Replacing the isopropyl group by *n*-propyl or by higher alkyl groups resulted in a sharp drop in activity. The same was found true for the benzyl, cyclopentyl and cyclohexyl groups. The order of amebacidal activity with variation in R_2 is similar to that found in several other series, $CHCl_2 > CCl_3 > CH_2Cl$. The compounds substituted in the phenyl ring, (*e.g.*, R = dichloro or 4-butoxy) were considerably more active than the unsubstituted derivatives where R = H.

Acknowledgment.—The authors wish to thank Mr. M. E. Auerbach and Mr. K. D. Fleischer and staffs for the analytical data and corrected melting points recorded. The authors are indebted also to the Biology Division and especially to Dr. D. A. Berberian for the screening data.

Experimental[5]

N-Alkylbenzylamines (Table I).—The following examples illustrate the procedures employed for the preparation of these compounds.

2,4-Dichlorobenzyl chloride (39.4 g.) was added dropwise with stirring to 72 g. of isopropylamine over a period of 1 hour. After standing at room temperature overnight the mixture was warmed on a steam-bath, poured into water, sodium hydroxide solution added, and the oil which separated was extracted with benzene. After drying the combined extracts, the benzene was removed by distillation and the product was fractionally distilled.

A mixture of 26.7 g. of 4-butoxybenzaldehyde and 9 g. of isopropylamine was warmed on a steam-bath for 30 minutes and then dissolved in 125 ml. of ethanol and reduced catalytically with palladium-on-charcoal catalyst. After filtering off the catalyst and removing the solvent the product was fractionally distilled.

N-Alkyl-N-benzylhaloacetamides (Tables II and III).—The following example illustrates the general procedure for the preparation of these compounds.

Dichloroacetyl chloride (7.5 g.) was added dropwise with stirring at 0° to a mixture of 10.9 g. of N-(2,4-dichlorobenzyl)-isopropylamine, 100 ml. of ethylene dichloride and 50 ml. of 1 *N* sodium hydroxide solution. After the addition was completed the mixture was allowed to warm up to room temperature and stirring was continued for one hour. The organic layer was separated, washed with 1 *N* hydrochloric acid, then water, and dried. The ethylene dichloride was removed by distillation and the residue which solidified was recrystallized from Skellysolve A.

Most of the other amides were recrystallized either from Skellysolve B or C.

Reaction of N-Methyl-4-isopropylbenzylamine with Methyl Dichloroacetate.—The reactions with methyl dichloroacetate were carried out in the following manner.

A mixture of 8.15 g. of N-methyl-4-isopropylbenzylamine and 7.35 g. of methyl dichloroacetate was allowed to stand at room temperature for 24 hours. (In those cases where a product was obtained a slightly exothermal reaction occurred when the reactants were mixed.) The material was dissolved in benzene and washed several times with 1 *N* hydrochloric acid, water, 2.5% sodium hydroxide solution and then water. After drying, the benzene was removed by distillation to give 9.5 g. (70%) of N-(4-isopropylbenzyl)-N-methyldichloroacetamide.

The acid washings were combined, made basic and the resulting oil was taken up in ethylene dichloride to give 2.5 g. (30%) of N-methyl-4-isopropylbenzylamine.

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(5) All melting points are corrected.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

Ortho Esters, Imidic Esters and Amidines. VI. Two General Methods of Synthesis of N-Phenylformimidic Esters Involving Transesterification[1,2]

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The reaction of alkyl orthoformates with aniline in the presence of acid catalyst to produce alkyl N-phenylformimidates has been shown to be general. Higher alkyl orthoformates can be obtained readily from methyl and ethyl orthoformates by acid-catalyzed transesterification. Combination of these two reactions leads to a synthesis of N-phenylformimidic esters from methyl and ethyl orthoformates. The same over-all result has been attained by the transesterification of methyl and ethyl N-phenylformimidates by the common alcohols. The second method has been found to be more generally useful.

In earlier papers in this series[3,4] we reported the synthesis of ethyl N-phenylformimidate by the reaction of ethyl orthoformate with aniline. The present communication describes the extension of this synthesis to methyl N-phenylformimidate and to several higher alkyl N-phenylformidates using methyl orthoformate or one of the higher alkyl orthoformates (equation 1) and introduces an efficient and practical method of synthesis of some of the higher alkyl N-phenylformimidates *via* the transesterification of methyl or ethyl N-phenylformimidate (equation 2).

$$C_6H_5NH_2 + CH(OR)_3 \rightleftharpoons C_6H_5N{=}CH{-}OR + 2ROH \quad (1)$$

$$C_6H_5N{=}CH{-}OR + R'OH \rightleftharpoons C_6H_5N{=}CH{-}OR' + ROH \quad (2)$$

(1) Paper V, THIS JOURNAL, **76**, 4379 (1954).

(2) Taken in part from the M.A. theses of Thomas D. Higgins, Jr. (1954) and Paul R. Noyes (1952), the University of Texas.

(3) R. M. Roberts, THIS JOURNAL, **71**, 3848 (1949).

(4) R. M. Roberts and R. H. DeWolfe, *ibid.*, **76**, 2411 (1954).

Recently, Alexander and Busch[5] described a convenient method of preparing higher orthoformic esters by the transesterification of ethyl orthoformate, although they were unable to obtain interchange using isopropyl or *t*-butyl alcohols. By substituting methyl orthoformate for ethyl orthoformate we have succeeded in effecting interchange with isopropyl alcohol. The interchange was, however, quite slow. The addition of a small amount of concentrated sulfuric acid markedly increased the rate of removal of methyl alcohol and ultimately a yield of 75% of isopropyl orthoformate was realized in a reasonable period of time.

The use of acid catalysis was found to be advantageous also in the transesterification of ethyl orthoformate by all of the primary and the low-boiling secondary alcohols studied. The yields of alkyl orthoformates were equal to or higher than those reported by Alexander and Busch, and the time required for removal of ethyl alcohol was

(5) E. R. Alexander and H. M. Busch, *ibid.*, **74**, 554 (1952).

TABLE I
ALKYL ORTHOFORMATES

Alkyl	Method	Yield, %	B.p., °C.	Mm.	$n_D^{(t°)}$	d^{25}	MR Sum.	MR Obsd.	Empirical formula	Analyses, %[c] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
n-Propyl	A	95	106–108	40	1.4058 (25)								
Isopropyl	A[a]	75	65–66	18	1.3940 (25)								
n-Butyl	A	92	132–133	21.5									
			147	40	1.4155 (25)								
n-Amyl	A	80	135–137	4	1.4237 (25)								
Isoamyl	A	95	105–106	1.5	1.4205 (25)								
n-Hexyl	A	87	152–153	1.8									
Diethylcyclohexyl	B		64	1.1	1.4328 (25) 1.4308 (30)	0.945	55.7	55.8	$C_{11}H_{22}O_3$	65.31	65.48	10.96	10.95
Ethyldicyclohexyl	B		109	1.1	1.4605 (25) 1.4585 (30)	0.977	72.0	71.8	$C_{15}H_{28}O_3$	70.27	70.47	11.01	11.05
Cyclohexyl	B, C	44	72.6–73.8[b]						$C_{19}H_{34}O_3$	73.50	73.46	11.04	11.25
3-Heptyl	C[a]	42	133	1.1	1.4322 (25) 1.4301 (30)	0.861	108.7	107.9	$C_{22}H_{46}O_3$	73.68	74.05	12.93	12.93

[a] Methyl orthoformate was the starting material. [b] M.p. [c] Analyses by Drs. G. Weiler and F. B. Strauss, Oxford, England.

considerably shortened (method A, Experimental section). Attempted acid-catalyzed interchange between methyl orthoformate and *t*-butyl alcohol or 2-methyl-2-hexanol led to extensive dehydration of the tertiary alcohols and hydrolysis of the ortho ester. In the absence of the acid catalyst no appreciable reaction occurred during heating for 48 hours or longer. Similarly, in the interchange between cyclohexyl alcohol and ethyl orthoformate, some dehydration occurred during the removal of ethyl alcohol and more during the recovery of the excess cyclohexyl alcohol. In the presence of a small amount of metallic sodium rather than sulfuric acid, no dehydration occurred but ethyl alcohol was produced very slowly. From the reaction mixture diethylcyclohexyl orthoformate, ethyldicyclohexyl orthoformate and cyclohexyl orthoformate were isolated. The best procedure for obtaining complete transesterification by cyclohexyl alcohol and the other high-boiling secondary alcohols was to use acid catalysis while removing ethyl alcohol but to add sodium before distilling the excess high-boiling alcohol and product (method C, Experimental section). The yields and properties of the alkyl orthoformates prepared are summarized in Table I.

Optimum conditions for the preparation of methyl N-phenylformimidate from methyl orthoformate and aniline (equation 1, R = CH_3) required the use of a larger excess of ortho ester and a larger proportion of catalyst (method D, Experimental section) than required for the ethyl ester. Even so, the yield was lower than that of the ethyl ester.[3]

The reactions of the other ortho esters with aniline (equation 1) were similar to those of ethyl orthoformate,[3,4] essentially the same procedure (method E) being followed in the reactions of the orthoformates other than methyl and *n*-butyl. The ease of separation of the various components varied considerably in the several preparations, and the conditions described in the Experimental section (procedures, column sizes, etc.) were chosen to effect the separations efficiently. The separation of excess[6] orthoformate from the product was complicated in one instance by the observation that *n*-butyl orthoformate and *n*-butyl N-phenylformimidate have almost identical boiling points and distil together during the working up of the product. By adding N,N'-diphenylformamidine to the mixture and heating with aniline hydrochloride, the ortho ester was converted to imidic ester according to the over-all equation[4]

$$(C_4H_9O)_3CH + C_6H_5N{=}CH{-}NHC_6H_5 \longrightarrow 2C_6H_5N{=}CH{-}OC_4H_9 + C_4H_9OH \quad (3)$$

Fortunately, this rather tedious process was not necessary for the other esters prepared, for methyl, ethyl, *n*-propyl and isopropyl N-phenylformimidates boiled sufficiently *higher* and amyl (and higher alkyl) N-phenylformimidates boiled sufficiently *lower* than the corresponding orthoformates to allow separation.[7] The yields and properties of the alkyl N-phenylformimidates prepared from the corresponding alkyl orthoformates are summarized in Table II.

Although the yields of formimidic esters by the route of equation 1 were quite satisfactory, the discovery that N-phenylformimidic esters could be transesterified (equation 2) provided a convenient alternative route of more general utility than that just described. As far as we know, there has been no previous report of the transesterification of an N-phenylformimidic ester, although the transesterification of an acetimidic ester in low yield has been reported.[8]

When ethyl N-phenylformimidate was heated with an alcohol higher-boiling than ethyl alcohol, ethyl alcohol could be removed from the reaction mixture by fractional distillation. Addition of acid (in the form of aniline hydrochloride) increased the rate of formation of ethyl alcohol; however, the reaction became more complex than simple trans-

(6) Shown to increase the yield in a study of ethyl N-phenylformimidate synthesis; R. M. Roberts and Paul J. Vogt, unpublished experiments.

(7) Calculations based on the Clausius–Clapeyron equation and available boiling point data indicated that separation difficulties would be encountered with all of the isomeric butyl compounds. Accordingly, no further reactions were attempted with butyl orthoformates.

(8) R. E. Benson, U. S. Patent 2,516,293, July 25, 1951; *C.A.*, **45**, 640 (1951).

TABLE II

ALKYL N-PHENYLFORMIMIDATES FROM ALKYL ORTHOFORMATES

Alkyl	Yield, %	Method	B.p., °C.	Mm.	$n_D^{(t°)}$	d^{25}	MR Sum.[a]	MR Obsd.	Empirical formula	Analyses, %[b] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Methyl	70	D	102–103	40	1.5377 (25)	1.035	40.2	40.8			[c]		
Ethyl	89	[d]	117–118	40	1.5275 (20)[e]	1.000	44.8	45.8					
					1.5248 (25)								
n-Propyl	79	E	134	40	1.5172 (25)	0.983	49.4	50.2	$C_{10}H_{13}NO$	73.58	73.44	8.03	7.96
					1.5149 (30)								
Isopropyl	83	E	121	39	1.5126 (25)						[f]		
n-Butyl	78	F	148	40	1.5132 (25)						[f]		
n-Amyl	79	E	112	1.1	1.5068 (25)	0.958	58.7	59.3	$C_{12}H_{17}NO$	75.37	75.72	8.95	8.90
					1.5046 (30)								
Isoamyl	70	E	82–83	1.1	1.5065 (25)	0.955	58.7	59.5	$C_{12}H_{17}NO$	75.37	75.36	8.95	8.83
					1.5042 (30)								
n-Hexyl	60	E	107–109	1.3	1.5045 (25)	0.951	63.3	64.0	$C_{13}H_{19}NO$	76.05	76.09	9.33	9.29
					1.5024 (30)								
Cyclohexyl	52	E	109	1.1	1.5372 (25)	1.026	61.1	61.8	$C_{13}H_{17}NO$	76.81	76.81	8.43	8.26
					1.5352 (30)								
3-Heptyl	51	E	98	1.1	1.4991 (25)	0.942	67.9	68.4	$C_{14}H_{21}NO$	76.66	76.63	9.65	9.78
					1.4971 (30)								

[a] From summation of atomic refraction values. [b] Analyses by Clark Microanalytical Lab., Urbana, Ill., and Drs. G. Weiler and F. B. Strauss, Oxford, England. [c] W. J. Comstock and F. Kleeberg, *Am. Chem. J.*, **12**, 498 (1890); O. Schmidt, *Ber.*, **36**, 2476 (1903). [d] Reference 3. [e] Incorrectly reported as $n^{25}D$ in reference 3. [f] See Table III.

TABLE III

ALKYL N-PHENYLFORMIMIDATES FROM TRANSESTERIFICATION

Alkyl	Yield, %	Method	B.p., °C.	Mm.	$n^{25}D$	d^{25}	MR Sum.[a]	MR Obsd.	Empirical formula	Analyses, %[b] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Isopropyl	80	G[c]	122	40	1.5130	0.971	49.4	50.5	$C_{10}H_{13}NO$	73.63	73.40	8.03	7.71
n-Butyl	94	G	147–149	40	1.5128	.968	54.0	55.0	$C_{11}H_{15}NO$	74.54	74.34	8.53	8.52
Isobutyl	78	G	142–143	40	1.5072	.963	54.0	54.6	$C_{11}H_{15}NO$	74.54	74.58	8.53	8.75
s-Butyl	85	G	138–139	40	1.5099	.962	54.0	55.1	$C_{11}H_{15}NO$	74.54	74.65	8.53	8.50
t-Butyl	51	H[c]	133	40	1.5143	.966	54.0	55.2	$C_{11}H_{15}NO$	74.54	74.66	8.53	8.23
t-Amyl	57	H	86–88	2	1.5121	.963	58.7	59.6	$C_{12}H_{17}NO$	75.35	75.38	8.96	8.82
n-Hexyl	75	G	113	2	1.5051	.949	63.3	64.2			[d]		
Cyclohexyl	87	H	115–117	1.5	1.5373	1.025	61.1	62.0			[d]		

[a] From summation of atomic refraction values; the value used for N was 4.10. [b] Analyses by Clark Microanalytical Lab., Urbana, Ill., and Drs. G. Weiler and F. B. Strauss, Oxford, England. [c] Methyl N-phenylformimidate was used as starting material. [d] See Table II.

esterification. A large proportion of N,N′-diphenylformamidine was found among the products, and the refractive index of the liquid products indicated contamination of the imidic ester by ortho ester. These substances can be accounted for by assuming reversal of the reaction of equation 1 giving aniline and an ortho ester (either simple or mixed) followed by reaction of the aniline with the ethyl (or alkyl) N-phenylformimidate to give N,N′-diphenylformamidine.[3,4,9] Another disadvantage of an acid catalyst for these transesterifications is the susceptibility of tertiary alcohols to dehydration (*vide supra*).

The mixture of imidic ester and ortho esters obtained from ethyl N-phenylformimidate and *n*-butyl alcohol was converted into pure *n*-butyl N-phenylformimidate by the procedure described above (equation 3). Although this two-step procedure might have been extended to other esters as well, it was not necessary, for transesterification could be effected at a reasonable rate in the absence of acid with the elimination of most of the undesired side reactions. Indeed, the policy of dissolving a small amount of pure sodium in the alcohol before addition of the imidic ester was adopted in order to neutralize any acids that might be present as impurities, on the walls of the glassware, etc. There was no evidence of catalysis by the alkoxide.[10]

Table III summarizes the yields and properties of the new alkyl N-phenylformimidates obtained by transesterification of methyl or ethyl N-phenylformimidate. Typical procedures are described in the Experimental section. When possible it is desirable to use ethyl N-phenylformimidate rather than methyl N-phenylformimidate as starting material, for three reasons: (1) the yield of the ethyl ester is higher than that of the methyl ester (equation 1), (2) ethyl orthoformate is cheaper than methyl orthoformate, and (3) use of the ethyl ester provides a higher reaction temperature in the transesterification, thereby increasing the rate of reaction.

In conclusion, when the two procedures for the preparation of alkyl N-phenylformimidates described here are compared, it appears that the more generally useful method for the preparation

(9) E. B. Knott, *J. Chem. Soc.*, 686 (1945).

(10) This is not surprising, since the hydrolysis of ortho esters is catalyzed by acids but not by bases; *cf.* J. N. Brønsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

of higher alkyl N-phenylformimidates is that of equation 2.

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Experimental[11]

The alcohols used as starting materials were Matheson, Coleman and Bell products. They were distilled (usually from sodium) through a Vigreux column before use. Methyl and ethyl orthoformates were obtained from Kay–Fries and were redistilled just before use. Aniline was redistilled before use.

The experiments summarized in Tables I and II are illustrated by the following procedures, one for each Method listed in the tables. The other experiments differed from those described in minor details, mainly in the type and size of distilling columns required for the separations.

Preparation of Alkyl Orthoformates. *n*-Propyl Orthoformate (Method A).—A mixture of 54.2 g. (0.37 mole) of ethyl orthoformate, 88.2 g. (1.47 moles) of *n*-propyl alcohol and two drops (*ca.* 0.05 g.) of concd. sulfuric acid was heated to boiling. A 32-in. glass helix-packed column equipped with a heated jacket and a total reflux, controlled take-off distilling head was used for the removal of ethyl alcohol as it was produced. The theoretical amount of ethanol (65 ml.) was collected in *ca.* three hours. The large column was replaced by a 10-in. Vigreux column insulated with Pyrex wool, and the excess *n*-propyl alcohol was distilled. The pressure was reduced to 40 mm., and 66.0 g. (95% of the theoretical amount) of *n*-propyl orthoformate was collected, b.p. 106–108° (40 mm.) (see Table I).

Diethyl Cyclohexyl Orthoformate and Ethyl Dicyclohexyl Orthoformate (Method B).—Cyclohexyl alcohol (200 g., 2.0 moles) and ethyl orthoformate (74 g., 0.50 mole) were heated with 0.3 g. of sodium. The 32-in. column and head described above were used for the removal of ethyl alcohol. After 8 days only 35 ml. (40% of the theoretical amount) had been removed, and the rate of appearance at the head of the column had become extremely slow. The excess cyclohexyl alcohol then was distilled through a short Vigreux column. The pressure was reduced and 78.2 g. of distillate was collected at 66–74° (1.8 mm.) and 28.5 g. at 124–126° (1.8 mm.). When the distilling flask was allowed to cool, its contents (10.9 g.) solidified. This was shown to be fairly pure cyclohexyl orthoformate (see below).

The fraction boiling at 66–74° (1.8 mm.) was redistilled. It was mainly diethylcyclohexyl orthoformate, b.p. 64° (1.1 mm.) (see Table I).

The fraction boiling at 124–126° (1.8 mm.) was redistilled. It was mainly ethyldicyclohexyl orthoformate, b.p. 109° (1.1 mm.) (see Table I).

In one preparation of isoamyl orthoformate in which a smaller than usual amount of sulfuric acid catalyst was used, the amount of ethyl alcohol removed readily was a fraction of the theoretical, and two low-boiling distillation fractions were obtained. Aparently mixed ortho esters may be obtained rather readily in the presence of little or no acid catalyst.[12]

Cyclohexyl Orthoformate (Method C).—A mixture of 200 g. (2.0 moles) of cyclohexyl alcohol, 74 g. (0.50 mole) of ethyl orthoformate and four drops (*ca.* 0.1 g.) of concd. sulfuric acid was heated under a 15-in. Vigreux column equipped with a heated jacket and a total reflux, controlled take-off distilling head. The ethyl alcohol which was removed contained some cyclohexene as shown by decolorization of bromine in carbon tetrachloride solution; 96.3 ml. of distillate, b.p. 78–79°, was obtained in a few hours. The reaction mixture was cooled and 1.0 g. of sodium was added to it. The excess cyclohexyl alcohol was then removed at atmospheric pressure without further dehydration. When the distilling flask was allowed to cool to room temperature, its contents crystallized. Hot ethyl acetate was added and the solution was filtered from insoluble sodium salts; the filtrate deposited crystals of cyclohexyl orthoformate, 67.5 g. (44% of the theoretical amount), m.p. 69–73°. The completely pure product melted at 72.6–73.8° (see Table I).

Preparation of Alkyl N-Phenylformimidates. Methyl N-Phenylformimidate (Method D).—In a 300-ml. flask were placed 116.5 g. (1.10 moles) of methyl orthoformate, 51.0 g. (0.55 mole) of aniline and 3.56 g. (0.028 mole) of aniline hydrochloride. The flask was attached to a 32-in. glass helix-packed column with a heated jacket and a total reflux, controlled take-off distilling head, and the mixture was refluxed until the column-head temperature was 64°. Methyl alcohol was then removed, 54 ml. being obtained in a two-hour period. The column was replaced by a 10-in. insulated Vigreux column for the removal of excess methyl orthoformate; 48.3 g. were distilled at a temperature of 100–103°. The flask was allowed to cool and the pressure was reduced to 40 mm. After a negligible forerun was discarded, methyl N-phenylformimidate was collected at 102–103.5° (40 mm.); it weighed 52.0 g. (70% of the theoretical amount). The residue in the flask (20 g.) was mostly N,N′-diphenylformamidine; in repeated experiments this may be used in reaction with methyl orthoformate[3] so that the over-all yield of methyl N-phenylformimidate may be considerably higher than 70%.

***n*-Propyl N-Phenylformimidate (Method E).**—A mixture of 66.0 g. (0.347 mole) of *n*-propyl orthoformate, 25.8 g. (0.277 mole) of aniline and 0.36 g. (0.003 mole) of aniline hydrochloride was heated in a flask attached to a 15-in. Vigreux column equipped with a heated jacket. The theoretical amount of *n*-propyl alcohol was distilled at 96°. The pressure was reduced to 36 mm., and 10.9 g. of excess *n*-propyl orthoformate was removed at 104°. The product then distilled at 130° (36 mm.); 35.5 g. (79% of the theoretical amount) was obtained (see Table II).

In the preparation of the *n*-amyl, isoamyl and *n*-hexyl esters, it was necessary to use a 32-in. glass helix-packed column to separate the products from excess ortho ester.

***n*-Butyl N-Phenylformimidate (Method F).**—*n*-Butyl orthoformate (88.6 g., 0.382 mole), aniline (23.6 g., 0.254 mole) and aniline hydrochloride (0.40 g., 0.003 mole) were heated under a 10-in. Vigreux column; *n*-butyl alcohol (36.8 g.) was removed as it formed. The pressure was reduced to 15 mm., and 65.5 g. of distillate boiling at 125–126° was obtained, $n^{25}D$ 1.4649. This was a mixture of *n*-butyl N-phenylformimidate and *n*-butyl orthoformate, mainly. Fifty grams of N,N′-diphenylformamidine and 1.6 g. of aniline hydrochloride were added, and the mixture was heated under a distilling column, as before. *n*-Butyl alcohol (25.4 g.) was removed by distillation. The pressure was reduced to 40 mm., and 35.2 g. of *n*-butyl N-phenylformimidate was collected at 148°, $n^{25}D$ 1.5132.

Reaction of Ethyl N-Phenylformimidate with *n*-Butyl Alcohol in the Presence of Acid.—Preliminary experiments were carried out in which the times required for ethyl alcohol to appear at the top of a distilling column were determined when mixtures of the ester and *n*-butyl alcohol were heated under the same conditions, except that in one experiment a small amount of aniline hydrochloride was added and in another a small amount of sodium *t*-butoxide. The ethyl alcohol was produced in the presence of acid in less than half the time required in the presence of base.

A mixture of ethyl N-phenylformimidate (1.00 mole), *n*-butyl alcohol (1.59 moles), and aniline hydrochloride (1.1×10^{-3} mole) was heated in a flask attached to a small vacuum-jacketed distilling column having a centered rod sheathed with Pyrex insulation fabric (*ca.* 10 theoretical plates). During *ca.* 3 hr., 0.77 mole of ethyl alcohol was removed. *n*-Butyl alcohol then was distilled, first at atmospheric pressure (b.p. 117°), then at 40 mm.; a total of 0.49 mole was obtained. Continued distillation gave 143 g. of liquid most of which boiled at 140–147° (40 mm.), $n^{25}D$ 1.4881, d^{25} 0.942. A residue of 38.7 g. remained which crystallized on cooling and was undoubtedly N,N′-diphenylformamidine.

A 30-g. portion of the distillate was mixed with 21 g. of N,N′-diphenylformamidine and 0.09 g. of aniline hydrochloride. The mixture was heated under reflux at atmospheric pressure for 45 minutes. The pressure was lowered to 40 mm., and, after a small amount of *n*-butyl alcohol was distilled, *n*-butyl N-phenylformimidate was collected, b.p. 147° (40 mm.), $n^{25}D$ 1.5128, d^{25} 0.968 (see Table III).

In a subsequent experiment carried out in the absence of acid (see method G below), a 94% yield of *n*-butyl N-phenyl-

(11) All boiling points are uncorrected.

(12) *Cf.* H. W. Post and E. R. Erickson, THIS JOURNAL, **55**, 3851 (1933).

formimidate, b.p. 147–149°, $n^{25}D$ 1.5123 was obtained, without the occurrence of the troublesome acid-catalyzed side reactions which lead to N,N'-diphenylformamidine and ortho ester.

The following experiments illustrate the methods used for all the compounds reported in Table III; experiments not described differed from these mainly in the type and size of distilling columns used and the length of time required to remove the alcohols produced by transesterification. It is necessary to use methyl N-phenylformimidate for the synthesis of isopropyl and *t*-butyl N-phenylformimidates because of the proximity of the boiling points of ethyl, isopropyl and *t*-butyl alcohols. Even when the methyl ester is used, a fairly efficient fractionating column is required; a 32-in. glass helix-packed column was found to be satisfactory. Several days of reflux with intermittent removal of the methyl alcohol produced were required in the synthesis of these two esters. By comparison, when *t*-amyl N-phenylformimidate was prepared by transesterification of *ethyl* N-phenylformimidate, only 2.5 hr. were required for the removal of the ethyl alcohol.

***sec*-Butyl N-Phenylformimidate (Method G).**—To 60 g. (0.81 mole) of *sec*-butyl alcohol was added 0.04 g. (2 m. atoms) of sodium. After the sodium had dissolved, 39.6 g. (0.27 mole) of ethyl N-phenylformimidate was added, and the mixture was heated in a flask attached to a 32-in. glass helix-packed column with a total reflux, controlled take-off distilling head. Within four hours 13 ml. of ethyl alcohol had been removed. The reaction was left on total reflux overnight and then an additional 2 ml. of ethyl alcohol was removed (a total of 15 ml. of the theoretical 15.8 ml.). The excess *sec*-butyl alcohol was distilled (b.p. 98.5°), 43 ml. of the theoretical 49 ml. being obtained. The column was allowed to drain and was then replaced by a 10-in. helix-packed column. The pressure was lowered to 40 mm., and 40.1 g. (85%) of *sec*-butyl N-phenylformimidate was obtained, b.p. 138–139° (40 mm.) (see Table III).

In the experiments with the higher-boiling alcohols, a shorter distilling column was satisfactory for the separation of the ethyl alcohol and indeed a short column was advantageous in the distillation of the product, which should be carried out at low pressure and temperature in order to avoid decomposition into phenyl isocyanide. Although the *n*-hexyl derivative was obtained by the direct fractional distillation procedure of method G, it is recommended that it and other high-boiling esters be prepared by method H, described below.

Cyclohexyl N-Phenylformimidate (Method H).—To 60 g. (0.60 mole) of cyclohexyl alcohol was added 0.2 g. of sodium. After the sodium had dissolved, 30 g. (0.20 mole) of ethyl N-phenylformimidate was added and the mixture was heated in a flask attached to a 10-in. Vigreux column with a total reflux, controlled take-off head. Within one hour 10.8 ml. (12 ml. theoretical) of ethyl alcohol had been collected. The column was drained and replaced by a simple distilling adapter, and the excess cyclohexyl alcohol and product were removed as rapidly as possible from the sodium alkoxide. The alcohol distilled at 64–66° (10 mm.) and the product at *ca.* 120–127° (2 mm.) (they were collected in the same flask). The mixture was then separated by distillation through a 6-in. Vigreux column; 41 ml. of cyclohexyl alcohol, b.p. 36–47° (1.4 mm.), and 35.2 g. (87%) of cyclohexyl N-phenylformimidate, b.p. 109–110° (1.4 mm.), were obtained (see Table III).

AUSTIN 12, TEXAS

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF J. T. BAKER CHEMICAL COMPANY]

p-Methoxy-2,2-bis-(p-methoxyphenyl)-acetophenone and Some Derivatives

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The reported reactions of 2,2-diphenylacetophenone suggested that the analogous compound containing *p*-methoxy groups on the benzene rings might be converted in one step to the synthetic estrogenic substance, chlorotris-(*p*-methoxyphenyl)-ethylene. Accordingly, *p*-methoxy-2,2-bis-(*p*-methoxyphenyl)-acetophenone has been prepared and its chemistry studied. It was found to give an oxime readily and failed to give the enol derivatives reported for 2,2-diphenylacetophenone. Thus, the compound with *p*-methoxy substituents reacted more as a ketone and less as an enol than is reported for the unsubstituted compound.

While absorption spectral data[1] indicate that 2,2-diphenylacetophenone (I) exists in the keto form in the liquid state, many of its chemical reactions suggest the enol form. For example, it was only with great difficulty and in low yield that Kohler[2] succeeded in converting it to the oxime after previous investigators[3] had failed. Attempts to cause reaction between I and hydrazine, phenylhydrazine or aniline also failed. However, I was readily converted to the acetate of the enol form with acetic anhydride, and was benzoylated when heated with benzoyl chloride and pyridine.[3] The reaction of I and phosphorus pentachloride is reported to give a 59% yield of chlorotriphenylethylene (II).[4]

A convenient method of preparing chlorotris-(*p*-methoxyphenyl)-ethylene (VII)[5] was desired in this Laboratory. The reported reactions of I suggested that VII might be prepared in suitable yield by the reaction of phosphorus pentachloride with *p*-methoxy-2,2-bis-(*p*-methoxyphenyl)-acetophenone (IV). The only reported preparation found for this latter material involved the condensation of anisoin and anisole using sulfuric acid, and yielded a mixture from which pure IV could not be obtained.[6] In the present work it was found that the use of sirupy phosphoric acid as the condensing agent gave much better results. Furthermore, the presence of an extra mole of anisole in the reaction mixture gave a solid complex V of anisole and IV which could be purified by recrystallization. The anisole was then readily removed from V by heating on the steam-bath at reduced pressure, leaving unchanged IV as a residue.

An alternate method of preparing IV involving the reaction of *p*-methoxyphenylmagnesium bromide with nitrile III was investigated. Though IV was obtained in 40% yield by this method, its separation from unreacted nitrile and high-melting material of unknown structure was difficult. Thus, the condensation of anisoin and anisole in the presence of phosphoric acid is the preferable method.

(1) H. Ley and W. Manecke, *Ber.*, **56**, 777 (1923).

(2) E. P. Kohler, *Amer. Chem. J.*, **36**, 194 (1906).

(3) (a) H. Biltz, *Ber.*, **32**, 650 (1899); (b) M. Delacre, *Bull. soc. chim. France*, [3] **13**, 857 (1895).

(4) E. Bergmann and A. Bondi, *Ber.*, **64**, 1467 (1931).

(5) This substance is known commercially as Tace and is marketed by the Wm. S. Merrell Company.

(6) E. C. Dodds, *et al.*, *Proc. Roy. Soc. (London)*, **132B**, 83 (1944); *C. A.*, **38**, 3639 (1944).