of **2b** available for exchange during the whole reaction period/total **2b** formed was 0.89 (= $1 - 1/kt$, eq 14[12]), while (cpm/mg from a)/(cpm/mg from c) was 0.88.

Registry No.—**2a**, 33299-99-9; **2b**, 33300-00-4; **3b**, 37705-53-6; **4b**, 37759-63-0; **5b**, 22831-64-7; **8a**, 1159-24-6; **8b**, 1167-32-4; **9b**, 37759-67-4; **9c**, 37759-68-5; **9d**, 37759-69-6; **9e**, 33299-98-8; **9g**, 37759-71-0; 3β-hydroxy-5-pregnen-20-one 145-13-1.

Acknowledgment.—The authors wish to thank Mr. Clarence Gust for the nmr spectra reported in this paper.

(35) The ratio of water to silica had to be within narrow limits to prevent destruction and still allow separation. The optimal amount of water may not be the same for all batches of silica.

(36) D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 470 (1962); A. M. Krubiner, N. Gottfried, and E. P. Oliveto, *J. Org. Chem.*, **34**, 3502 (1969).

Lactonization of Methyl *o*-Formylbenzoate by Secondary Amines

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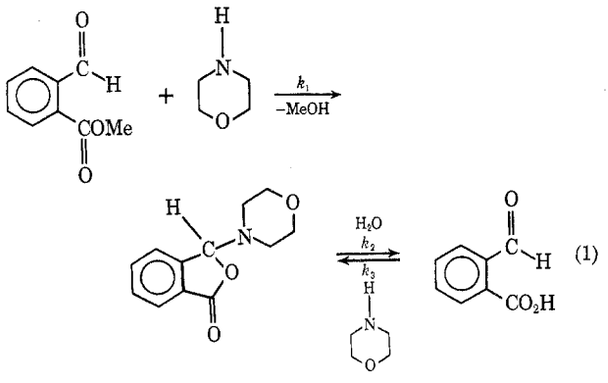
The unusual stability in dioxane of lactones formed by the reactions of MOFB with amines permitted a kinetic study of the effect of amine structure on the course of the reaction. While many classes of amines effected the reaction, the reactions of cyclic secondary amines were especially fast. The second-order rate constants for these fast reactions at 21° were dependent on ring size (pyrrolidine, 34.0 m^{-1} sec^{-1}; piperidine, 27.5; 1*H*-hexahydroazepine, <1), on ring substituents (4-pipecoline, 30.0; 3-pipecoline, 22.5; 2-pipecoline, <1; 2,6-dimethylpiperidine, 2-ethylpiperidine, and 2,6-dimethylpyrrolidine did not react), and on ring heteroatoms (piperazine, 468; 1 methylpiperazine, 7.4; morpholine, 3.7; 1,4-dimethylpiperazine did not react). With the exception of piperazine, the second-order rate constants at 25° paralleled the pK_B values according to the Brønsted relation $\log k_2 = 0.33 \log K_B + 2.39$. Thermodynamic activation parameters at 25° are given for some of the compounds.

The mechanism of ortho carbonyl group participation in the hydrolysis of methyl benzoates has in recent years received a great deal of attention.[1,2] The most extensively studied system involves the amine-assisted hydrolysis of methyl *o*-formylbenzoate.[3,4] The proposed mechanism (eq 1) for the hydrolysis of the ortho-substituted esters accounts for the enormous rate enhancement over the meta and para ester analogs.



(1)

The purpose of this investigation was to attempt to determine some of the structural requirements of the amine nucleophile which promote the rapid formation of the intermediate complex as shown in eq 1. Preliminary work with nonaqueous solvents showed that the intermediate, which quickly hydrolyzed in water, remained quite stable for periods of 24 hr or longer in dioxane solvent. Therefore, the work described below

(1) M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, **84**, 4589 (1962).
(2) M. S. Newman and A. L. Leegwater, *ibid.*, **90**, 4410 (1968).
(3) M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *ibid.*, **87**, 4545 (1965).
(4) G. Dahlgren and D. M. Schell, *J. Org. Chem.*, **32**, 3200 (1967).

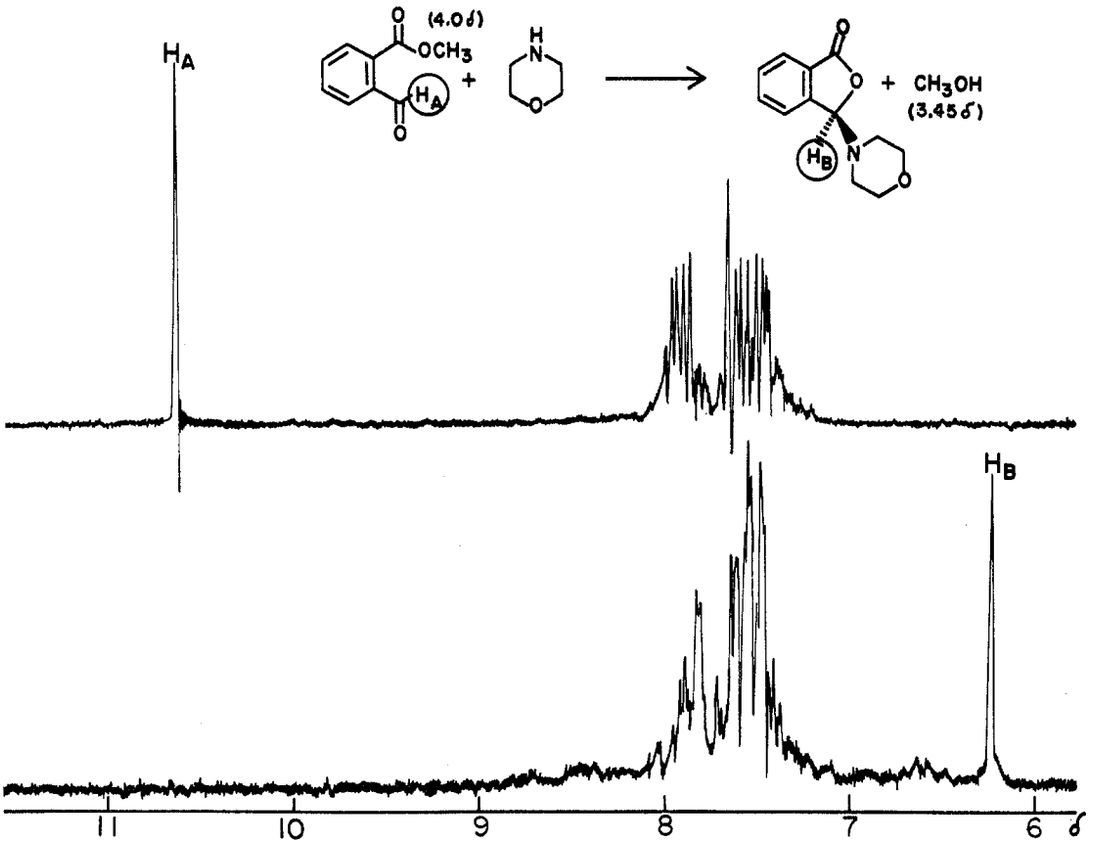


Figure 1.—Pmr spectra for lactonization of MOFB by morpholine. Upper curve represents the reactants and lower curve the products.

was done in dry dioxane solvent and involves only the formation of the lactone, as shown in the first step of eq 1.

Experimental Section

Materials. Methyl o-Formylbenzoate (MOFB) was prepared by the method of Bender and coworkers[8] using ethereal diazomethane and phthaldehydic acid (Aldrich Chemical). The MOFB product was a slightly yellow liquid and had a melting point of 14° (lit.[5] mp 14°) and boiling point of 134–135° (12 mm) [lit.[4] bp 135–136° (12 mm)]. The ir spectrum of the product showed two carbonyl stretching frequencies at 1703 and 1727 cm^{-1} in agreement with the infrared assignments of Bowden and Taylor.[6]

In some preparations the MOFB was observed to be contaminated by its pseudo ester (3-methoxyphthalide), most of which could be removed by partial liquification of the frozen sample.[3] After purification the MOFB was found to contain less than 1% pseudo ester by ir and pmr techniques.

The amines used in this study were the highest grade available and were double distilled from potassium hydroxide solutions and in the case of aromatic amines from solutions containing zinc dust[7] just prior to use.

The 1,4-*p*-dioxane solvent used in this study was prepared by the method of Fieser and Fieser.[8] Dioxane not immediately used was frozen and stored as a solid. All ultraviolet spectra were done on a Cary 14 spectrophotometer and the pmr data were obtained on a Bruker 90 spectrometer.

Kinetic Procedure.—The rate of lactonization was followed by observing the disappearance of MOFB in the region of 285 nm on a Durrum D150/D131 stopped flow/temperature jump spectrophotometer, interfaced with an AD4/IBM 1130 hybrid computer.[9] Pseudo-first-order kinetic conditions were applied throughout using a 200- to 1000-fold excess amine over MOFB concentration. The pseudo-first-order rate constants, k_0, were determined using computer averaging of at least eight individual runs. We also calculated a grand k_0 obtained by treating all of the individual accumulated points as a single run. Invariably, the average k_0 and the grand k_0 were the same within experimental error. In all cases the correlation coefficient for the least squares fit on the individual runs was at least 0.999 (<1% standard deviation on k_0). The second-order rate constants were obtained from a plot of the pseudo-first-order rate constants *vs.* the molality of the excess amine nucleophile.

(5) K. V. Auwers and A. Heinze, *Ber.*, **52B**, 595 (1919).
(6) K. Bowden and G. R. Taylor, *J. Chem. Soc. B*, 1395 (1971).
(7) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 1276.
(8) Reference 7, p 333.
(9) The details of this interfacing will appear in a subsequent paper.

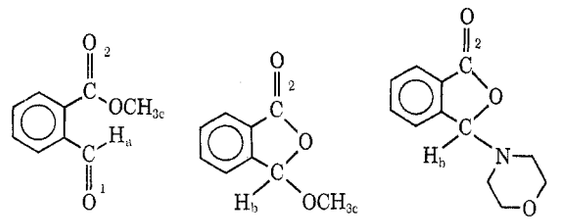
Results and Discussion

The addition of morpholine to MOFB, as observed by pmr, results in the loss of the aldehydic proton (H_A) and the appearance of the methinyl proton (H_B) (Figure 1). Equivalent changes in the infrared spectra can also be observed. The MOFB infrared spectrum is characterized by two carbonyl stretching frequencies, one at 1727 cm^{-1} for the ester carbonyl group and the other at 1703 cm^{-1} for the aldehydic carbonyl group. Morpholine addition results in the loss of both of these absorptions and is accompanied by the appearance of a new carbonyl stretch at 1780 cm^{-1}. A comparison (Table I) of the pmr and ir spectra of MOFB, the reaction product, and the pseudo ester (3-morpholinophthalide) shows that the morpholine addition has effected lactonization. Amines other than secondary cyclic showed no evidence of lactonization over the time scale of the test (reaction half-lives in the second to millisecond range). A summary of the amines studied in this work is given in Table II.

The lactonization rate was found to be sensitive to a variety of parameters related to the structure of the cyclic secondary amine. An increase in ring size

TABLE I

PMR AND IR DATA ON MOFB (I), 3-MORPHOLINOPHTHALIDE (II), AND MOFB–AMINE ADDITION PRODUCT (III)



I II III

	I	II	III
H_a, δ	10.4		
H_b, δ		6.3	6.2
H_c, δ	3.9	3.6	
C=O 1, cm^{-1}	1703		
C=O 2, cm^{-1}	1727	1780	1780

TABLE II

AMINE REACTIVITY IN LACTONIZATION OF MOFB IN DIOXANE AT 21°

Reactive	Nonreactive
1*H*-Hexahydroazepine	Aniline
2,5-Dimethylpyrrolidine	Butylamine
2-Pipecoline	Cyclohexylamine
3-Pipecoline	Diethylamine
4-Pipecoline	2,6-Dimethylaniline
Morpholine	2-Ethylpiperidine
Piperazine	*N*-Methylaniline
1-Methylpiperazine	*N*-Methylcyclohexylamine
Piperidine	Pyridine
Pyrrolidine	Pyrolle
	1,4-Dimethylpiperazine

from pyrrolidine (5) to 1*H*-hexahydroazepine (7) caused a 30-fold rate decrease (Table III). This behavior is consistent with the idea that the inactivity of the aliphatic secondary amines as lactonization nucleophiles is due to steric restriction at the lone pair of the nitrogen. In general, as ring size increases, the –C–N–C– bond angle increases, thereby presenting a steric inhibition to complex formation of the amine nitrogen lone pair electrons and the electron-deficient carbon of the MOFB carbonyl group. However, the modest change in rate in going from pyrrolidine to piperidine and the substantial rate change from piperidine to 1*H*-hexahydroazepine contradicts this simple structural interpretation of the rate behavior.

TABLE III

SECOND-ORDER RATE CONSTANTS FOR THE LACTONIZATION OF MOFB BY SECONDARY CYCLIC AMINES OF INCREASING RING SIZE[a]

Amine	Ring size	k_2, mol^{-1} sec^{-1}[b]
Pyrrolidine	5	34.0 ± 1.0
Piperidine	6	27.5 ± 0.6
1*H*-Hexahydroazepine	7	<1

[a] Dioxane solvent at 21°. [b] Obtained from plots of pseudo-first-order constants *vs.* molality of amine.

A similar rate reduction is observed when a methyl group is moved from the 4 to the 3 to the 2 position in the six-membered ring amine nucleophile (see Table IV). The modest rate constant differences observed in moving a methyl group from the 3 to the 4 position of the piperidine ring system (3-pipecoline and 4-pipecoline) is not considered significant. However, the lactonization rate reduction observed when a methyl group is placed in the 2 position (2-pipecoline), and the complete lack of reaction when an ethyl group is substituted for the methyl group in the 2 position (2-ethylpiperidine) and when 2 methyl groups are placed in the 2 and 6 position (2,6-dimethylpiperidine) lend support to the idea that the nitrogen lone-pair electrons are participating in the rate-determining step. Additional support was given to this notion when we examined 2,5-dimethylpyrrolidine as a lactonization nucleophile and again found no immediate reaction. However, on standing for 8 hr the MOFB was converted to the lactone. We may infer that on long standing, the 2,6-dimethylpiperidine would also effect the reaction, as would 2-pipecoline and 2-ethylpiperidine.

TABLE IV

SECOND-ORDER RATE CONSTANTS FOR THE LACTONIZATION OF MOFB BY SUBSTITUTED SECONDARY CYCLIC AMINES[a]

Amine	k_2, mol^{-1} sec^{-1}
Piperidine	27.5 ± 0.6
4-Pipecoline	30.0 ± 2.0
3-Pipecoline	22.5 ± 0.9
2-Pipecoline	<1
2,5-Dimethylpyrrolidine	*b*
2-Ethylpiperidine	*b*
2,6-Dimethylpiperidine	*b*

[a] Dioxane solvent, 21°. [b] No reaction in the millisecond to second range. Lactonization effected in 4–8 hr.

The rate of lactonization was also observed to vary as a function of the 4 heteroatom in the piperidine ring structure. In the series piperidine (–CH_2– in the 4 position), morpholine (–O–), piperazine (–NH–), 1-methylpiperazine (–NCH_3–), and 1,4-dimethylpiperazine the second-order rate constants were observed to vary over a factor of 100 (Table V). The most surprising result is the large second-order constant for piperazine. This effect was at first thought to be the result of the 5% methanol–dioxane used as the solvent rather than pure dioxane (piperazine is only very slightly soluble in dioxane). However, subsequent examination of piperidine and morpholine lactonizations in 5% methanol–dioxane gave rate constants identical with those found in pure dioxane. In these latter cases the intercept (k_s) of the first-order rate constant *vs.* molality curves, which should be the origin, did decrease in the same manner as was observed in the piperazine case. The change of intercept with change in solvent composition will be more fully examined in subsequent work.

TABLE V

SECOND-ORDER RATE CONSTANTS FOR THE LACTONIZATION OF MOFB BY RING-SUBSTITUTED CYCLIC SECONDARY AMINES[a]

Amine	k_2, mol^{-1} sec^{-1}
Piperazine	468[b] ± 9
Piperidine	27.5 ± 0.6
1-Methylpiperazine	7.4 ± 0.3
Morpholine	3.7[c] ± 0.1
1,4-Dimethylpiperazine	*d*

[a] Dioxane at 21° except piperazine, where 5% MeOH/dioxane was used. [b] Statistical correction of 2 not made. [c] Reference 3 reports a value of 11 ± 1 M^{-1} sec^{-1} in aqueous media. [d] No reaction.

The unusual rate enhancement with piperazine was observed in aqueous solution earlier by Dahlgren and Schell.[4] In that study piperazine was a factor of 665 more effective a catalyst for the complete hydrolysis of MOFB than morpholine. In the present lactonization study the second-order rate constant for piperazine is a factor of 126 larger than that for morpholine or one-half of that if we make the statistical correction for the second amine group of piperazine.

Standard equations were used to determine the activation parameters over the temperature range 21–39° and the results are recorded in Table VI. It

TABLE VI
THERMODYNAMIC FUNCTIONS OF ACTIVATION FOR THE LACTONIZATION OF MOFB BY SELECT CYCLIC SECONDARY AMINES[a]

Amine	$\Delta H^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
Morpholine	1.6 ± 0.2	2.8 ± 0.1	15 ± 1
Piperazine	1.2 ± 0.1[b]	2.58 ± 0.07	12.6 ± 0.6
1-Methylpiperazine	1.7 ± 0.3	3.0 ± 0.1	16 ± 2

[a] Dioxane at 21° except for piperazine where 5% MeOH/dioxane was used. [b] Reference 4 reports a value of 1.3 ± 0.1 kcal/mol in aqueous media.

is interesting to note that the enthalpy of activation determined for the piperazine-catalyzed lactonization of MOFB in dioxane is essentially the same as that for the piperazine-catalyzed hydrolysis of MOFB in water.[4]

Finally, where pK_B values were available the second-order rate constants and the pK_B's were found to obey the Brønsted relation (eq 2). That is, in the case of

$$\log k_2 = 0.33\ (\pm 0.02) \log K_B + 2.39\ (\pm 0.07) \qquad (2)$$

pyrrolidine (pK_B = 2.695),[10] piperidine (2.877),[10] 1-methylpiperazine (4.50),[11] and morpholine (5.64),[12] the rate of nucleophile attack on the carbonyl carbon of the aldehyde function of MOFB parallels the affinity of the nucleophile for the protons of water. However, piperazine (pK_B = 4.21),[10] whose second-order rate constant according to eq 2, should equal 10.2 l. mol^{-1} sec^{-1}, actually gave an observed value of 500 l. mol^{-1} sec^{-1} at 25°. It is this latter observation which has piqued our curiosity and led us to preparing bicyclic systems containing the piperazine geometry but preventing participation by the second amine group in, perhaps, a proton abstraction role.

Registry No.—I, 4122-56-9; II, 4122-57-0; III, 4195-21-5; pyrrolidine, 123-75-1; piperidine, 110-89-4; 1*H*-hexahydroazepine, 111-49-9; 4-pipecoline, 626-58-4; 3-pipecoline, 626-56-2; 2-pipecoline, 109-05-7; piperazine, 110-85-6; 1-methylpiperazine, 109-01-3; morpholine, 110-91-8.

(10) D. D. Perrin, *Aust. J. Chem.*, **17**, 484 (1964).
(11) F. Erb and N. Garot, *Bull. Soc. Pharm. Lille*, **1**, 59 (1964).
(12) H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956).

Thermal Decomposition of Benzyl Triphenylacetate and Benzyl Diphenyl-*p*-tolylacetate. The Possibility of 1,4-Aryl Migration and α-Lactone Formation[1a,b]

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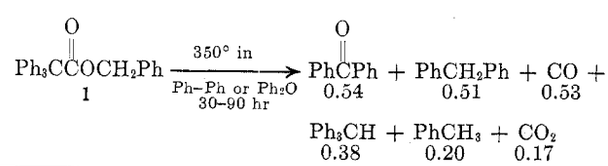
The thermal decomposition of benzyl triphenylacetate at 350° for 30–90 hr in the liquid phase gives 0.54, 0.51, and 0.53 mol/mol ester of benzophenone, diphenylmethane, and carbon monoxide, respectively, in addition to 0.38, 0.20, and 0.17 mol/mol ester of triphenylmethane, toluene, and carbon dioxide, respectively. The thermal decomposition of benzyl diphenyl-*p*-tolylacetate under comparable conditions for 30 hr gives 0.29, 0.27, 0.15, and 0.34 mol/mol ester of benzophenone, phenyl-*p*-tolylmethane, *p*-methylbenzophenone, and diphenylmethane, respectively, plus 0.30 mol/mol ester of diphenyl-*p*-tolylmethane. A mechanism is proposed for the formation of the arylphenylmethanes and benzophenones which involves a 1,4-aryl migration to produce the arylphenylmethane and α-lactone which rapidly decarbonylates to give the benzophenone.

The thermal decomposition of benzyl triphenylacetate (**1**) at 350° in biphenyl or diphenyl ether (*ca.* 15% **1** in solution) for 30–90 hr in a sealed tube gives rise to fairly high and approximately equal yields of benzophenone, diphenylmethane, and carbon monoxide in addition to triphenylmethane, toluene, and carbon dioxide (throughout this paper yields are given in mol/mol ester unless otherwise indicated).



Yields were determined by glpc and nmr analyses and are averages of 6–8 runs. The use of biphenyl or diphenyl ether as solvent made no significant difference. In fact, the pyrolysis of a neat sample of **1** for 5 hr at 350° gave 0.52, 0.46, and 0.25 mol/mol ester of benzophenone, diphenylmethane, and triphenylmethane, respectively. The gaseous products were collected and determined as described previously.[2]

Ester **1** was reported[3] to decompose at its boiling point to give triphenylmethane, 37% carbon dioxide,

(1) (a) This research was partially supported by Public Health Service Grant GM 13799 from the National Institute of General Medical Sciences and Grant 3219-A from the Petroleum Research Fund administered by the American Chemical Society. We thank these organizations for their support. (b) Based on work by D. E. Z., and M. L.-S. L. in Partial fulfillment of the requirements for the Ph.D. and M.S. degrees, respectively, at I. S. U. (c) Alfred P. Sloan Research Fellow, 1970–1972.

(2) D. E. Zabel and Walter S. Trahanovsky, *J. Org. Chem.*, **37**, 2413 (1972), and references cited therein.
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