either direction) when their effects are transmitted to the reducible group.

Experimental

Cinnamic Acids.—*trans*-Cinnamic acid was an Eastman Kodak White Label sample. *p*-Nitrocinnamic acid was prepared by nitration of cinnamic acid and purified *via* its ethyl ester.[11] *p*-Iodocinnamic acid was prepared by iodination of cinnamic acid with iodine in acetic acid in the presence of nitric acid[12] and purified by chromatography on magnesol and elution with acetone.

o- and *p*-methyl-, chloro-, and bromo-, *m*-nitro-, and *p*-hydroxy- and *p*-methoxy-, as well as *p*-iodocinnamic acids were prepared by reaction of the appropriate benzaldehyde with malonic acid in 95% ethanol in the presence of piperidine.[13]

o- and *m*-hydroxy- and methoxy- and *o*-nitrocinnamic acids were prepared *similarly in pyridine solution with piperidine*.[14]

o- and *m*-methoxybenzaldehydes were prepared by methylation of the hydroxybenzaldehyde with methyl sulfate and sodium hydroxide.[15] *o*- and *p*-chloro- and bromobenzaldehydes were prepared by Etard oxidation of the corresponding toluenes,[16] and *o*-nitrobenzaldehyde was prepared by oxidation of *o*-nitrotoluene in acetic acid and anhydride followed by hydrolysis of the so-formed diacetate.[17]

The hydrocinnamic acids were prepared by hydrogenation of the cinnamic acids in acetic acid using a platinum oxide catalyst.

The corrected melting points were determined on a Köfler block and are recorded in Tables II and III.

Absorption Spectra.—The absorption spectra were determined in purified 95% ethanol using a Beckman DK2 spectrometer and 1-cm. cells at concentrations such that the optical density was 0.8–0.2 (see Table I).

Polarographic Reductions.—The polarographic determinations were made in 0.175 *M* tetra-*n*-butylammonium iodide–0.05 *M* tetra-*n*-butylammonium hydroxide in 75% dioxane–water (D^{25}_{25} 1.037, dioxane purified by refluxing with sodium) using standard conditions[5] and employing a Sargent Model XI polarograph. The half-wave reduction potentials were measured against a saturated calomel electrode (Table I). The capillary had a drop time of 3.6 sec. and mercury flow of 1.51 mg./sec.

Acknowledgment.—This study was supported in part by grants from the Rockefeller Foundation, New York, New York.

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[11] W. Davey and J. R. Guilt, *J. Chem. Soc.*, 204 (1950).

[12] R. L. Datta and N. R. Chatterjee, *J. Am. Chem. Soc.*, **41**, 295 (1919).

[13] A. I. Vogel, "Practical Organic Chemistry," Longmans Green and Co., New York, N. Y., 1948, p. 682.

[14] J. Koo, M. S. Fish, G. N. Walker, and J. Blake, *Org. Syn.*, **31**, 35 (1951).

[15] *Cf.* D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 37.

[16] O. H. Wheeler, *Can. J. Chem.*, **36**, 667 (1958).

[17] Ref. 13, p. 666.

Action of Trifluoroacetic Anhydride on N-Substituted Amic Acids[1,2]

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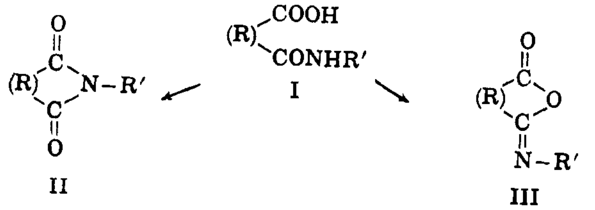
The action of trifluoroacetic anhydride on various N-aryl amic acids was investigated to determine whether dehydration by this reagent always forms isoimides. N-Substituted maleamic and phthalamic acids were dehydrated to isoimides, and the method appears to be general for the synthesis of N-aryl maleisoimides and phthalisoimides. Several products were obtained from saturated amic acids depending on the number of carbon atoms separating the amide and carboxyl groups, but in no instance was a saturated isoimide formed. Although the α- and β-N-methylcamphoramic acids were not dehydrated by trifluoroacetic anhydride, the reported dehydrations by acetyl chloride and phosphorus oxychloride to isoimides, the only report of saturated isoimides, have been confirmed. Maleisoimdes have been found to react with piperidine by ring opening to form diamides rather than by addition to the carbon–carbon double bond, and this reaction has been used to confirm the structure of N-1-naphthylmaleisoimide. The intensities of the two characteristic infrared bands of cyclic isoimides have been shown to be useful in distinguishing isoimides from imides.

The dehydration of N-substituted amic acids (I) is known to produce imides (II) or isoimides (III), depending on the conditions employed for the dehydration and on the nature of the amic acid. The literature on imides is quite extensive, and a variety of reagents has been used in the synthesis of imides. The reagents most commonly employed to effect dehydration of amic acids to imides are phosphorus pentoxide,[3,4] acetic anhydride plus fused sodium acetate,[5] acetyl chloride,[6,7] and thionyl chloride.[3,8,9] Simple heating of the amic acid or direct fusion of a mixture of the anhydride and amine without isolation of the intermediate amic acid are also very common methods. Various other dehydrating agents have been employed less extensively: in the preparation of phthaloylamino acids, for example, numerous techniques have been developed for dehydration under relatively mild conditions to avoid decomposition or racemization of the amino acid.[9–11]



The reagents reported to dehydrate amic acids to isoimides are fewer in number and, judging from the literature, several would appear not to be general in their action. These reagents, in chronological order of

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[1] Support of this work by a Frederick Gardner Cottrell grant from the Research Corporation is gratefully acknowledged.

[2] Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961, p. 111-Q of the abstracts.

[3] A. E. Kretov and N. E. Kul'chitskaya, *Zh. Obshch. Khim.*, **26**, 208 (1956); *Chem. Abstr.*, **50**, 13771 (1956).

[4] A. Piutti, *Atti reale accad. Lincei, Classe sci. fis. mat. e nat.*, [5] **18**, **II**, 312 (1909); *Chem. Abstr.*, **4**, 2451 (1910).

[5] N. E. Searle, U.S. Patent 2,444,536 (1948); *Chem. Abstr.*, **42**, 7340 (1948).

[6] E. Giustiniani, *Gazz. chim. ital.*, **28**, **II**, 189 (1898).

[7] K. von Auwers, *Ann.*, **309**, 316 (1899).

[8] W. H. Warren and R. A. Briggs, *Ber.*, **64**, 26 (1931).

[9] F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 3315 (1949).

[10] A. K. Bose, F. Greer, and C. C. Price, *J. Org. Chem.*, **23**, 1335 (1958).

[11] B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *ibid.*, **19**, 1786 (1954).

their reported use in the synthesis of isoimides, are acetyl chloride,[12] phosphorus oxychloride,[12] trifluoroacetic anhydride,[13] trifluoroacetic anhydride plus triethylamine,[14] other halogenated aliphatic acid anhydrides plus triethylamine,[14] ethyl chloroformate plus triethylamine,[14] N,N'-dicyclohexylcarbodiimide,[14] and acetic anhydride plus sodium acetate.[15,16] Of these, however, acetyl chloride, phosphorus oxychloride, ethyl chloroformate plus triethylamine, and acetic anhydride plus sodium acetate also have been used to form imides; trifluoroacetic anhydride alone has been reported to effect the dehydration of only one amic acid to the corresponding isoimide, and acetic anhydride plus sodium acetate formed isoimides only in certain instances.[15]

Isoimides constitute a potentially interesting class of compounds on which there has been relatively little investigation until recently and which appear to be reaction intermediates in several reactions. There is evidence to suggest that one path in the formation of imides by dehydration of amic acids may proceed *via* isoimides.[14,17] Isoimides have been postulated as intermediates in the reaction of phthaloyl chloride with ammonia to form *o*-cyanobenzoic acid,[18] in the synthesis of β-cyano esters from N-unsubstituted amic acids,[19] in the reaction of amides with carboxylic anhydrides to form nitriles or imides,[20] in the interconversion of nitriles and carboxylic acids,[21] in the reaction of ketimines with carboxylic acids,[22] in the reaction of imidoyl chlorides with salts of carboxylic acids,[23] and in the reaction of the N-methyl-5-phenylisoxazolium cation with acetate.[24] In some of these reactions the product isolated was the imide, assumed to have resulted by isomerization of an initially formed isoimide.

We have been interested in a general study of the chemistry of isoimides and, as part of this investigation, we have studied the formation of isoimides by the dehydration of amic acids. The results obtained employing trifluoroacetic anhydride as the dehydrating agent are reported in this paper.

N-Substituted Maleamic and Phthalamic Acids.—With only one exception, trifluoroacetic anhydride in dioxane was found to dehydrate N-arylmaleamic and N-arylphthalamic acids to N-arylmaleisoimides[25] and N-arylphthalisoimides, respectively, with yields generally in the range of 70–90% (*cf.* Tables I and II). The method was essentially that employed by Tsou, *et al.*,[13] in which a slight excess of trifluoroacetic anhydride is added to a solution or suspension of the amic acid in dioxane at room temperature. Since the hydrolysis of maleisoimides is catalyzed by acids,[15] Cotter, *et al.*,[14] have proposed that, in those instances in which trifluoroacetic anhydride has been found to be ineffective, the initially formed isoimide is subsequently hydrolyzed, presumably during the work-up procedure, catalyzed by the trifluoroacetic acid formed as a by-product. In an experiment designed to test this hypothesis, they treated maleanilic acid with trifluoroacetic anhydride in the presence of sufficient triethylamine to neutralize the liberated trifluoroacetic acid and obtained the maleisoimide in 50% yield.

This interpretation would appear to account satisfactorily for the failure to obtain maleisoimides from the action of trifluoroacetic anhydride on certain maleamic acids. Nevertheless, in our studies dehydration in the absence of any added base was successful in all but one instance. The yield of N-phenylmaleisoimide was low (30%); this isoimide appeared to be somewhat less stable toward hydrolysis than the other aryl maleisoimides. Since N-(*m*-nitrophenyl)maleisoimide was found to hydrolyze very rapidly during the isolation, the reaction mixture was poured into 10% sodium bicarbonate solution to prevent hydrolysis. With N-(1-naphthyl)maleamic acid, however, even this modified procedure was not completely successful. An impure oil having infrared absorption bands at 5.60 and 5.99 μ (sh 5.85 μ) characteristic of cyclic isoimides was obtained, but it could not be purified, and the elemental analysis was unsatisfactory owing to hydrolysis to the amic acid. That the product was the isoimide was shown by the reaction with piperidine (following). The N-(1-naphthyl)maleamic acid was studied because Tsou, *et al.*, had tried trifluoroacetic anhydride on only three amic acids: N-(1-naphthyl)-, N-(5-hydroxy-1-naphthyl)-, and N-(4-hydroxy-1-naphthyl)maleamic acids. Only the last compound was dehydrated to an isoimide, the other two being recovered unchanged. Consequently, a better test of Cotter's hypothesis that the failure to obtain these isoimides results from hydrolysis of the initially formed isoimides is with one of these naphthyl derivatives. The method of Cotter, *et al.*, using triethylamine in the dehydration mixture was also employed; an oil identical in infrared spectrum to that obtained using trifluoroacetic anhydride alone was obtained, and elemental analysis was again unsatisfactory and indicated hydrolysis. These observations thus support the interpretation of Cotter, *et al.*, and demonstrate that hydrolysis of isoimides can be prevented by pouring the reaction mixture into bicarbonate as well as by having triethylamine present during the dehydration.

Saturated Amic Acids.—Since trifluoroacetic anhydride was found to be a general reagent for the formation of isoimides in the maleic and phthalic series the action of this anhydride on a homologous series of saturated amic acids was investigated since the only examples of a saturated isoimide ring are the camphorisoimides.[12] The results of treatment of N-arylmalonamic, -succinamic, -glutaramic, and -adipamic acids

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(12) S. Hoogewerff and W. A. van Dorp, *Rec. trav. chim.*, **12**, 12 (1893); **13**, 93 (1894); **14**, 252 (1895).

(13) K. C. Tsou, R. J. Barrnett, and A. M. Seligman, *J. Am. Chem. Soc.*, **77**, 4613 (1955).

(14) (a) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961); (b) C. K. Sauers and R. J. Cotter, U.S. Patent 2,995,577 (1961); *Chem. Abstr.*, **56**, 5839 (1962).

(15) A. E. Kretov, N. E. Kul'chitskaya, and A. E. Mal'nev, *J. Gen. Chem. USSR*, **31**, 2415 (1961).

(16) T. L. Fletcher and H. L. Pan, *J. Org. Chem.*, **26**, 2037 (1961).

(17) W. R. Roderick, paper presented at the Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, La., 1961.

(18) S. Hoogewerff and W. A. van Dorp, *Rec. trav. chim.*, **11**, 84 (1892).

(19) C. K. Sauers and R. J. Cotter, *J. Org. Chem.*, **26**, 6 (1961).

(20) D. Davidson and H. Skovronek, *J. Am. Chem. Soc.*, **80**, 376 (1958).

(21) W. G. Toland and L. L. Ferstandig, *J. Org. Chem.*, **23**, 1350 (1958).

(22) C. L. Stevens and M. E. Munk, *J. Am. Chem. Soc.*, **80**, 4065 (1959).

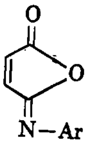
(23) F. Cramer and K. Baer, *Ber.*, **93**, 1231 (1960).

(24) R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961).

(25) We prefer to use the term *isoimide* as a class name, adding the usual prefix to indicate the parent acid: *e.g.*, *maleisoimide* rather than *isomaleimide*. This usage is consistent with the nomenclature of imides and amic acids and should lessen any confusion with acids the names of which include the prefix *iso* (*e.g.*, tetrahydroisophthalic acid). Isoimides are named systematically as imino derivatives of lactones: *e.g.*, 3-(4-methoxyphenylimino)phthalide and 5-(4-methoxyphenylimino)-2(5H)-furanone.

TABLE I

N-ARYLMALEISOIMIDES

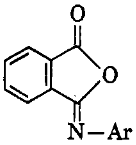


Ar	Molecular formula	M.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-Dimethylaminophenyl	$C_{12}H_{12}N_2O_2$	137	85	66.65	66.43	5.59	5.72	12.96	12.78
p-Methoxyphenyl	$C_{11}H_9NO_3$	71	75	65.02	63.81	4.46	4.26	6.89	6.85
p-Ethoxyphenyl	$C_{12}H_{11}NO_3$	71–74	75	66.35	66.08	5.10	5.11	6.45	6.40
p-Tolyl	$C_{11}H_9NO_2$	74	70	70.58	70.77	4.85	5.00	7.48	7.45
Phenyl	$C_{10}H_7NO_2$	60	30	69.36	...[a]	4.07	...	8.09	...
o-Nitrophenyl	$C_{10}H_6N_2O_4$	107–109	82	55.05	55.04	2.77	2.79	12.84	13.08
m-Nitrophenyl	$C_{10}H_6N_2O_4$	57	50	55.05	55.05	2.77	2.79	12.84	12.92
p-Nitrophenyl	$C_{10}H_6N_2O_4$	112–113	80	55.05	54.05	2.77	2.74	12.84	12.69

[a] Could not be purified; reported as a pure compound (ref. 14).

TABLE II

N-ARYLPHTHALISOIMIDES



Ar	Molecular formula	M.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-Dimethylaminophenyl	$C_{16}H_{14}N_2O_2$	170	55	72.16	71.93	5.30	5.59	10.52	10.58
o-Methoxyphenyl	$C_{15}H_{11}NO_3$	121	70	71.14	71.26	4.37	4.29	5.53	5.62
p-Methoxyphenyl	$C_{15}H_{11}NO_3$	134	80	71.14	70.60	4.37	4.34	5.53	5.66
o-Tolyl	$C_{15}H_{11}NO_2$	136	80	75.93	75.84	4.67	4.49	5.90	5.98
p-Tolyl	$C_{15}H_{11}NO_2$	123	80	75.93	76.07	4.67	4.41	5.90	5.85
Phenyl	$C_{14}H_9NO_2$	112[a]	80	75.32	...	4.06	...	6.28	...
o-Chlorophenyl	$C_{14}H_8NO_2Cl$	139	90	65.25	65.35	3.13	3.30	5.44	5.44
p-Chlorophenyl	$C_{14}H_8NO_2Cl$	160	89	65.25	65.64	3.13	3.23	5.44	5.39
o-Nitrophenyl	$C_{14}H_8N_2O_4$	162	60	62.69	62.22	3.01	3.16	10.45	10.41
m-Nitrophenyl	$C_{14}H_8N_2O_4$	138	50	62.69	62.56	3.01	3.03	10.45	10.60
p-Nitrophenyl	$C_{14}H_8N_2O_4$	172	91	62.69	62.49	3.01	3.07	10.45	10.58

[a] Lit. m.p. 116°.

TABLE III

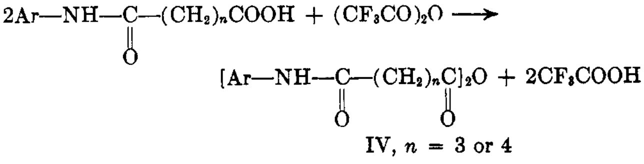
PRODUCTS OBTAINED FROM THE ACTION OF TRIFLUORACETIC ANHYDRIDE ON SATURATED AMIC ACIDS

Amic acid	Product	M.p., °C.	Yield, %
N-Phenylmalonamic	Polymer ?	*ca.* 210	77
N-Phenylsuccinamic	Succinic dianilide	231	60
N-(*p*-Methoxyphenyl)-succinamic	Amic acid recovered		
N-Phenylglutaramic	N-Phenylglutaramic anhydride	145	40
N-(*p*-Methoxyphenyl)-glutaramic	N-(*p*-Methoxyphenyl)-glutaramic anhydride	159	50
N-Phenyladipamic	N-Phenyladipamic anhydride	138	50

with trifluoroacetic anhydride under the same conditions employed for N-substituted maleamic and phthalamic acids are summarized in Table III.

Treatment of N-phenylmalonamic acid (malonanilic acid) with trifluoroacetic anhydride gave products which, although they could not be identified, appeared not to be the imide and which are definitely not the isoimide. The products were amorphous, without definite melting point, gave unsatisfactory analyses, and could not be purified. The action of thionyl chloride on malonanilic acid has been reported to give the imide,[8] but the properties of the product and difficulty in reproducing the reaction suggest a polymer.[26] Phosphorus pentachloride has been reported to convert malonanilic acid to a trichloroquinoline.[27] We have treated malonanilic acid with these two reagents and found the products to be very similar but not identical with those obtained with trifluoroacetic anhydride. The action of dehydrating agents on malonamic acids is, therefore, complex; all that can be concluded from the previous data is that imide or isoimide are not formed.

N-(*p*-Methoxyphenyl)succinamic acid was recovered unchanged from treatment with trifluoroacetic anhydride, but N-phenylsuccinamic acid was converted to succinic dianilide. N-Phenylglutaramic, N-(*p*-methoxyphenyl)glutaramic, and N-phenyladipamic acids were each dehydrated to the respective amic acid anhydrides (IV). The amic acid anhydride structures



$$2\text{Ar—NH—}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{—(CH}_2)_n\text{COOH} + (\text{CF}_3\text{CO})_2\text{O} \longrightarrow [\text{Ar—NH—}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{—(CH}_2)_n\underset{\text{O}}{\underset{\|}{\text{C}}}]_2\text{O} + 2\text{CF}_3\text{COOH}$$

IV, n = 3 or 4

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[26] F. E. King, *J. Chem. Soc.*, 1318 (1949).

[27] L. Rügheimer, *Ber.*, **17**, 736 (1884).

were assigned on the basis of the following chemical, spectral, and analytical evidence. The product from N-phenylglutaramic acid had three infrared absorption bands in the carbonyl region at 5.55, 5.75, and 6.05 μ, as well as an N-H band at 2.98 μ, indicating that the product was neither the isoimide or imide. The bands indicated an amide and an anhydride and were similar to those reported by Thamm for N-aryl succinamic anhydrides obtained from the action of ketenes on amic acids.[28] Elemental analyses supported the structural assignments, although the per cent carbon was low, probably the result of hydrolysis to amic acid. Chemical evidence included hydrolysis of these products to the amic acids and ammonolysis with aniline to give both the amic acids and dianilides.

With this failure to dehydrate saturated amic acids to isoimides using trifluoroacetic anhydride, the action of another fluorinated anhydride, heptafluorobutyric anhydride, was studied with the succinamic acids, since these seemed most likely to give rise to stable isoimides. Because of the different and unexpected products obtained, it was necessary to investigate the action of this reagent on each of the other types of amic acid as well. The products from the other amic acids, however, were in each case the same as those obtained using trifluoroacetic anhydride. With the two succinamic acids studied, an acyl exchange occurred rather than dehydration. Thus N-phenylsuccinamic acid gave heptafluorobutyranilide, and N-(p-methoxyphenyl)-succinamic acid gave p-methoxyheptafluorobutyranilide. Succinic anhydride, which should be the other product, was not isolated.

Because of the failure to obtain saturated isoimides from the amic acids discussed earlier as well as from several other saturated amic acids, the reported preparations of the N-methylcamphorisoimides[12] were repeated. Treatment of N-methyl-α-camphoramic acid with acetyl chloride gave N-methyl-α-camphorisoimide. Treatment of N-methyl-β-camphoramic acid with phosphorus oxychloride gave, in very low yield, a mixture of N-methylcamphorimide and a compound having carbonyl absorptions similar to those of the α-isoimide and hence, presumably, the β-isoimide. The assignment of the isoimide structure to the product from the α-amic acid was confirmed by determination of the intensities of the infrared absorption bands (following). The existence of these saturated isoimides is thus confirmed. Trifluoroacetic anhydride, however, did not dehydrate these amic acids.

Interpretation of Results.—From the data presented it can be seen that the action of trifluoroacetic anhydride on amic acids may result in the formation of isoimides or of several other products. The formation of the various products observed can be rationalized by the scheme shown in Fig. 1. It is likely that the N-aryl amic acid first reacts with trifluoroacetic anhydride to form a mixed anhydride.[29] The mixed anhydride can undergo intramolecular cyclization in three ways: elimination of trifluoroacetic acid with formation of imide; elimination of trifluoroacetic acid with formation of isoimide; or elimination of trifluoroacetanilide with formation of anhydride. Reaction of the mixed anhydride with a second molecule of amic acid forms the amic acid anhydride, which may be isolated or may undergo a cyclization analogous to the third cyclization path of the mixed anhydride, forming diamide and anhydride. It is conceivable that the amic acid anhydride could also cyclize by elimination of amic acid and formation of imide or isoimide, analogous to the first two paths for the mixed anhydride.

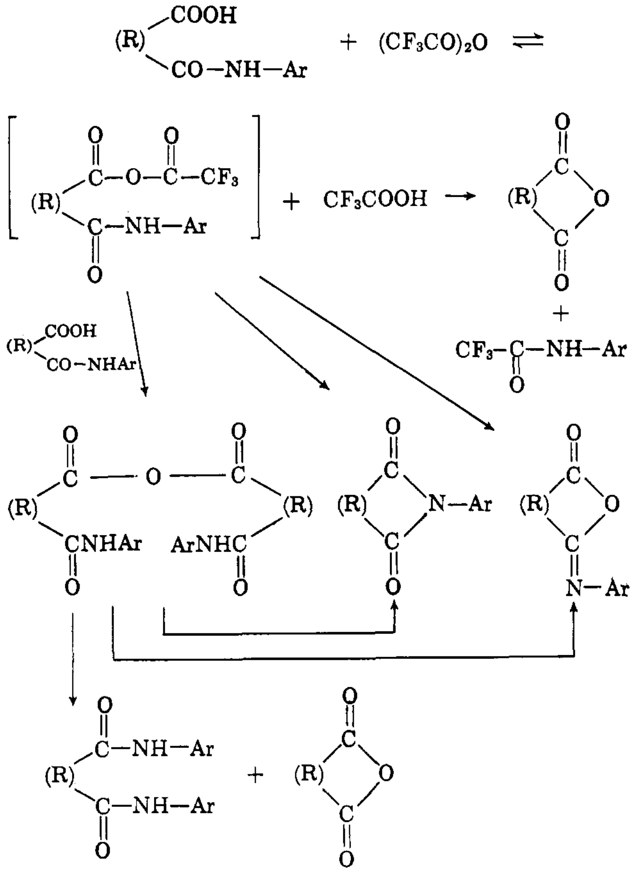

Fig. 1.—Possible scheme for the reaction of trifluoroacetic anhydride with amic acids.

Each of these intermediates and products has been obtained from amic acids in other studies. Evidence for the mixed anhydride as an intermediate in the dehydration of amic acids has been obtained,[17] and acetic succinamic anhydrides have been obtained by other means.[28] N-Aryl succinamic acid anhydrides have been reported as products from the action of diphenylketene on the amic acids.[28] Diamides have been obtained from the treatment of N-phenylmaleamic acid with phosphorus oxychloride,[30] from treatment of N-(p-ethoxyphenyl)maleamic acid with acetyl chloride,[31] and from thermal decomposition of *d,l-erythro*-dimethylsuccinanilic acetic anhydride.[28] Acyl exchange has been observed in the treatment of maleamic acids with excess acetic anhydride[3] and in the action of trifluoroacetic anhydride on peptides.[32]

In this scheme all amic acids are assumed to form the mixed anhydrides; subsequent behavior of the anhydride depends mainly on the structure of the amic acid. Formation of a cyclic product occurs when the most

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[28] R. C. Thamm, Ph.D. dissertation, University of Illinois, 1957; *cf. Dissertation Abstr.*, **17**, 2428 (1957).

[29] J. M. Tedder, *Chem. Rev.*, **55**, 787 (1955).

[30] W. A. van Dorp and P. M. Haarst, *Rec. trav. chim.*, **19**, 311 (1900).

[31] W. R. Roderick, *J. Am. Chem. Soc.*, **79**, 1710 (1957).

[32] F. Weygand, R. Geiger, and U. Glöckler, *Ber.*, **89**, 1543 (1956); *cf.* K. D. Kopple and E. Bachli, *J. Org. Chem.*, **24**, 2053 (1959).

stable ring, a five-membered ring,[33] is formed; thus N-substituted phthalamic and maleamic acids form isoimides. The failure of succinamic acids to cyclize is not surprising even though they would form a five-membered ring, since studies have shown that succinic derivatives cyclize much less readily than maleic derivatives owing to the existence of the former in conformations unfavorable toward cyclization.[34] As predicted, succinic derivatives which are forced into favorable conformations by several α-substituents cyclize more readily.[34] Bicyclic amic acids in which the carboxyl (and, therefore, the mixed anhydride) and amide groups are held in a conformation favorable for cyclization should be dehydrated readily to cyclic products, and this is the case. For example, the reaction of 3,6-*endo*-methylene-1,2,3,6-tetrahydrophthalic anhydride with aniline gives the imide directly; when the amic acid is isolated, it cannot be recrystallized and spontaneously dehydrates to the imide.[35] The same factor is undoubtedly responsible for the relative ease of formation of camphorisoimides, since the carboxyl and amide groups of the camphoramic acids are fixed in a conformation suitable for cyclization. In the reaction of succinamic acids with heptafluorobutyric anhydride, cyclization of the mixed anhydride presumably does occur, except by path three to form succinic anhydride. With the mixed anhydrides from longer chain amic acids, cyclization does not occur readily and the mixed anhydride reacts with a second molecule of the amic acid to form the amic acid anhydride.

The action of fluorinated acid anhydrides on amic acids depends, therefore, on the number of carbon atoms separating the carboxyl and amide groups and, at least in the case of succinamic acids, on the nature of the N-substituent and the nature of the dehydrating agent. The action of dehydrating agents on amic acids probably is also dependent upon other experimental conditions, such as temperature and reaction time, so that different products may be obtained from the action of a given dehydrating agent on an amic acid under different conditions.[17]

Reaction of Isoimides with Piperidine.—In the course of other attempts to prepare saturated isoimides by means other than the dehydration of amic acids, the reaction of piperidine with isoimides was studied. Various reagents, including piperidine, have been shown to add to N-arylmaleimides to form N-arylsuccinimides.[36] The addition of such reagents to the carbon–carbon double bond of a maleisoimide would give a succinisoimide. Of course, the isoimide ring should be more susceptible to nucleophilic attack than the imide ring, and ring cleavage may occur more readily than addition. Maleisoimides have been reported to react with amines by ring cleavage.[37]

Treatment of N-(p-methoxyphenyl)maleisoimide with piperidine at room temperature did not result in addition to give the desired α-piperidylsuccinisoimide. Instead, ring cleavage occurred forming the diamide, the piperidide of N-(p-methoxyphenyl)maleamic acid. Hence it would appear that saturated isoimides cannot be obtained by this route. This difference of maleimides and maleisoimides in their reactivity toward amines can be utilized to differentiate between these two structures. Thus with N-(1-naphthyl)maleisoimide, a viscous red oil which could not be purified or analyzed owing to its ready hydrolysis, the reaction with piperidine gave a product for which infrared, chemical, and analytical data indicated the piperidide of N-(1-naphthyl)maleamic acid. The formation of this product under such mild conditions is consistent with the isoimide structure, but not with the imide structure.

Infrared Absorption of Isoimides.—The N-arylmaleisoimides and N-arylphthalisoimides prepared in this study all exhibited two strong bands in the carbonyl region at 5.54 (C=O) and 5.88 μ (C=N), in agreement with the findings of other workers. While it is generally possible to distinguish isoimides from the corresponding imides, which also absorb in this region, in a few instances the bands of isoimides are at wave lengths quite different from the average wave lengths and hence they are not sufficient for assignment of the isoimide structure. It appeared that the intensities of the absorptions might be more characteristic of the structure than the wave lengths and would at least provide additional data to support the isoimide structure for certain members.

Accordingly, quantitative spectra of isoimides and the corresponding imides in dioxane solution were determined for the region 5.0–6.0 μ, and apparent molecular extinction coefficients were calculated from the maximum absorptions.[38] The results, presented in Table IV, show that it is possible to distinguish isoimides from imides by extinction coefficients. The value of the apparent molecular extinction coefficient of the longest wave-length band is of the order of 200–400 for isoimides and 850–1300 for imides. The difference is so large that it enables assignment of structure to an imide or isoimide in the absence of the infrared spectrum of the isomer.

The method was employed to confirm the assignment of the isoimide structure when it was in doubt. The mull spectrum of N-(p-dimethylaminophenyl)phthalisoimide, for example, has bands at 5.57 (sh), 5.67, and 5.95 μ and is more characteristic of an imide than of an isoimide. In dioxane solution there are only two bands, at 5.57 μ (ϵ 369) and 5.93 μ (ϵ 167); and, although the bands are at somewhat longer wave lengths than observed for other phthalisoimides, the intensities definitely are in the range for isoimides. N-Methyl-α-camphorisoimide was studied since there are no modern physical data to support this sole example of a saturated isoimide. This isoimide has absorptions at 5.63 μ (ϵ 314) and 5.85 μ (ϵ 471), whereas the imide has absorptions at 5.78 μ (ϵ 241) and 5.96 μ (ϵ 1233). Here the wave lengths differ quite widely from those of imides and isoimides in the maleic and phthalic series, but the apparent extinction coefficients fall in the appropriate

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(33) H. C. Brown, J. H. Brewster, and H. Schechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(34) T. C. Bruice and U. K. Pandit, *ibid.*, **82**, 5858 (1960).

(35) (a) M. S. Morgan, R. S. Tipson, A. Lowry, and W. E. Baldwin, *ibid.*, **66**, 404 (1944); (b) S. W. Fox and F. N. Minard, *ibid.*, **74**, 2085 (1952).

(36) A. Mustafa, W. Asker, S. Khattab, and S. M. A. D. Zayed, *J. Org. Chem.*, **26**, 787 (1961), and previous papers cited therein.

(37) C. K. Sauers and R. J. Cotter, U. S. Patents 3,023,240 (1962) [*Chem. Abstr.*, **57**, 11100 (1962)] and 3,041,376 (1962).

(38) While apparent molecular extinction coefficients lack the precision of integrated absorption intensities [D. A. Ramsay, *J. Am. Chem. Soc.*, **74**, 72 (1952); L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 2nd Ed., 1958, p. 271; T. L. Brown, *Chem. Rev.*, **58**, 581 (1958)], the use of the former in studies where the differences between different structures are large is justified by their ease of calculation.

TABLE IV

APPARENT MOLECULAR EXTINCTION COEFFICIENTS OF N-ARYL IMIDES AND ISOIMIDES IN DIOXANE

N-Substituent	Imides						Isoimides			
	λ, μ	ε	λ	ε	λ	ε	λ	ε	λ	ε
Phthalic series										
o-CH_3O—C_6H_4—	5.60	94	5.73	313	5.80	1240	5.53	372	5.85	415
p-CH_3O—C_6H_4—	5.60	70	5.72	189	5.80	1110	5.55	366	5.91	273
o-CH_3—C_6H_4—	5.60	99	5.73	226	5.81	1136	5.54	359	5.87	371
p-CH_3—C_6H_4—	5.61	83	5.74	255	5.82	1288	5.54	358	5.90	256
o-Cl—C_6H_4—	5.59	114	5.73	391	5.78	1146	5.52	329	5.85	509
p-Cl—C_6H_4—	5.60	89	5.74	395	5.81	974	5.54	340	5.88	383
Average	5.60	92	5.73	294	5.80	1149	5.54	354	5.88	367
Maleic series										
p-CH_3O—C_6H_4—					5.80	844	5.56	334	5.95	134
p-CH_3—C_6H_4—					5.79	847	5.55	358	5.93	205
p-$(CH_3)_2N$—C_6H_4—					5.82	852	5.58	617	5.65	304
Average					5.80	848	5.56	436	5.84	214

range and clearly support the assigned structures. For structural assignments where isomers absorb in the same region such that the range of wave lengths for one isomer overlaps the range for the other, as with imides and isoimides, the ranges of intensities of the absorptions may be widely separated and hence of considerable value in differentiating between isomeric structures.

Experimental[39]

Amic Acids.—The amic acids were prepared by reaction of equimolar amounts of the anhydride and of the amine at room temperature in solvents such as chloroform, ether, or benzene. The crude amic acids were dissolved in dilute sodium bicarbonate, and the resultant solutions were filtered and acidified. The amic acids were obtained in yields of 70–80% after purification and generally were used without recrystallization. Three new amic acids were prepared.

(a) **N-(p-Dimethylaminophenyl)phthalamic acid** was obtained in 53% yield as off-white crystals (from ethanol), m.p. 261–264°.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.61; H, 5.63; N, 9.86. Found: C, 67.60; H, 5.50; N, 10.02.

(b) **N-(p-Dimethylaminophenyl)maleamic acid** was obtained in 83% yield as scarlet crystals (from ethanol), m.p. 212°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.55; H, 5.98; N, 11.96. Found: C, 61.18; H, 5.20; N, 11.68.

(c) **N-(p-Methoxyphenyl)succinamic acid**[40] was obtained in 81% yield as slightly pink crystals (from water), m.p. 162.5–163.0°.

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.23; H, 5.94; N, 6.22.

Imides.—To support the assignment of isoimide structures, many of the corresponding imides were prepared for comparisons of infrared spectra. The imides were obtained by dehydration of the amic acid using acetic anhydride and sodium acetate or by direct heating. One new imide was prepared. **N-(p-Dimethylaminophenyl)maleimide** was obtained in 80% yield as reddish brown crystals (from acetone), m.p. 153–154°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.55; N, 12.96. Found: C, 66.42; H, 5.65; N, 12.75.

Maleisoimides and Phthalisoimides.—Since the procedures employed in the dehydration of N-substituted maleamic and phthalamic acids to isoimides were essentially the same for all compounds, only a general procedure is described.

To a solution or suspension of the amic acid in dry dioxane, 1.0 to 1.5 equivalents of trifluoroacetic anhydride was added. The solutions were allowed to stand at room temperature for 5 to 60 min.; the suspensions were stirred for 1 hr. at room temperature, during which time the amic acid went into solution. The solutions were poured into water to precipitate the products, which were collected within a few minutes and washed successively with water, 10% sodium bicarbonate, and water; in a few instances the precipitates were allowed to stand in 10% sodium bicarbonate for 30 min. The isoimides were crystallized from aqueous acetone. The yields, physical properties, and analyses of the isoimides prepared by this procedure are listed in Tables I and II.

The action of heptafluorobutyric anhydride was studied on N-(p-methoxyphenyl)maleamic acid and on N-(p-methoxyphenyl)-phthalamic acid using the same general procedure. The products, N-(p-methoxyphenyl)maleisoimide, obtained in 45% yield, m.p. 71°, and N-(p-methoxyphenyl)phthalisoimide, obtained in 65% yield, m.p. 134°, were identical in infrared spectra and melting points with the products obtained using trifluoroacetic anhydride.

Amic Acid Anhydrides.—Treatment of N-phenylglutaramic, N-(p-methoxyphenyl)glutaramic, and N-phenyladipamic acids with trifluoroacetic anhydride or heptafluorobutyric anhydride according to the general procedure described earlier yielded the amic acid anhydrides in each instance. To confirm the amic acid anhydride structures, each of the products was hydrolyzed to the original amic acid and treated with aniline or p-anisidine to form a mixture of the amic acid and the dianilide. Thus, from N-phenylglutaramic anhydride and aniline, both N-phenylglutaramic acid and glutaric dianilide were isolated and identified by melting points and infrared spectra.

(a) **N-Phenylglutaramic anhydride** was obtained in 40% yield as colorless crystals (from ethanol), m.p. 145°.

Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.52; H, 6.09; N, 6.88.

(b) **N-(p-Methoxyphenyl)glutaramic anhydride** was obtained in 50% yield as colorless crystals, m.p. 159°.

Anal. Calcd. for $C_{24}H_{28}N_2O_7$: C, 63.16; H, 6.14; N, 6.14. Found: C, 62.56; H, 5.95; N, 6.17.

(c) **N-Phenyladipamic anhydride** was obtained in 50% yield as colorless crystals, m.p. 135–138°.

Anal. Calcd. for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.60; N, 6.60. Found: C, 66.58; H, 6.51; N, 6.60.

Products from Succinamic Acids.—N-(p-Methoxyphenyl)-succinamic acid was recovered unchanged from treatment with trifluoroacetic anhydride. Similar treatment of N-phenylsuccinamic acid gave succinic dianilide in 60% yield as colorless needles (from acetone), m.p. 230.5–231.0° (lit.[41] m.p. 230°).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.41; H, 6.03; N, 10.25.

Treatment of N-phenylsuccinamic acid with heptafluorobutyric anhydride gave heptafluorobutyranilide in 30% yield, m.p. 85° (lit.[42] m.p. 92°). Product was identical in infrared spectrum and melting point with the amide prepared directly from aniline and heptafluorobutyric anhydride, and a mixture showed no depression in melting point. From N-(p-methoxyphenyl)succinamic acid and heptafluorobutyric anhydride, p-methoxy-

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(39) Melting points are not corrected. Analyses were performed by the Weiler and Strauss Microanalytical Laboratories, Oxford, England, and by Galbraith Laboratories, Inc., Knoxville, Tenn.

(40) This acid has been reported [A. Piutti, *Ber.*, **29**, 84 (1896)] without analytical data and as having a m.p. of 156–157°, with the imide, m.p. 162–163°. A sample of imide prepared from the amic acid had a m.p. of 161.0–162.5°.

(41) G. F. Morrell, *J. Chem. Soc.*, **105**, 1733 (1914).

(42) R. N. Hazeldine, *ibid.*, 2789 (1950).

heptafluorobutyranilide was obtained in 21% yield as colorless needles, m.p. 97°. The product was identical with the amide prepared directly from *p*-anisidine.

Products from N-Phenylmalonamic Acid.—Treatment of this amic acid with trifluoroacetic or heptafluorobutyric anhydrides gave a colorless powder in yields of 60–80% (calculated as dehydration product). The melting point varied with different preparations (210°, 186–190° dec.) and appeared to depend on the rate of heating. The infrared spectrum contained bands at 3.08 and 5.95 μ.

Anal. Calcd. for $C_9H_7NO_2$ (malonanilic acid–water): C, 67.07; H, 4.38; N, 8.69. Found: C, 66.63; H, 5.05; N, 8.49, corresponding to $C_9H_8NO_2$.

The products from thionyl chloride were colored, amorphous solids with broad melting range (205–220°). Attempted hydrolysis of an orange sample by boiling potassium hydroxide solution formed on acidification hydrogen sulfide and a green precipitate. The green solid had an infrared spectrum differing from that of the orange solid only in the sharpness of the carbonyl absorption.

Camphorisoimides and Related Compounds.—The literature procedures[12] were followed for the preparation of compounds in this series. N-Methyl-α-camphoramic acid was obtained by direct reaction of aqueous methylamine with suspended *d*-camphoric anhydride. N-Methylcamphorimide was prepared by heating the α-amic acid above its melting point and then distilling the melt. The yellow distillate did not solidify at room temperature; the infrared spectrum had four carbonyl bands indicating a mixture of camphoric anhydride (5.52, 5.65 μ) and the imide (5.80, 6.00 μ). One crystallization from ether and two from absolute ethanol gave needles, m.p. 38–40° (lit. m.p. 40–42°) having only the imide carbonyl bands. N-Methyl-β-camphoramic acid was obtained by dehydration of the α-amic acid to imide followed by hydrolysis of the crude imide. The β-amic acid was separated from α-amic acid, formed in smaller amounts, by fractional crystallization. The α-amic acid was dehydrated by heating with acetyl chloride followed by treatment with aqueous hydroxide to liberate the free isoimide; N-methyl-α-camphorisoimide was isolated in 16% yield as fine crystals (from ether), m.p. 132–133°. The β-amic acid was dehydrated with phosphorus oxychloride to a neutral product (9% yield) having four carbonyl bands indicating imide (5.80, 5.98 μ) and, presumably, β-isoimide (5.63, 5.90 μ).

Reaction of Isoimides with Piperidine.—The method was that of Mustafa, *et al.*[36] The products were not the amine adducts of the maleisoimides as shown by insolubility in acid and by infrared bands at 3.02 (N—H) and 5.97 μ (amide C=O) and absence of the original isoimide bands.

(a) **Piperidide of N-(*p*-methoxyphenyl)maleamic acid** was obtained in 40% yield as pale yellow crystals (from aqueous ethanol), m.p. 151.0–154.0°. The low yield resulted from the presence of amic acid in the sample of maleisoimide, indicated by the precipitation of the piperidinium salt of N-(*p*-methoxyphenyl)maleamic acid in 42% yield immediately on addition of piperidine; this salt was identified by comparison of its infrared spectrum with that of the salt prepared directly from the amic acid and piperidine.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.54; H, 6.96; N, 9.85.

(b) **Piperidide of N-(1-naphthyl)maleamic acid** was obtained in 86% yield as off-white needles (from acetone), m.p. 150.0–152.0°.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54, N, 9.09. Found: C, 73.82; H, 6.38; N, 9.10.

(c) **α-Piperidyl-N-(1-naphthyl)succinimide.**—The piperidine adduct of N-(1-naphthyl)maleimide was prepared for comparison with the diamide obtained from the isoimide. The product was obtained in 74% yield as a semisolid which after several recrystallizations from 95% ethanol gave colorless crystals, m.p. 147–151°. The infrared spectrum had no N–H absorption and a sharp imide band at 5.86 μ, with shoulders at 5.66 and 5.95 μ.

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 74.04; H, 6.77; N, 9.08.

Infrared Measurements.—Qualitative spectra were obtained in Nujol mulls on a Perkin-Elmer Infracord spectrophotometer, Model 137-B. Quantitative spectra were determined in purified dioxane[43] in an 0.0252-mm. cell on a Perkin-Elmer Model 21 spectrophotometer.

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[43] L. F. Fieser, "Experiments in Organic Chemistry;" 3rd Ed.; D. C. Heath and Co., Boston, Mass., 1955, p. 285.

Novel Method for the Preparation of Acid Anhydrides by Means of Diphenylmercury and Tertiary Phosphine

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The reactions of phenylmercuric acetate with triethyl phosphite or tri-*n*-butylphosphine have been investigated. Further, a novel method for the preparation of acid anhydrides by means of diphenylmercury and tri-*n*-butylphosphine has been studied. The reactions of two moles of carboxylic acids with one mole each of diphenylmercury and of tri-*n*-butylphosphine gave the corresponding carboxylic acid anhydrides in high yields along with mercury, benzene, and tri-*n*-butylphosphine oxide. Similarly, pyrophosphates or sulfonic acid anhydride were prepared in high yields by the reactions of two moles of phosphoric monoesters or sulfonic acid with one mole each of diphenylmercury and of tri-*n*-butylphosphine. The mechanisms of these reactions are discussed.

It recently has been found that mercuric and mercurous carboxylates are reduced by means of triethyl phosphite or tertiary phosphines to give mercury and the corresponding acid anhydrides in good yields.[1]

$$(RCO_2)_2Hg + R_3'P \longrightarrow Hg + (RCO)_2O + R_3'P{=}O$$
$$R' = C_2H_5O\text{–},\ n\text{-}C_4H_9\text{–},\ C_6H_5\text{–}$$

In the present study, the reduction of phenylmercuric acetate by the trivalent phosphorus compounds was tested first under the assumption that it would, when reduced, yield mercury and acetophenone. Indeed, an exothermic reaction was observed when the acetate reacted with triethyl phosphite at room temperature. Mercury and acetophenone, however, were not obtained, but ethyl acetate was produced in 74% yield along with a large amount of white crystals (I), m.p. 163–166°. These white crystals (I) were shown to be diethyl phenylmercuric phosphonate by means of elemental analysis and infrared absorption spectrum which has characteristic bands attributable to phosphorus–oxygen double bonds (1260 cm.⁻¹) and to a monosubstituted benzene ring (1600, 730 and 695 cm.⁻¹).

This reaction may proceed through an initial formation of adduct II of phenylmercuric acetate, and triethyl phosphite; this, subsequently, is transformed into III, conceivably by way of an internal nucleophilic displacement. The intermediate (III) thus formed has

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[1] T. Mukaiyama, H. Nambu, and I. Kuwajima, *J. Org. Chem.*, **28**, 917 (1963).