[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Interaction of the Acid Chloride of 2-Benzoylbenzoic Acid with Phenols. I. Aryl Esters and Phenylaryloxyphthalides[1]

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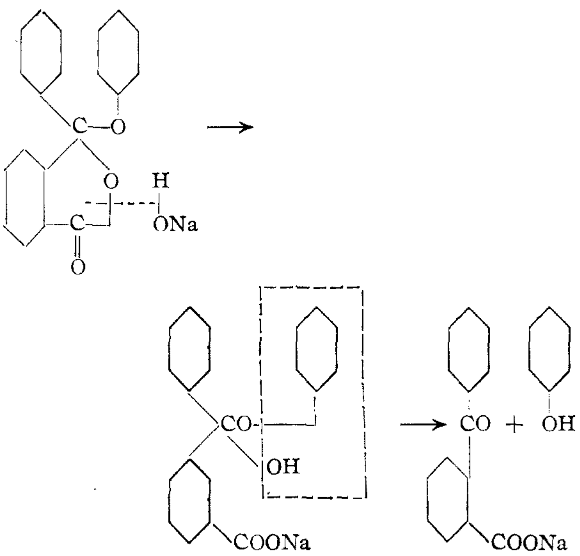
It has been shown that the phenyl ester of 2-(4'-methoxybenzoyl)-benzoic acid rearranges readily and practically quantitatively, under the influence of aluminum chloride, to yield phenolphthalein.[3] It now seemed desirable to determine whether or not aryl esters of 2-benzoylbenzoic acid, in general, could be transformed by aluminum chloride into diarylphthalides.

We began our investigation with a study of the phenyl ester of 2-benzoylbenzoic acid. The preparation of the latter substance was attempted by three methods: interaction of the acid chloride with (a) potassium phenolate, (b) with phenol and (c) with phenol in the presence of pyridine. Instead of the mere formation of the phenyl ester three isomeric products were obtained, the nature and quantity of each dependent, in general, upon the method employed. One of the products was 4'-hydroxydiphenylphthalide; the other two were, presumably, the true phenyl ester and phenylphenoxyphthalide, respectively.[4]

It was impossible to differentiate the phenyl ester from the phenylphenoxyphthalide by chemical means; both compounds are hydrolyzed by alkali with the formation of 2-benzoylbenzoic acid and phenol. The hydrolysis of the phenoxyphthalide may be explained by the following formulation.

When heated with aluminum chloride, or mixed with concd. sulfuric acid, the ester and the phenoxyphthalide both yielded 4'-hydroxydiphenylphthalide.



Reaction of the acid chloride of 2-benzoylbenzoic acid with six other phenols was studied; in all instances, except one, an ester and a phenylaryloxyphthalide were obtained and in some cases a diarylphthalide[5] was also produced.

Experimental Part

The general procedure (a) is illustrated below in the case of phenol and the acid chloride of 2-benzoylbenzoic acid.

The products obtained with various phenols are recorded in Table I.

(a) The Acid Chloride and the Potassium Derivative of the Phenol.—A mixture of 27 g. of 2-benzoylbenzoic acid and 29 g. of thionyl chloride (Pract.) was allowed to react for twelve hours, unchanged thionyl chloride removed under diminished pressure,[6] the chloride dissolved in dry, thiophene-free benzene; potassium phenolate,[7] prepared from 17 g. of phenol, 6.9 g. of potassium and 400 cc. of absolute ether was added.[8] After twelve hours the material was filtered through a Jena filter, the filtrate

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[1] This paper represents the first part of a dissertation to be submitted to the Graduate School by Mr. Swisher in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] The Upjohn Company Fellow.

[3] Blicke and Weinkauff, THIS JOURNAL, **54**, 331 (1932).

[4] An intensive study has been made by others of alkyl esters of various 2-benzoylbenzoic acids and the existence of two isomeric forms—a ketoid (true ester) and a lactoid (phenylalkoxyphthalide)—established [Meyer, *Monatsh.*, **25**, 475, 1177 (1904); Hantzsch and Schwiete, *Ber.*, **49**, 215 (1916); Hantzsch, *ibid.*, **52**, 1572 (1919); and others]. In these instances the particular modification of the ester obtained depended upon the manner in which the acid chloride had been prepared, and only one modification was formed in any given reaction.

Our results in the case of phenol and 2-benzoylbenzoic acid are decisively different in that the same reaction products (both forms of the ester) were produced regardless whether the acid chloride had been prepared by the use of thionyl chloride, phosphorus pentachloride or by chlorination of phenylphthalide.

[5] The diarylphthalides will be discussed in Part II of this paper.

[6] The first eight times the chloride was prepared it was obtained as an oil, but in all subsequent experiments the material crystallized spontaneously. The chloride was washed several times with small amounts of absolute ether.

[7] In order to obtain the phenolate free from unchanged phenol it was prepared in a specially constructed side-arm flask fitted with a stirrer and a reflux condenser. The phenolate was filtered through a Jena filter and washed thoroughly with absolute ether. Special precautions were observed to prevent contact with atmospheric moisture.

[8] In the case of all other phenols 500 cc. of benzene was used instead of ether and the mixture was heated.

shaken with sodium hydroxide solution, the benzene–ether layer separated and the solvents removed. The residue, 30 g., was boiled with ether and the insoluble portion recrystallized from alcohol; m. p. 162–163°; yield 4 g. The solvent was removed from the ether extract and the residue, 24.5 g., recrystallized from alcohol; m. p. 80–82°.

Since some of the esters and arylaryloxyphthalides are insoluble in ether and benzene, the precipitate which contained the potassium chloride was placed in a dish; after some time the material was added, cautiously in small portions, to sodium hydroxide solution and the organic product recrystallized.

Potassium phenolate was added to the acid chloride, prepared from 27 g. of 2-benzoylbenzoic acid, 24.5 g. of phosphorus pentachloride and 300 cc. of carbon disulfide;[9] there was obtained 24 g. of the compound of m. p. 80–82° and 4 g. of the compound of m. p. 162–163°.

The following experiment describes the behavior of the chloride obtained from phenylphthalide. A slow stream of dry chlorine was passed into 25 g. of phenylphthalide,[10] heated to 115–120°,[11] for twenty-four hours. A stream of dry air was passed through the hot mixture to remove chlorine and hydrogen chloride, the yellow, sirupy liquid dissolved in benzene and treated with potassium phenolate. There was formed 18 g. of the product of m. p. 80–82° and 3 g. of the compound which melted at 162–163°.

(b) The Acid Chloride and Phenol.—To the acid chloride, obtained from 0.1 mole of 2-benzoylbenzoic acid, there was added 0.1 mole of the phenol, dissolved or suspended in 150 cc. of benzene. After eighteen hours any crystalline material present was triturated with 10% sodium hydroxide solution, washed with water and recrystallized. The benzene filtrate was shaken with alkali, then with water, dried and the solvent removed. The oily residue became crystalline when cooled and treated with a small amount of ether.

In the case of phenol, α- and β-naphthol this method yielded only a diarylphthalide.

(c) The Acid Chloride, the Phenol and Pyridine.—The acid chloride, obtained from 0.1 mole of the acid, was dissolved in benzene and added to 0.1 mole of phenol, dissolved in 25 cc. of dry pyridine. After two to six days the reaction mixture contained a precipitate of pyridine hydrochloride, in some cases admixed with ester. The mixture was treated with 30 cc. of concd. hydrochloric acid, shaken thoroughly and any insoluble material removed and treated separately. The benzene layer was shaken twice with 30-cc. portions of hydrochloric acid and then with sodium carbonate solution; insoluble material was removed and purified. Finally, the benzene layer was shaken with sodium hydroxide solution, in order to extract any hydroxydiarylphthalide present, washed with water, dried, the solvent removed and the product purified.

Interaction of the Phenyl Ester and Phenoxyphthalide with Aluminum Chloride and with Sulfuric Acid.—Since the ester and the phthalide reacted in the same manner, these processes are illustrated only in the case of the lower melting product. A mixture of 2 g. of the compound, 2 g. of anhydrous aluminum chloride and 10 cc. of tetrachloroethane was heated at 100° for five hours, the mixture treated with ice and steam distilled. The residue was dissolved in 10% sodium hydroxide solution, filtered

TABLE I

ARYL ESTERS AND PHENYLARYLOXYPHTHALIDES

Phenol used		M. p., °C., of ester or phthalide[a]	Method used[b,c]	Color with concd. H_2SO_4[d]
Phenol	(1)	80–82	(*a*) (c)	Orange
Phenol	(2)	162–163	(a) (*c*)	Orange
4-Bromophenol	(3)	92–94	(c)	Yellow-green, green, orange
4-Bromophenol	(4)	170–172	(b)	Green, dark green, yellow
Thiophenol	(5)	112–113	(a)	Deep red
Thiophenol	(6)	117–118	(b)	Deep red
o-Xenol	(7)	103–105	(*a*) (c)	Orange-red
o-Xenol	(8)	195–197	(*b*) (c)	Orange-red
p-Xenol	(9)	163–165	(*a*) (c)	Orange-pink, violet, red-brown
p-Xenol[e]	(10)	117–119	(a) (*b*) (c)	Purple, violet, red-violet
α-Naphthol	(11)	102–104	(*a*) (c)	Orange, violet, green-brown
β-Naphthol	(12)	103–105	(*a*) (c)	Yellow-green, red-green, green-brown
β-Naphthol	(13)	198–199	(c)	Green, green-brown

Compound	Formula	Analyses, %	
		Calcd.	Found
1	$C_{20}H_{14}O_3$	C, 79.45; H, 4.67	C, 79.34; H, 4.68
2	$C_{20}H_{14}O_3$	C, 79.45; H, 4.67	C, 79.24; H, 4.82
3	$C_{20}H_{13}O_3Br$	Br, 20.98	Br, 21.07
4	$C_{20}H_{13}O_3Br$	Br, 20.98	Br, 20.90
5	$C_{20}H_{14}O_2S$	S, 10.08	S, 10.09
6	$C_{20}H_{14}O_2S$	S, 10.08	S, 10.16
7	$C_{26}H_{18}O_3$	C, 82.51; H, 4.80	C, 82.58; H, 4.81
8	$C_{26}H_{18}O_3$	C, 82.51; H, 4.80	C, 82.62; H, 4.72
9	$C_{26}H_{18}O_3$	C, 82.51; H, 4.80	C, 82.55; H, 4.76
10	$C_{26}H_{18}O_3$	C, 82.51; H, 4.80	C, 82.45; H, 4.78
11	$C_{24}H_{16}O_3$	C, 81.79; H, 4.58	C, 81.70; H, 4.58
12	$C_{24}H_{16}O_3$	C, 81.79; H, 4.58	C, 81.92; H, 4.54
13	$C_{24}H_{16}O_3$	C, 81.79; H, 4.58	C, 81.61; H, 4.41

1. Calcd. mol. wt., 302; found, 303 (benzene, Menzies' method).
2. Calcd. mol. wt., 302; found, 309 (benzene, Menzies' method).

When hydrolyzed with alcoholic sodium hydroxide 0.0854 g. of compound 1 yielded 0.0266 g. of phenol (U. S. P. X method); calcd. 0.0266 g. From 0.1037 g. of compound 2 there was obtained 0.0321 g. of phenol; calcd. 0.0322 g. In each instance the 2-benzoylbenzoic acid formed was identified by its melting point.

All of the other compounds listed above yielded, upon hydrolysis, the corresponding phenol and 2-benzoylbenzoic acid.

[a] Compounds 1, 3, 5, 6, 7 and 10 were recrystallized from alcohol; compounds 11 and 12 from alcohol which contained a small amount of acetic acid; compounds 2, 4, 8 and 9 from acetic acid; compound 13 from ethyl acetate.

[b] The highest yield was obtained in the method italicized.

[c] The isomeric compounds obtained by the use of *o*-xenol, *p*-xenol and β-naphthol, respectively, in method (c) can be separated by the use of alcohol since the higher melting compound is much less soluble.

[d] The first color was obtained with cold acid, the second when the mixture was warmed, the third when the mixture cooled.

[e] By use of method (c) an alkali-insoluble gum was also obtained which, upon hydrolysis, yielded α-naphthol and 2-benzoylbenzoic acid.

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[9] Haller and Guyot, *Bull. soc. chim.*, [3] **25**, 54 (1901).

[10] Ullmann, *Ann.*, **291**, 23 (1896).

[11] At higher temperatures we found that anthraquinone was formed.

and the filtrate acidified. The precipitate was dissolved in acetic acid and the solvent allowed to evaporate. The material, 4'-hydroxydiphenylphthalide, was recrystallized from acetic acid; mixed m. p. 165–167°.[12]

A solution was made of 5 g. of the lower melting compound in 25 cc. of concd. sulfuric acid; after one-half hour the solution was poured onto ice, the cold mixture filtered, the granular product dissolved in benzene, the solution shaken with sodium carbonate solution and then extracted with 10% sodium hydroxide. Upon acidification of the latter 4 g. of 4'-hydroxydiphenylphthalide was obtained of m. p. 165–166°.

Summary

The interaction of the acid chloride of 2-benzoylbenzoic acid with (a) the potassium derivative of various phenols, with (b) the phenols alone and with (c) the phenols in the presence of pyridine was studied. In general it may be stated that three isomeric compounds are produced—two compounds which are presumably the aryl ester of benzoylbenzoic acid and the phenylaryloxyphthalide, respectively, and the hydroxydiarylphthalide.

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[12] Baeyer [*Ann.*, **354**, 173 (1907)] recorded the melting point as 167°.

[Contribution from the Chemical Laboratory of Stanford University]

The Monophenyl Nitrogen Esters of Biuret

By J. S. Blair

Biuret is one of the most familiar mixed aquo ammono pyrocarbonic acids.[1]

The commonly accepted structural formula for this substance, $H_2NCONHCONH_2$, postulates the existence of two isomeric mono-esters, in which the substituting group is attached to nitrogen. The phenyl mono-esters are the only ones which have been thoroughly studied, and discrepancies appear in the literature which seem strange in the case of such simple derivatives of so common a substance.

One well-defined substance has found general acceptance as the unsymmetrical phenyl biuret, and has been prepared by several investigators using several different methods. However, some investigators[2] cite temperatures in the neighborhood of 156° as the melting point of the substance, while others[3] give values in the neighborhood of 165°. Dains and Wertheim[4] observed both melting points according to the sample.

Since this state of affairs would almost make it appear that two substances might be involved, the preparative methods of Lakra and Dains, of Gatewood (Reference a) and of Dains and Wertheim were followed in obtaining samples for comparison. It was found that the discrepancy is due to the decomposition of the substance, without charring, and with such slow evolution of gas that it may easily be unobserved. Dr. G. E. P. Smith, formerly of this Laboratory, has found that this type of behavior is general for this class of compounds, and has worked out a "decomposition curve" method for examination of such substances which will be described in a forthcoming paper and which has some advantages over the Maquenne block. The point of principal importance in the present instance is that complete liquefaction at constant temperature is not a sufficient criterion of purity. Indeed, it was found that samples prepared by the method of Lakra and Dains would, as first obtained, liquefy more rapidly at a given temperature than those prepared by the method of Dains and Wertheim, and these in turn more rapidly than those prepared by the method of Gatewood. Yet any of the three materials would appear to "melt" as a pure substance. However, after repeated recrystallization from hot water, practical coincidence in the "decomposition curves" of samples from the three sources was ultimately attained. That these samples were identical was then further established by mixed "melting points" determined simultaneously with "melting points" on the pure components of the mixtures, so that the rate of heating would be identical. No lowering, due to mixing, was observed, and the conclusion

[1] Blair, This Journal, **48**, 87 (1926); Blair and Smith, *ibid.*, **56**, 907 (1934).

[2] Pickard and Carter, *J. Chem. Soc.*, **79**, 843 (1900); McKee, *Am. Chem. J.*, **26**, 254 (1901); Lakra and Dains, This Journal, **51**, 2222 (1929).

[3] Schiff, *Ann.*, **352**, 79 (1907); Fromm and Wenzl, *Ber.*, **55**, 812 (1922); Gatewood (a) This Journal, **45**, 146 (1923); (b) *ibid.*, **47**, 410 (1925); Davis and Blanchard, *ibid.*, **51**, 1809 (1929).

[4] Dains and Wertheim, *ibid.*, **42**, 2307 (1920).