ranoside, 17478-58-9; 9-[3,5,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α,β-D-glucofuranosyl]adenine picrate, 17519-23-2.

Acknowledgment.—This work was supported by Grants No. CA-03232-09 and CA-03232-10 from the Department of Health, Education and Welfare, U. S. Public Health Service, National Institutes of Health, Bethesda, Md (The Ohio State University Research Foundation Projects 759H and 759I). Preliminary work on a portion of this problem was performed by P. McWain.

The Baeyer–Villiger Reaction of Alkyl Aryl Ketones[1]

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The Baeyer–Villiger reaction of nitroacetophenones with trifluoroperoxyacetic acid was studied. The normal preferential aryl migration was observed with the *meta* and *para* isomers, whereas a reversal of migration aptitudes of the nitrophenyl and methyl groups was observed with the *ortho* isomer (Ar/Me ratio, 0.06–0.10). A unique participation of the protonated "Criegee intermediate" has been suggested to account for the unusually active methyl migration. The study was extended to other nuclear substituted aromatic ketones. The electronic effects and possible participation of the substituents are discussed. The relative migration aptitudes of the substituents investigated were determined by product distributions.

In the course of degradation studies of tryptophan, it was necessary to study the oxidation of 2′-aminoacetophenone. The oxidizing agent, trifluoroperoxyacetic acid, which is effective for the oxidation of anilines to the corresponding nitro compounds, was employed.[3] It was found that the amino ketone was oxidized initially to the nitro ketone, 2′-nitroacetophenone (**1**), which then underwent the Baeyer–Villiger reaction to yield a mixture of methyl *o*-nitrobenzoate and *o*-nitrophenyl acetate. Pure 2′-nitroacetophenone was treated with excess peroxy acid under similar conditions, and the products were isolated and hydrolyzed to *o*-nitrobenzoic acid and *o*-nitrophenol. The ratio of phenol to the benzoic acid was found to be 0.06 by isolation procedure and 0.10 by a titration method (Table I). These values may be taken as a reflection of the ratio of methyl and aryl migration and unambiguously indicate that, in 2′-nitroacetophenone, the methyl group migration is about ten times the nitrophenyl migration.

For comparison the *meta* and *para* isomers, 3′- and 4′-nitroacetophenone (**2** and **3**), were treated in the same manner, and the products were analyzed by titration (Table I). The phenol/benzoic acid ratios with these two isomers were greater than unity, indicating that the normal preferential aryl migration had occurred even in the presence of the electron-withdrawing effect of the nitro group.

The unusual reversed order of preference for migration observed with the *ortho*-nitro compound **1** was considered to be of significance. The change in migration aptitude observed with this compound indicates that the nitro group in the *ortho* position participates in such a manner as to create a net effect which either retards the aryl migration, facilitates the methyl migration, or is involved in both of these effects.

Of the three nitroacetophenones, only the *meta* and *para* isomers (**2** and **3**) have been studied previously.[4–7] Conducting rate studies by following the consumption of peroxybenzoic acid in the oxidation of **2** and **3**, Friess and Soloway[7] were unable to isolate the expected ester products. Hawthorne and Emmons[5] gave only the rate constants for the reaction of 3′-nitroacetophenone (**2**) and other substituted acetophenones including 4′-bromo- and 4′-methylacetophenones. The 4′-chloroacetophenone was found to give 2.9% of methyl migration.[6] The product distribution in the reaction of **3** with trifluoroperoxyacetic acid is given in Table I.

When oxidized by peroxybenzoic acid in chloroform, all acetophenones which were studied gave no detectable amount of the corresponding methyl benzoate.[7] In other words, in no case was there evidence for methyl migration. Similarly, only phenols were obtained from peroxyacetic acid oxidation of 4′-nitro- and 4′-methoxyacetophenone.[4,8]

The order of preference for migration among alkyl groups in this rearrangement has been reported to be tertiary > secondary > primary > methyl.[4,6,9] Phenyl approximates isopropyl, cyclopentyl, and benzyl in migratory aptitude.[6] Thus, it can be generalized that methyl ketones will give mostly, if not entirely, acetate esters.[10] Furthermore, electron-releasing substituents enhance, whereas electron-attracting substituents decrease, the migratory aptitude of aryl groups.[6,11]

One could postulate the participation of the nitro group in the decomposition of the protonated Criegee intermediate **4**. The nucleophilic attack of the oxygen atom of the nitro group at one of the oxygen atoms of the peroxy ester linkage aids the leaving of the trifluoroacetic acid molecule, leading to the formation of a six-membered cyclic intermediate **5**.

(1) Presented at the 1st Annual Midwest Regional American Chemical Society Meeting, Kansas City, Mo., Nov 1965.

(2) Taken in part from the Ph.D. Dissertation presented by J. P. Li, to the Graduate School of the University of Kansas, Jan 1966.

(3) W. D. Emmons, *J. Amer. Chem. Soc.*, **76**, 3470 (1954).

(4) Y. Yukawa and T. Yokoyama, *Nippon Kagaku Zasshi*, **73**, 371 (1952); *Mem. Inst. Sci. Ind. Res. Osaka Univ.*, **9**, 180 (1952).

(5) M. F. Hawthorne and W. D. Emmons, *J. Amer. Chem. Soc.*, **80**, 6398 (1958).

(6) M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *ibid.*, **80**, 6393 (1958).

(7) S. L. Friess and A. H. Soloway, *ibid.*, **73**, 3968 (1951).

(8) A. V. Wacek and A. V. Bezard, *Chem. Ber.*, **74**, 845 (1941).

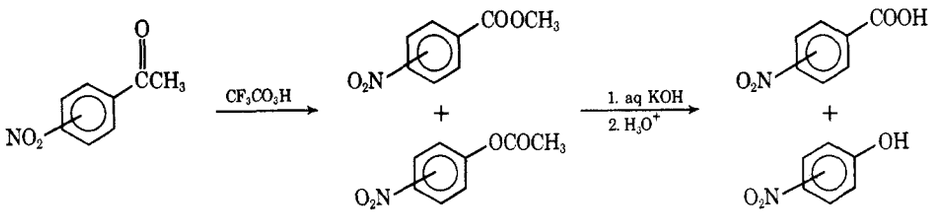
(9) S. L. Friess, *J. Amer. Chem. Soc.*, **71**, 2571 (1949).

(10) P. A. S. Smith, in "Molecular Rearrangements," part 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 577–589.

(11) W. von E. Doering and L. Speers, *J. Amer. Chem. Soc.*, **72**, 5515 (1950).

TABLE I

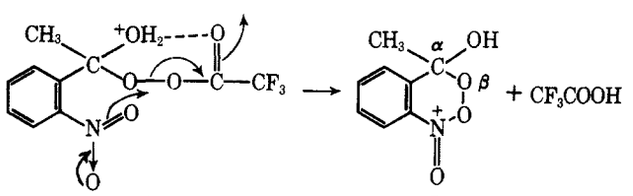
PRODUCT DISTRIBUTION OF THE BAEYER–VILLIGER REACTION OF NUCLEAR-SUBSTITUTED ACETOPHENONES



Compound	R	Total yield of products, %	Substituted benzoic acid, %	Substituted phenol, %	Ar/Me	Method
1	2′-NO_2	38[a]	94	6	0.06	Isolation
		68.4	90.7	9.3	0.10	Titration
2	3′-NO_2	100.0	37	63	1.70	Titration
3	4′-NO_2	90.6	31	69	2.22	Titration
		93	31.5	68.5	2.17	Titration
		(70	13	87	6.7	Uv)[b]
	H	48.8	0	100	Very large	Uv
		(90	0	100	Very large	Ir)[b]

[a] Recovery of starting nitro ketone, 23.6%. [b] Reference 6.

In the phenonium ion involved in a phenyl 1,2 shift, the migrating phenyl ring is presumably perpendicular to the bond between the migration origin and the migration terminus.[12] In the intermediate **5**, the plane



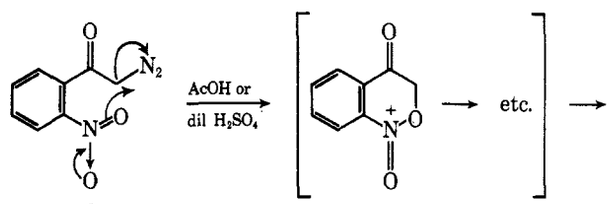
4 5

of the benzene ring and the C_α–O_β bond form a dihedral angle of *ca.* 15–20°. To migrate, the benzene ring must twist 70–75° more before its π electrons can approach the terminus oxygen atom (O_β). In a bicyclic system such as **5**, a twist of the aromatic ring in this manner is extremely difficult. Furthermore, the positive charge at the nitrogen atom may exert a strong negative inductive effect on the benzene ring, and further separation of charges may also occur.

All of these effects could act in retarding the aryl migration with the net result being a predominating shift of the methyl group.

This type of *ortho*-nitro-group participation has been suggested to account for the acid-catalyzed conversion of *o*-nitrobenzoyldiazomethane (**6**) into N-hydroxyisatin (**7**),[13,14] and the base-catalyzed formation of 2-nitrosobenzophenone (**9**) from nitrobenzhydryl *p*-toluenesulfonate (**8**).[15]

The results obtained from the three isomeric nitroacetophenones indicated that the Ar/Me ratios decreased in the order *para* > *meta* ≫ *ortho*. This order is parallel to the increasing distances between the nitro group and the migrating center. If no *ortho* effect existed in this system, the resonance effect of the electron-withdrawing nitro group would be expected to



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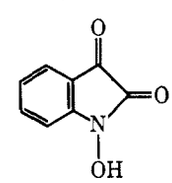

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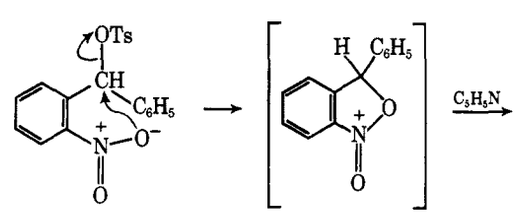

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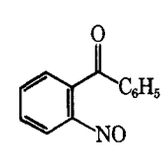

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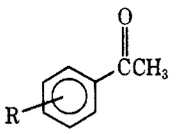
give Ar/Me ratios in the order *meta* > *para* ≅ *ortho*. Since the observed order was *para* > *meta* ≫ *ortho*, it may be tentatively concluded that the inductive effect plays a partial role in limiting the aryl migration. This same order, *para* > *meta* > *ortho* was observed for the aryl migration in the trifluoromethylacetophenones (**10–12**) which would have the influence of only a strong inductive effect.

In hope of deducing any possible electronic and anchimeric effects of the nitro group, a series of isomeric acetophenones with various substituents on the ring have been selected and studied. They were the trifluoromethylacetophenones (**10–12**), acetylbenzoic

(12) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 575.
(13) J. A. Moore and D. H. Ahlstrom, *J. Org. Chem.*, **26**, 5254 (1961).
(14) E. C. Taylor and D. R. Eckroth, *Tetrahedron*, **20**, 2059 (1964).
(15) W. B. Dickinson, *J. Amer. Chem. Soc.*, **86**, 3580 (1964).

TABLE II

PRODUCT DISTRIBUTION OF THE BAEYER–VILLIGER REACTION OF SUBSTITUTED ACETOPHENONES



Compound	R	Total yield of products, %	Substituted benzoic acid, %	Substituted, phenol, %	Ar/Me	Method
10	2′-CF_3	...	Minor	Major	>1	Isolation
		25.7	29.97	70.03	2.33	Titration
		27.4	33.33	66.66	2.00	Titration
11	3′-CF_3	53.9	19.11	80.89	4.25	Titration
		65.3	8.39	91.61	10.92	Titration
12	4′-CF_3	72.7	12.79	87.21	6.98	Titration
		25.0	21.25	78.75	3.71	Titration
13	2′-COOH	42.0	5.66	94.34	16.6	Isolation
		53.4	0	100	*a*	Isolation + uv
		50.0	0	100	*a*	Isolation + uv
14	4′-COOH	85.7	3.45	96.55	28.0	Isolation
		85.0	0	100	*a*	Isolation + uv
		99.0	0	100	*a*	Isolation + uv
15	2′-$COOCH_3$	72.7	11.64	88.36	7.7	Isolation
		92.1	7.39	92.61	12.46	Titration
		88.7	9.49	90.51	9.54	Titration
		66.0	0	100	*a*	Isolation + uv
		94.8[b]	24.0	76.0	3.17	Glpc
16	4′-$COOCH_3$	76.5	3.55	96.45	27.2	Isolation
		79.0	0	100	*a*	Isolation + uv
		94.0[b]	2.04	97.96	48	Glpc
17	2′-OCH_3	73.1	10.13	89.87	8.87	Titration
		81.8	13.18	86.82	6.59	Titration
18	3′-OCH_3	54.8	24.27	75.73	3.12	Titration
		47.9	37.29	62.71	1.68	Titration
19	4′-OCH_3	75.1	12.12	87.88	7.25	Titration
		79.5	16.46	83.54	5.07	Titration

[a] Very large. [b] Analyzed as the unhydrolyzed esters.

acids (**13**, **14**), methyl acetylbenzoates (**15**, **16**), and methoxyacetophenones (**17**–**19**) (Table II). The above ketones were oxidized with trifluoroperoxyacetic acid under identical conditions.

The potentiometric titration with tetrabutylammonium hydroxide in nonaqueous media, described by Cundiff and Markunas,[16] was adopted as a general analysis procedure and supplemented by other methods, such as ultraviolet spectrometry and gas chromatography, wherever suitable for the particular mixture of products. Preliminary experiments on some of these ketones enabled the isolation and identification of the expected products. The purified products were compared with the authentic compounds by infrared spectra, melting points, and thin layer chromatographic techniques.

Acetylsalicylic acid, methyl acetylsalicylate, and *p*-hydroxybenzoic acid acetate were refluxed separately with trifluoroacetic acid in chloroform or dichloromethane. The substances were quantitatively recovered, unchanged in each case. These experiments showed that these compounds, being primary products of the Baeyer–Villiger reaction, did not undergo Fries rearrangement or any other chemical transformation under the reaction conditions used.

The results obtained from these ketones are listed in Table II. The Ar/Me ratios obtained with these acetophenones were considerably larger than unity in comparison with the nitroacetophenones. Although the Ar/Me ratio varied considerably from one run to another for a given ketone, it is apparent that the normal preferential aryl migration was observed consistently in all compounds investigated, including all *ortho* isomers.

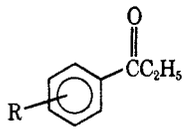
That the Ar/Me ratio dropped from 48 for the *para* isomer **16** to 3.17 for the *ortho* isomer **15** by gas–liquid partition chromatographic analysis is worthy of consideration. This large change suggests a large amount of methyl migration occurring in the oxidation of **15**. It appears that the carboxyl group indeed participated in a manner similar to that proposed for the nitro group, so as to aid the methyl migration, but not to the extent that caused reversal of migration aptitudes. No neighboring-group participation by the trifluoromethyl and methoxy groups occurred.

It is well known that an ethyl group migrates more readily than a methyl group owing to its greater ability to sustain a positive charge. Taking this into consideration, the Ar/Et ratios obtained from the nitropropiophenones would be expected to be smaller than, but parallel to, the Ar/Me ratios of the nitroacetophenones. Therefore, the oxidation reaction was extended to the isomeric nitropropiophenones (Table III).

The unsubstituted propiophenone (**20**) exhibited the normal preferential phenyl migration over alkyl migration, as expected. The oxidation of 3′-nitropropiophenone (**22**) afforded a high percentage of ethyl *m*-

(16) R. H. Cundiff and P. C. Markunas, *Anal. Chem.*, **28**, 792 (1956).

TABLE III
PRODUCT DISTRIBUTION OF THE BAEYER–VILLIGER REACTION OF SUBSTITUTED PROPIOPHENONES



Compound	R	Total yield of products, %	Substituted benzoic acid, %	Substituted phenol, %	Ar/Et	Method
20	H	72.2	39.05	60.95	1.56	Titration
		...	Minor	Major	>1	Isolation
21	2′-NO_2	39.8	62.76	37.24	0.59	Titration
		26.5	98.11	1.89	0.02	Isolation
22	3′-NO_2	48.0	82.06	17.95	0.22	Titration
		90.0	100	0	0	Isolation
23	4′-NO_2	29.7	55.77	44.23	0.82	Titration
		100	100	0	0	Isolation

nitrobenzoate but no *m*-nitrophenylpropionate. The ethyl *m*-nitrobenzoate thus obtained was hydrolyzed with aqueous potassium hydroxide, giving *m*-nitrobenzoic acid in quantitative yield. In another experiment, the oxidation products were hydrolyzed without isolation, and *m*-nitrobenzoic acid was obtained in 90% yield.

Analysis of the acidic products by titration established a ratio of 0.22.

With the *ortho* and *para* isomers, **21** and **23**, no attempt to isolate the benzoates and propionates was made. These esters were hydrolyzed without separation or purification. Both *o*-nitrobenzoic acid and *o*-nitrophenol were obtained in pure form from 2′-nitropropiophenone (**21**). 4′-Nitropropiophenone (**23**) afforded only *p*-nitrobenzoic acid by isolation procedure. No *p*-nitrophenol could be detected in the crude product by uv spectroscopy. Analysis by titration, however, indicated the formation of definite amounts of nitrophenols from **21** and **23**.

The results in Table III indicate that (1) the Ar/Et ratios associated with all three nitropropiophenones are smaller than unity and (2) these ratios are of about the same order.

Contrary to the corresponding homologs (the nitroacetophenones) and like 2′-nitropropiophenone (**21**), 3′- and 4′-nitropropiophenones (**22** and **23**) gave reversed migration preference of the aryl and alkyl groups. This may suggest that in the Baeyer–Villiger reaction the migration aptitudes decrease in the order phenyl > ethyl > nitrophenyl > methyl.

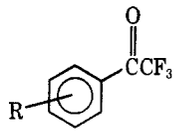
The Ar/Et ratios, being of the same order in magnitude, failed to indicate the importance of the inductive effect or of the resonance effect exerted by the nitro group in the oxidation of these aromatic ketones. Since participation by the nitro group is impossible in the *meta* and *para* isomers, **22** and **23**, and yet ethyl migration occurred to about the same extent as in the *ortho* isomer **21**, the role of nitro group participation in the oxidation of **21** cannot be assigned.

In summary, it can be postulated that, in the decomposition of the Criegee intermediate, there are three competing reactions: (a) nucleophilic displacement at the oxygen by aryl, (b) nucleophilic displacement at the oxygen by alkyl, and (c) nucleophilic displacement at the oxygen by an *ortho* substituent.

No report of the migration of a trifluoromethyl group could be found in the literature. It was speculated that peroxy acid oxidation of 2,2,2-trifluoroacetophenones would be a good reaction for the study of the migration of CF_3. Owing to the influence of the fluorine atoms, the carbon atom of a trifluoromethyl group is considerably more electronegative in comparison to that of a methyl group. Accordingly, the trifluoromethyl group would be expected to have a smaller migration ability than a methyl group and, in turn, than a phenyl group.

Preliminary experiments showed that 2,2,2-trifluoroacetophenone (**24**) gave good yields of benzoic acid upon the treatment of the ketone under Baeyer–Villiger conditions, followed by base-catalyzed hydrolysis (Table IV). Some phenol was also formed in the reaction, as the residue obtained from the extracts of the acidified hydrolysate had a phenollike odor, gave a positive ferric chloride test (violet color), and exhibited a sharp band at 2.78 μ in the ir spectrum in chloroform. The formation of phenol indicated that at least some phenyl migration occurred. As for the benzoic acid produced, there was no indication whether it arose from the Baeyer–Villiger product, trifluoromethyl benzoate, or directly from the unchanged starting material as a result of a haloform-type reaction. It is known that trifluoroacetophenone is decomposed by alkali through the haloform-type reaction to fluoroform and benzoate. When trifluoroacetophenone was refluxed with trifluoroacetic anhydride in chloroform in the presence of a few drops of trifluoroacetic acid for 4 hr, the reaction mixture showed no change in the uv spectrum, and 90% of the starting ketone could be recovered. Therefore, the ketone did not produce benzoic acid under the Baeyer–Villiger reaction conditions when per acid was absent. An attempt was made to isolate the Baeyer–Villiger products, trifluoromethyl benzoate and phenyl trifluoroacetate; however, the products or the corresponding hydrolytic products could not be isolated readily in a quantitative or semiquantitative manner. Unreacted ketone decomposed readily and thus gave spurious results. Thus in the data reported for compound **24** the phenol percentage is apparently small owing to the isolation of a large amount of benzoic acid, at least part of which arises from a haloform reaction.

TABLE IV
PRODUCT DISTRIBUTION OF THE BAEYER–VILLIGER REACTION OF SUBSTITUTED 1,1,1-TRIFLUOROACETOPHENONES



Compound	R	Total yield of products, %	Substituted benzoic acid,[a] %	Substituted phenol, %	Method
24	H	71.9	92.62	7.38	Isolation
		37.2	72.58	27.42	Titration
25	2′-NO_2	38.3	56.73	43.27	Titration
26	3′-NO_2	48.6	78.01	21.99	Titration

[a] Ar/CF_3 ratios could be not calculated owing to the uncertain route of formation of the benzoic acids.

Nonaqueous titration of the reaction products of the three trifluoroacetophenones, **24–26**, gave consistent results; however, further investigation is required before the conclusion that the trifluoromethyl group has preferential migration over the phenyl or substituted phenyl group.

In the oxidation studies of the aromatic ketones described above, two phenomena were generally observed: (1) for a given substituted ketone, the *ortho* isomer usually gave inferior yields of products to the other two isomers; and (2) the rate of oxidation was influenced by the nature of the substituent. Electron-withdrawing ring substituents (NO_2, CF_3, COOR) retarded and electron-releasing substituents (OCH_3) increased the rate of the reaction. The effects of the substituents on the reaction rates have been studied and discussed by Hawthorne and Emmons.[5]

Experimental Section[17]

Materials.—The alkyl aryl ketones, which were obtained from commercial sources, were purified by redistillation or recrystallization, and their physical constants and nmr spectra were measured to check the identity and purity. Other were prepared according to reported methods or standard procedures. The chloroform used as solvent in the Baeyer–Villiger reactions was analytical reagent grade obtained from Mallinckrodt Chemical Works and was freshly passed through a neutral alumina column (Woelm, grade I) immediately before use. Hydrogen peroxide (90%) was purchased from FMC Corp., New York, N. Y., and trifluoroacetic anhydride, from Eastman Kodak Co., which was used without further purification.

Methyl *o*-Acetylbenzoate (15).—To a solution of *o*-acetylbenzoic acid [Aldrich; recrystallized from *n*-hexane–benzene, mp 114.5–115.2° (lit.[18] mp 115°); 1.64 g, 10 mmol] in diethyl ether (50 ml), an ethereal solution of diazomethane was added slowly with stirring until the yellow color of diazomethane persisted. The reaction mixture was allowed to stand at room temperature for several hours. Concentration of the reaction solution *in vacuo* afforded a pale oily residue. The pure product **15** was obtained as an almost colorless liquid by distillation: bp 94–95° (2 mm) [lit.[19] bp 137–139° (14 mm)]; $n^{20}D$ 1.5252; nmr (CCl_4) δ 2.49 (singlet, 3 H), 3.93 (singlet, 3 H), 7.43–8.15 (multiplet, 4 H).

Methyl *p*-Acetylbenzoate (16).—The ester **16** was prepared by the procedure described above utilizing *p*-acetylbenzoic acid [Sapon Laboratories, Oceanside, N. Y.; recrystallized from methanol–*n*-hexane–benzene, mp 209.0–209.9° (lit.[20] mp 208°); 10 mmol] and diazomethane generated from N-methyl-N′-nitro-N-nitrosoguanidine (17.7 mmol). The ester **25** was recrystallized from *n*-hexane–benzene to give white, silky needles: mp 95.0–95.5° (lit.[21] mp 95.2–95.4°); nmr ($CDCl_3$) δ 2.69 (singlet, 3 H), 4.06 (singlet, 3 H), 8.25 (symmetrical doublet with satellites, base spreading over 8.05–8.49, 4 H).

2′-Nitropropiophenone (21) and 3′-Nitropropiophenone (22).—These compounds were prepared by the procedure of Zenitz and Hartung[22] involving the nitration of propiophenone.

A. 2′-Nitropropiophenone (21).—The oily residue (32.4 g, 0.18 mol, 36% yield) was distilled to yield a yellow liquid: bp 97–99° (0.15–0.2 mm) [lit.[22] bp 152–155° (2–3 mm)]; $n^{20}D$ 1.5446; λ_{max}^{EtOH} 258 mμ (ϵ 7260); λ_{max}^{neat} 5.88 (C=O), 6.55 and 7.41 μ (NO_2); nmr (CCl_4) δ 1.17 (triplet, J = 7–8 cps, 3 H), 7.24 (quartet, J = 7–8 cps, 2 H), 1.8–2.73 (multiplet, 4 H).

B. 3′-Nitropropiophenone (22).—The crystalline product obtained in the nitration of propiophenone was recrystallized from 95% EtOH to yield almost white or faintly yellow prismatic granules: 37 g (0.21 mol, 41% yield); mp 99.0–100.0° (lit.[22] mp 98–99°); λ_{infl}^{EtOH} 255 mμ (ϵ 8500); λ_{max}^{KBr} 5.92 (C=O), 6.58, and 7.46 μ (NO_2); nmr (CH_2Cl_2) δ 1.23 (triplet, J = 7.3 cps, 3 H), 3.11 (quartet, J = 7.3 cps, 2 H), 7.73 (triplet, J = 7.6 cps, 1H), 8.23–8.56 (multiplet, 2 H), 8.76 (triplet, J = 2 cps, 1 H).

4′-Nitropropiophenone (23).—It was prepared according to Sugimoto.[23] The compound was recrystallized twice from EtOH to yield orange prisms: mp 87.0–88.0° (lit.[23] mp 90°); 2.82 g (15.7 mmol, 23.4% yield); λ_{max}^{EtOH} 262.6 mμ (ϵ 8000); $\lambda_{max}^{CCl_4}$ 5.89 (C=O), 6.54 and 7.45 μ (NO_2); nmr ($CDCl_3$) δ 1.27 (triplet, J = 7.2 cps, 3 H), 3.08 (quartet, J = 7.2 cps, 2 H), 8.15 and 8.38 (a pair of distorted doublets, J = 9 cps, 4 H).

Nitration of 2,2,2-Trifluoroacetophenone (24).—In a two-necked, 1-l. round-bottomed flask equipped with a thermometer and a pressure-equalizing dropping funnel, fuming HNO_3 (Fisher Certified reagent, 90%, d 1.50; 430 ml) was placed, stirred, and cooled in an ice–salt bath. 2,2,2-Trifluoroacetophenone (K and K Laboratories, Inc., $n^{20}D$ 1.4635; 87 g, 0.5 mol) was added dropwise at a rate so that the temperature of the reaction mixture was maintained at −3 to −8°. The addition required 40 min. The reddish orange reaction solution was stirred at −2 to −5° for 15 min, poured into 2 l. of ice and H_2O, and stirred. The water phase was decanted from the pale mixture of solid and oily liquid that separated at the bottom and was extracted with C_6H_6 (five 150-ml portions). The resulting C_6H_6 solution was washed with a small amount of H_2O, filtered, dried ($MgSO_4$), and concentrated *in vacuo*. The brown residue was distilled. The unreacted starting material was collected at 65–66° (29 mm), 23.35 g (0.134 mol; 26.8% recovery). Later fractions collected at 139–142° (29 mm) gave a mixture of 2′- and 3′-nitro-2,2,2-trifluoroacetophenones, 43.2 g (0.197 mol, 29.4% total yield based on 0.5 mol of the starting ketone **24** or 53.8% yield based on the consumed amount of **24**).

3′-Nitro-2,2,2-trifluoroacetophenone (26).—The mixture of 2′- and 3′-nitro-2,2,2-trifluoroacetophenones obtained above was stored in a refrigerator. Crystals formed and were collected by filtration. The process was repeated on the filtrate until no more crystals were obtained. The crystals were combined and recrystallized three times from benzene–petroleum ether (bp 36–40°) to yield pale prisms, mp 55.0–55.8°. The product **26** distilled at 140–141° (28 mm): $\lambda_{max}^{CCl_4}$ 5.77 (C=O), 6.5 (doublet), 7.4 (NO_2), 8.24, 8.4, 8.68 μ (CF_3); λ_{max}^{KBr} 5.79 (C=O), 6.5, 7.4 (NO_2), 8.2, 8.4, 8.7 μ (CF_3); λ_{max}^{EtOH} 257 mμ (ϵ 7435); nmr (CCl_4) δ 8.87 (broad, half band width, 4.5 cps, 1 H), 8.53 (triplet, J = 8 cps, further split 2 H), 2.13 (triplet, J = 8 cps, 1 H).

Anal. Calcd for $C_8H_4F_3NO_3$: C, 43.85; H, 1.84; N, 6.39. Found: C, 43.89; H, 1.73; N, 6.30.

2′-Nitro-2,2,2-trifluroracetophenone (25).—The liquid phases and mother liquors obtained above were combined, and purified by column chromatography. The distillates and the residue in the pot were combined (*ca.* 6 g), dissolved in a small amount of CH_2Cl_2, and introduced into a silicic acid column (Mallinckrodt, 100 mesh; 150 g in 3 × 43 cm). Elution of the components with CH_2Cl_2–petroleum ether (bp 30–60°) afforded 2.81 g of **25** and 2.11 g of **26**.

2′-Nitro-2,2,2-trifluoroacetophenone (**25**), eluted from the column, was a gas chromatographically pure, pale liquid: $n^{20}D$ 1.4850; $\lambda_{max}^{CCl_4}$ 3.24, 3.46, 5.70 (C=O), 6.51, 7.41 (NO_2), 8.22, 8.41, 8.7 μ (CF_3); λ_{max}^{EtOH} 261.8 mμ (ϵ 2200); $\lambda_{max}^{cyclohexane}$ 255 mμ (ϵ 7370); nmr (CCl_4) three groups of multiplets at 446–508 cps.

Anal. Calcd for $C_8H_4F_3NO_3$: C, 43.85; H, 1.84; N, 6.39. Found: C, 44.10; H, 1.84; N, 6.26.

The Baeyer–Villiger Reaction. General Procedure.—Hydrogen peroxide (90%) (0.6 g, 16 mmol) was suspended by stirring

(17) Melting points were determined on a calibrated Thomas–Hoover capillary melting point apparatus and were corrected. Refractive indices were determined on a Carl Zeiss refractometer. Ir spectra were recorded on Beckman IR-8 and IR-10 infrared spectrophotometers. Uv data were obtained on a Cary recording spectrophotometer Model 14. Nmr spectra were measured on a Varian A-60 spectrometer, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (δ). Gas–liquid partition chromatography was conducted on an F & M Model 810-19 analytical gas chromatograph, using a flame detector and columns (1/8 in. × 4 ft) packed with 5% w/w diethylene glycol adipate (LAC-446, F & M Scientific Corp.) on Gas Chrom P (70–80 mesh, Applied Science Laboratories, Inc.) at 170°. Helium carrier gas flow was approximately 75 ml/min at 40 psi. Microanalyses were performed on an F & M carbon, hydrogen, and nitrogen analyzer Model 185 in this department. Removal of solvent by evaporation *in vacuo* was accomplished by using a Calab Model C rotary evaporator, normally at temperatures below 25°.

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(19) R. Riemschneider, H. G. Kaahn, and L. Hörner, *Monatsh. Chem.*, **91**, 1034 (1960).

(20) R. Meyer, *Ann. Chem.*, **219**, 234 (1883).

(21) Monsanto Chemical Co., British Patent 636,196 (1950); *Chem. Abstr.*, **44**, 8951*d* (1950).

(22) B. L. Zenitz and W. H. Hartung, *J. Org. Chem.*, **11**, 444 (1946).

(23) N. Sugimoto, *Chem. Abstr.*, **49**, 11707b (1955).

in $CHCl_3$ (10 ml) in an ice bath. Trifluoroacetic anhydride (5.9 g, 28 mmol) was added, and the mixture was stirred in the cold for 15 min. To the resulting peroxy acid solution, the ketone (10 mmol) in $CHCl_3$ (10 ml) was added, and the mixture was refluxed in an oil bath at *ca.* 70° for 5 hr. After cooling, the reaction mixture was concentrated to dryness *in vacuo* to remove $CHCl_3$, excess trifluoroacetic anhydride, and the trifluoroacetic acid produced. The residue was stored over KOH pellets under reduced pressure overnight.

For the oxidation of 5 mmol of ketone, half quantities of the peroxide and acid anhydride were used, and the amount of the solvent was reduced proportionately.

Base Hydrolysis of the Baeyer–Villiger Reaction Products.—The residue obtained from the Baeyer–Villiger reaction mixture (from 10 mmol of the ketone) was mixed with 2 *N* aqueous KOH (10 ml), and sufficient absolute EtOH was added to secure solution, if necessary. The mixture was stirred at 25° overnight, extracted with CH_2Cl_2, cooled in an ice bath, acidified with concentrated HCl (to congo red paper), and extracted with EtOEt (or CH_2Cl_2). The EtOEt extracts were washed with a small quantity of H_2O, filtered, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue was analyzed by the appropriate method.

Isolation of the Substituted Benzoic Acid and Phenol.—The acidic substances obtained from the hydrolysate were chromatographed on a silicic acid column (Mallinckrodt, 100 mesh, 1 × 13 cm), using CH_2Cl_2 as the eluting solvent. The residues obtained from the fractions were weighed and identified by ir and uv spectroscopy and/or melting point. The yields and ratio of the phenol and the benzoic acid were calculated.

Titration of the Product Mixtures.—Titrations were conducted on a Sargent Model D recording titrator. The delivery rate was 0.7 ml/min with a 10-ml buret.

The Baeyer–Villiger products of the nitroacetophenones were titrated in dilute EtOH with 0.1 *N* NaOH, using a Beckman standard combination electrode.

For nonaqueous titrations, a Beckman general purpose glass electrode (silver–silver chloride internal) and a modified Beckman sleeve junction calomel electrode were used. The calomel electrode was modified by replacing the saturated aqueous KCl solution with a saturated KCl solution in anhydrous MeOH.[16] Benzene (Fisher Certified reagent), pyridine (Fisher Certified reagent or Mallinckrodt Analytical Reagent), and CH_3CN (Baker Analyzed reagent) were used without further treatment. Anhydrous MeOH was prepared according to Vogel.[24] The tetrabutylammonium hydroxide titrant was prepared according to Cundiff and Markunas[16] from tetrabutylammonium iodide (polarographic grade, The G. Frederick Smith Chemical Co., Columbus, Ohio) and silver oxide (Mallinckrodt, purified powder), and standardized by titrating against benzoic acid (National Bureau of Standards). The reservoir for the titrant was connected to an ascarite tube and $MgClO_4$ tube.

The residue obtained from the acidified hydolysate was dissolved in pyridine, transferred quantitatively to a 25-ml volumetric flask, and diluted to the mark. Aliquots (1.00 ml) of this solution were diluted with pyridine or acetonitrile (25 ml) and titrated potentiometrically with 0.1 *N* tetrabutylammonium hydroxide solution. In separate titrations, the corresponding, authentic benzoic acid and phenol were added separately to the samples to confirm their presence. Mixtures of known composition were titrated as controls for the procedure, and the results were within the confidence limits. The yields and ratio of the phenol and the benzoic acid were calculated.

The Baeyer–Villiger Reaction of Methyl *o*-Acetylbenzoate (15) and Analysis of Products by Gas Chromatography.—To the peroxy acid, generated from 90% H_2O_2 (4 drops) and trifluoroacetic anhydride (1 g) in $CHCl_3$ (10 ml), a $CHCl_3$ solution of **15** (173 mg, 0.97 mmol, in 5 ml) was added, and the mixture was refluxed at 70° for 5 hr. The yellow reaction solution was evaporated *in vacuo*. The residue thus obtained was dissolved in EtOAc (Fisher Certified reagent), washed with H_2O (three 5-ml portions), filtered, and dried ($MgSO_4$). Evaporation of the solution afforded an oil, 178.6 mg (0.92 mmol as $C_9H_{10}O_4$, 94.8% total yield of both products). Analysis by glpc (at 150°, helium flow rate, 60 ml/min) indicated it to contain methyl acetylsalicylate, dimethyl phthalate, and traces of impurities. The relative peak areas 3.17:1.

The Baeyer–Villiger Reaction of Methyl *p*-Acetylbenzoate (16) and Analysis of Products by Gas Chromatagraphy.—The reaction was performed as with the *ortho* isomer, employing the same amount of peroxy acid and identical conditions. Methyl *p*-acetylbenzoate (199 mg, 1.117 mmol) afforded an oil (265.4 mg). Glpc analysis indicated that both methyl *p*-acetoxybenzoate and dimethyl terephthalate were obtained and represented 94% total yield. The relative peak areas 48:1. The ir spectrum of the oily residue closely resembled that of authentic methyl *p*-acetylbenzoate.

Registry No.—**1,** 577-59-3; **2,** 121-89-1; **3,** 100-19-6; **10,** 17408-14-9; **11,** 349-76-8; **12,** 709-63-7; **13,** 577-56-0; **14,** 586-89-0; **15,** 1077-79-8; **16,** 3609-53-8; **17,** 4079-52-1; **18,** 586-37-8; **19,** 100-06-1; **20,** 93-55-0; **21,** 17408-15-0; **22,** 17408-16-1; **23,** 3758-70-1; **24,** 434-45-7; **25,** 17408-17-2; **26,** 657-15-8.

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