[Contribution from the Laboratory of Organic Chemistry of the State University of Iowa]

REDUCTION OF THE 2-NITROPHENYL ESTERS OF CERTAIN ACIDS

L. CHAS. RAIFORD and WILLIAM G. HUEY

Received July 28, 1941

Hübner and Stünkel (1) reduced 2-nitrophenyl benzoate with tin and hydrochloric acid, dissolved the resulting tin double salt in alcohol, decomposed it cold with hydrogen sulfide, and obtained 2-phenylbenzoxazole, which had previously been prepared by Ladenburg (2) by treatment of 2-aminophenol with benzoyl chloride and subsequent distillation of the first product. Böttcher (3) repeated and confirmed the observations of the previous workers but found, in addition, that when the tin double salt was decomposed in hot alcoholic solution it gave mainly 2-benzoylaminophenol mixed with but a small portion of 2-phenylbenzoxazole. The formation of these products may involve intermediates I and II, neither of which was isolated.

The formation of 2-benzoylaminophenol in that experiment represents the migration of acyl from oxygen to nitrogen, which was found later to occur in many other cases. Bender (4) reduced 2-nitrophenyl ethyl carbonate and obtained what he thought was the corresponding 2-aminophenyl derivative, but noted that the substance showed no basic properties. Ransom (5), working under the direction of Stieglitz, proved that Bender's compound is 2-hydroxyphenylurethan and must have been formed by the migration of the carboethoxy radical from oxygen to nitrogen. Similarly, Lellmann and Bonhöffer (6) reduced the 2-nitrophenyl ester of diphenylcarbamic acid and obtained a compound that had the expected composition, and which they regarded as 2-aminophenyl diphenylcarbamate with the structure later assigned by Herzog (7) to a product he obtained by the action of diphenylcarbamyl chloride on 2-aminophenol. More recent work by Raiford and Alexander (8) indicates that Lellmann and Bonhöffer's compound cannot have the structure they assigned, but is 2-diphenylcarbamylaminophenol, and must have been formed by a migration of acyl from oxygen to nitrogen in the 2-amino compound which was the first product of reduction.

The tendency of 2-N-acylaminophenols to form cyclic compounds is also well known. Following Ladenburg's work, Hübner and Stünkel (1) found that heating 2-benzoylaminophenol above its melting point converts it into 2-phenylbenzoxazole. Groenvik (9) heated 2-hydroxyphenylurethan above 200° and found that alcohol was eliminated and benzoxazolone was formed. In later work Moore (10) found that reduction of the methyl, ethyl, *n*-propyl, and *n*-butyl 2-nitro-4-bromo-5-methylphenyl carbonates gave the corresponding 2-amino compounds which, under the usual laboratory conditions, promptly rearranged to the isomeric 2-hydroxyphenylurethans, as found by Ransom for the unsubstituted compound. In addition, Moore showed that under the conditions of his work portions of the urethans containing the ethyl, propyl, and butyl radicals lost the elements of the related alcohols and suffered ring closure to give benzoxazolone. This type of change was also observed by Raiford and Inman (11) who found that when the N-carboaryloxy derivatives of 2-aminophenol and its substitution products are dissolved in caustic alkali solution they are converted into benzoxazolone and a phenol is eliminated. In some

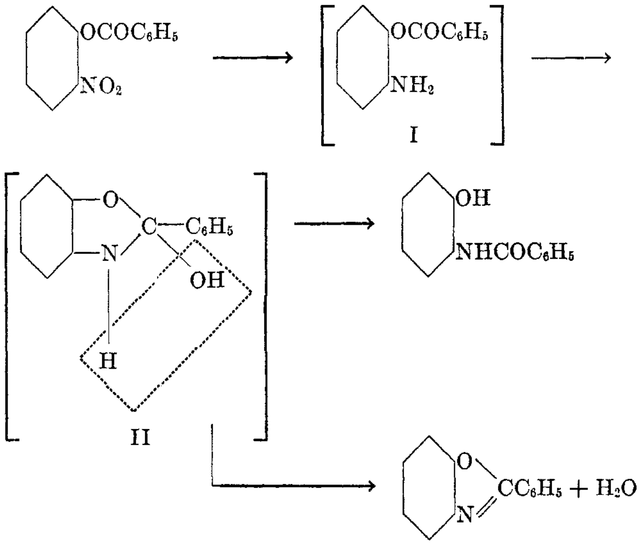
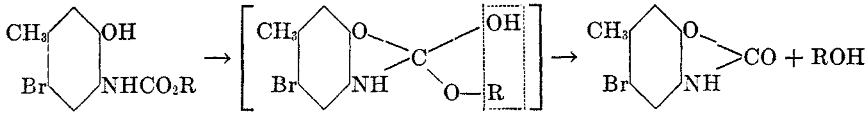
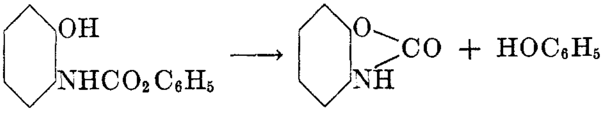


FIG. 1





instances the change takes place slowly when the product is stored at room temperature (12).

In the light of the above observations it was of interest to extend this work and, in particular, to test the reaction of an *o*-nitrophenyl ester of a heterocyclic acid. 2-Nitrophenyl furoate and several of its substitution products were prepared and their behavior studied. Reduction of the unsubstituted compound at the temperature of an ice-bath gave chiefly 2-(α-furyl)benzoxazole, m.p., 85–87°, and a small portion of an alkali-soluble product, m.p., 225–226°, which was found not to be identical with 2-furoylaminophenol, m.p., 161°, nor with N-furoylbenzoxazolone, m.p., 141–143°, either of which might have been expected under the conditions. The product in question contains chlorine, and is still under investigation. When reduction was carried through at a higher temperature the chief product was 2-furoylaminophenol, along with a smaller portion of furylbenzoxazole, and none of the high-melting compound. This might occur as indicated in Figure 1. It was of interest here to note the effect of halogen as a substituent. Reduction of 2-nitro-4-bromophenyl and 2-nitro-4-bromo-5-methylphenyl furoate, respectively, at low temperatures gave mixtures of the corresponding benzoxazoles and the 2-furoylaminophenols, but chiefly the latter in each case. When two bromine atoms were present none of the benzoxazole was obtained. Thus, reduction of 2-nitro-4,6-dibromophenyl furoate and 2-nitro-4-bromophenyl 5-bromofuroate, respectively, gave only the related 2-furoylaminophenols.

EXPERIMENTAL

2-Nitrophenyl alkyl carbonates. These compounds were obtained by the interaction of a caustic alkali solution of the required nitrophenol and the necessary alkyl chlorocarbonate. To the phenolate solution an ether solution of the carbonate was added and the mixture was shaken until the red color of the phenolate had disappeared. The ether layer containing the desired product was removed, dried over potassium carbonate, the ether distilled, and the residue purified by crystallization from a suitable solvent. Analytical data and other properties for these products are given in Table I.

Reduction of the o*-nitrophenyl alkyl esters.* This was carried out in accordance with the general directions of Ransom (5) with the modifications indicated below. The nitrophenyl alkyl carbonate was ground to a fine powder and was then added to concentrated hydrochloric acid. For each gram of ester, 15–18 cc. of acid was used, the mixture was stirred rapidly, and an excess of granulated tin was added in small quantities during a period of half an hour, while the temperature of the mixture was kept below 20°. Within three-fourths hour the blue-green color of the carbonate had disappeared and there remained in the flask the tan to nearly colorless product in the form of the amine hydrochloride.

To determine whether the reduction was complete the following test was made. A small portion of the reaction mixture, held on the end of a glass rod or thermometer, was brought into a test tube containing some 50% solution of potassium hydroxide at about −10°. If reduction was incomplete a red color was produced. This color was probably due to the potassium salt of the *o*-nitrophenol that had been formed by hydrolysis of the carbonate used as starting material. When the color test was negative the whole reduction mixture was cooled to about −12° and slowly poured with stirring into an excess of the 50% alkali solution, also cooled to −12°. The cold alkali mixture was then extracted three times with ether (25–30 cc. used each time), the extract washed three times with ice-water and then dried for some hours over anhydrous sodium sulfate. The dry ether solution was decanted and dry hydrogen chloride was bubbled through it. A flocculent colorless solid, the amine hydro-

TABLE I

2-NITRO-4-BROMOPHENYL ALKYL CARBONATES

ALKYL	YIELD, %	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANAL., HALOGEN	
						Calc'd	Found
Methyl......	48[a]	Alcohol	Pale yellow needles	61–63	$C_8H_6BrNO_5$	28.98	29.12
Ethyl........	74[a]	Alcohol	Pale yellow needles	75–77[b]	$C_9H_8BrNO_5$	27.58	27.91
n-Propyl.....	91	Alcohol	Nearly colorless blunt needles	49–51	$C_{10}H_{10}BrNO_5$	26.31	26.51
n-Butyl......			Tan oil	181° 5–6 mm.	$C_{11}H_{12}BrNO_5$	25.15	25.23

[a] These refer to purified material.

[b] Upson (16) reported 76° for this compound but did not record analytical data.

TABLE II

2-CARBOALKOXYAMINO-4-BROMOPHENOL DERIVATIVES[a]

ALKYL	YIELD %[b]	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANAL., HALOGEN	
						Calc'd	Found
Methyl......	40	Alcohol	Colorless plates	168[d]	$C_8H_8BrNO_3$	32.52	32.53
Ethyl........	52	Alcohol	Colorless plates	141[d]	$C_9H_{10}BrNO_3$	30.76[c]	32.00
n-Propyl.....	30	Alcohol	Colorless plates	113–114[d]	$C_{10}H_{12}BrNO_3$	29.19	29.04
n-Butyl......		Alcohol	Long colorless plates	121–123[d]	$C_{11}H_{14}BrNO_3$	27.77	27.94

[a] These compounds do not suffer ring closure on standing at room temperature, as was found by Huey (12), in the study of the corresponding aryl compounds.

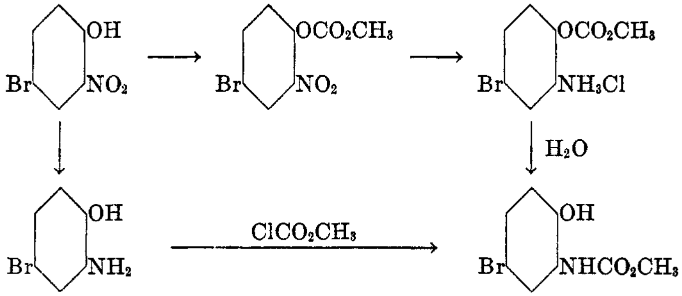
[b] These values represent purified material.

[c] This compound was previously obtained by Upson (16) who reported that it melted at 140–142° and gave a satisfactory analysis for carbon and hydrogen.

[d] The melting points of the hydrochlorides of the isomeric 2-aminophenyl alkyl carbonates were: methyl, 147–148°; ethyl, 141–143°; *n*-propyl, 136°; *n*-butyl, 138°.

chloride, was deposited. This salt was next dissolved in warm alcohol, the solution was allowed to stand for a short time, and was then diluted with an equal volume of water. The water caused hydrolysis of the salt to the 2-aminophenyl alkyl carbonate which then rearranged to the isomeric 2-hydroxyphenylurethan.

To establish the structure of this and other rearranged products in this group, each was prepared in another way. A portion of the corresponding *o*-aminophenol, dissolved in dioxane, was mixed with dimethylaniline, and to this liquid was slowly added the required alkyl chlorocarbonate with cooling and stirring. The mixture was then warmed to about 50°, allowed to stand for one hour, and poured into a large volume of water. The solid that separated was collected, dissolved in 5% caustic alkali solution, and the liquid treated with dilute hydrochloric acid. The product that separated was crystallized from a suitable solvent. Data for these products are given in Table II.



FUROIC ACID DERIVATIVES

N-Furoylbenzoxazolone. Thirteen and five-tenths grams of benzoxazolone (13) was dissolved in 80 cc. of pyridine, and to this was slowly added with stirring and cooling 10% more than one molecular proportion of furoyl chloride. The reaction flask was then allowed to stand in an ice-bath until no more solid separated after which four volumes of water was added, the mixture was stirred and allowed to remain for half an hour, and was then filtered. A yield of 83% was obtained. Crystallization from alcohol gave colorless glistening needles that melted at 141–143°.

Anal. Calc'd for $C_{12}H_7NO_4$: N, 6.11. Found: N, 6.20.

5-Bromofuroic acid. This compound has previously been prepared by a number of workers. Canzoneri and Oliveri (14) obtained a product that melted at 185–186°, and gave acceptable analyses for C, H, and Br. They recorded no yield. Hill and Sanger (15) treated dry furoic acid with bromine vapor at an elevated temperature and obtained yields between 40% and 60% of the desired product, which they found to melt at 183–184°. In the present work the bromination was carried out at the temperature of a boiling water-bath in the apparatus described below. One end of a piece of glass tubing about 50 mm. long and 25 mm. inside diameter was sealed to the middle of the inside of the base of a one-liter Erlenmeyer flask so as to provide a separate well. The flask was fitted by a ground glass joint to a long Allihn condenser, the inner tube of which extended down into the well for about 1 cm. when the condenser was in place. The upper end of the condenser was connected with a train of three wash bottles containing water, lime water, and sodium hydroxide solution, respectively.

Twenty grams of powdered furoic acid was placed in the flask and distributed as uniformly as possible over the bottom in such a way that none entered the well. Into the latter was introduced, by means of a long-stemmed tap funnel, 33 g. of bromine, the condenser was attached, the flask was placed in a bath of boiling water, and heating was continued until the vapors of bromine had disappeared, usually five to seven hours. The average yield for nine runs was 85% of a product that showed a melting range of 165–172°. This solid was dissolved in the minimum quantity of boiling water, decolorizing carbon was added, and the mixture was boiled and filtered. The compound that separated was further purified by four additional crystallizations, and was obtained in large colorless foliated flakes that melted at 190–191°. The average yield of material purified in this way was 54%.

Anal. Calc'd for $C_5H_3BrO_3$: Br, 41.88. Found: Br, 41.90.

5-Bromofuroyl chloride. A mixture of 38.2 g. of furoic acid and 100 cc. of thionyl chloride was placed in a suitable flask, connected to a return condenser by a ground glass joint and heated at about 80° for four hours. The mixture was transferred to a distilling flask, unchanged thionyl chloride was removed under reduced pressure, until a dark colored crystalline residue was obtained. The condenser was then replaced by a distilling flask which was kept immersed in an ice-bath, and the distillation continued at still lower pressure. The product passed over at 89° and 8 mm. and was obtained in the form of colorless irregularly-shaped plates that melted at 54–56°.

Anal. Calc'd for $C_5H_2BrClO_2$: Hal., 55.13. Found: Hal., 54.66.

5-Bromofuranilide. To a solution containing 1.9 g. of aniline in 10 cc. of dioxane, 2.1 g. of the required acid chloride was added, the mixture was allowed to stand for an hour, a few cc. of dilute hydrochloric acid was added, and the whole was poured with stirring into several volumes of water. Repeated crystallization of the product from alcohol gave long colorless needles that melted at 145°.

Anal. Calc'd for $C_{11}H_8BrNO_2$: Br, 30.07. Found: Br, 30.04.

2-Nitrophenyl furoate and substitution products. To obtain these products the required nitrophenol was heated with a solution of an equimolecular proportion of caustic potash until all was dissolved, the liquid was stirred and cooled to about 30° so as to cause most of the salt to separate in the form of fine crystals, after which one molecular proportion of furoyl chloride was slowly dropped in with stirring, and the resulting mixture was stirred for some hours, until the red color of the potassium salt had almost disappeared. The solid product was collected by filtration, and purified by crystallization from a suitable solvent. Analytical data and other properties are given in Table III.

Reduction of 2-nitrophenyl furoic acid esters. Two and thirty-three hundredths grams of 2-nitrophenyl furoate was dissolved in 10 cc. of boiling alcohol, and the solution was stirred and cooled in an ice-bath to favor the formation of small crystals. When the temperature was between 5° and 0°, 12.5 cc. of a hydrochloric acid solution of stannous chloride (prepared by dissolving the dihydrate in concentrated hydrochloric acid, in the proportion of 1 g. to 1 cc.) was added dropwise, the mixture was stirred until all solid dissolved, which sometimes required as long as ten hours, and was then set aside at room temperature for two days. Next, two volumes of concentrated hydrochloric acid was added and the mixture was cooled in an ice-bath for several hours. The green crystals that appeared were removed, washed with cold dilute hydrochloric acid, and finally with ice-water. On the theory that the product was 2-furoylaminophenol, the yield was 85%. The material showed a melting range of 70° to 170°, indicating a mixture. The solid was shaken with 5% solution of sodium hydroxide, the mixture was filtered and the filtrate (F) was reserved. The alkali-insoluble portion was dissolved in concentrated hydrochloric acid and from this liquid it was precipitated unchanged by neutralization or large dilution, which suggested that it might be 2-aminophenyl furoate. It was identified as 2-(α-furyl)

TABLE III

2-Nitrophenyl Furoate and Substitution Products

ADDITIONAL SUBSTITUENTS IN PHENYL	SUBSTITUENT IN FUROYL	YIELD %	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANALYSES			
							Halogen		Nitrogen	
							Calc'd	Found	Calc'd	Found
Unsubs.	5-Bromo-	Nearly quant.	Absolute alcohol	Pale green needles	83–84	$C_{11}H_7NO_5$			6.01	6.15
4-Bromo-		Nearly quant.	Absolute alcohol	Pale green needles	88–89	$C_{11}H_6BrNO_5$	25.64	25.56[a]		
4-Bromo-		85	Absolute alcohol	Cream plates	135	$C_{11}H_5Br_2NO_5$	40.92	41.07		
4,6-Dibromo-		Nearly quant.	Carbon tetrachloride	Pale green cubes	133–134	$C_{11}H_5BrNO_5$	40.92	41.26		
4-Bromo-5-methyl-		95	Alcohol	Pale green plates	74–76	$C_{12}H_8BrNO_5$	24.54	24.46		

[a] When this product was purified by crystallization from carbon tetrachloride, analysis for halogen gave 26.26%, indicating adsorption of some solvent.

TABLE IV

2-(α-FURYL)BENZOXAZOLES

SUBSTITUENTS IN PHENYL	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANALYSES			
					Halogen		Nitrogen	
					Calc'd	Found	Calc'd	Found
Unsubstituted	60% Alcohol	Colorless plates	83–85	$C_{11}H_7NO_2$	—	—	7.56	7.68
5-Bromo-	Alcohol	Pale brown prisms	92–93	$C_{11}H_6BrNO_2$	30.30	30.58	—	—
5-Bromo-6-methyl-	80% Alcohol	Colorless needles	122–124	$C_{12}H_8BrNO_2$	28.77	28.83	—	—

TABLE V

SUBSTITUTION PRODUCTS OF 2-FUROYLAMINOPHENOL

SUBSTITUENT IN PHENYL	SUBSTITUENT IN FUROYL	YIELD %	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANALYSES			
							Halogen		Nitrogen	
							Calc'd	Found	Calc'd	Found
Unsubstituted		95	Alcohol	Tan plates	161–162	$C_{11}H_9NO_3$	—	—	6.89	7.01
4-Bromo-		58	Alcohol	Nearly colorless needles	238	$C_{11}H_8BrNO_3$	28.36	27.62	—	—
4-Bromo-5-methyl-		60	Alcohol	Fine colorless needles	239–240	$C_{12}H_{10}BrNO_3$	27.02	27.14	—	—
4-Bromo-	5-Bromo-	Nearly quant.	Acetone	Small needles	282–284 decomp.	$C_{11}H_7Br_2NO_3$	44.32	44.65	—	—

benzoxazole. Analytical data for this and others obtained in a similar way are shown in Table IV.

When filtrate (F) was acidified, it gave a product that melted at 225–226°, but which was not the expected 2-furoylaminophenol. To obtain the latter the following experiments were carried through. To a solution of 10 g. of 2-aminophenol in a mixture of 32.6 cc. of pyridine and 25 cc. of dioxane was added with cooling and stirring 30 g. of furoyl chloride in 30 cc. of dioxane, the mixture was allowed to stand overnight, one volume of water was added, and the liquid was made faintly acid with hydrochloric acid. A 93% yield of product separated. Crystallization from absolute alcohol gave heavy brown needles that melted at 113–114° and were identified as 2-furoylaminophenyl furoate.

Anal. Calc'd for $C_{16}H_{11}NO_5$: N, 4.71. Found: N, 4.68.

A mixture of 16.8 g. of the above diacyl derivative and 100 cc. of 6% caustic alkali solution was warmed until all solid had dissolved, the liquid was cooled and acidified. The yield of product was 95%. Analytical data and other properties for this and related *o*-furoylaminophenols are given in Table V.

SUMMARY

1. A number of 2-nitrophenyl alkyl esters of carbonic acid have been reduced in acid solution. In each case the 2-amino derivative was isolated and its direct rearrangement to the isomeric 2-hydroxyphenylurethan was observed. The latter were found to be stable under the conditions of these experiments.

2. Reduction of 2-nitrophenyl furoate at the temperature of the ice-bath gave chiefly 2-(α-furyl)benzoxazole. When a bromine atom was present in the phenyl residue some of the corresponding benzoxazole was again obtained, but the chief product was the 2-furoylaminophenol. When the dibromo compounds were used, the furoylaminophenols only could be isolated.

Iowa City, Iowa.

REFERENCES

(1) Hübner and Stünkel, *Ann.*, **210**, 384 (1881).
(2) Ladenburg, *Ber.*, **9**, 1526 (1876).
(3) Böttcher, *Ber.*, **16**, 629, 1933 (1883).
(4) Bender, *Ber.*, **19**, 2268 (1886).
(5) (a) Ransom, *Ber.*, **31**, 1055 (1898); *Am. Chem. J.*, **23**, 1 (1900). (b) Ransom, *Am. Chem. J.*, **23**, 43 (1900).
(6) Lellmann and Bonhöffer, *Ber.*, **20**, 2125 (1887).
(7) Herzog, *Ber.*, **40**, 1833 (1907).
(8) Raiford and Alexander, *J. Org. Chem.*, **5**, 300 (1940).
(9) Groenvik, *Bull. soc. chim.*, [2] **25**, 178 (1876).
(10) Moore, Thesis, Iowa, **1934**, p. 28.
(11) Raiford and Inman, *J. Am. Chem. Soc.*, **56**, 1586 (1934).
(12) Huey, Dissertation, Iowa, **1937**, p. 29.
(13) Graebe and Rostovzeff, *Ber.*, **35**, 2751 (1902).
(14) Canzoneri and Oliveri, *Gazz. chim. ital.*, **14**, 176 (1884).
(15) Hill and Sanger, *Ann.*, **232**, 46 (1886).
(16) Upson, *Am. Chem. J.*, **32**, 28 (1904).