[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE UNIVERSITY OF IOWA]

The Migration of Acyl Groups in Certain Derivatives of *o*-Aminophenol[1]

BY L. CHARLES RAIFORD[2] AND ARTHUR L. LEROSEN[3]

Studies carried out in this Laboratory[4,5,6] have shown that when two different acyl groups, derived from carboxylic acids, are introduced into an *o*-aminophenol, generally the same diacyl derivative is obtained, regardless of the order of introduction. On hydrolysis the heavier acyl group has usually been found on nitrogen.

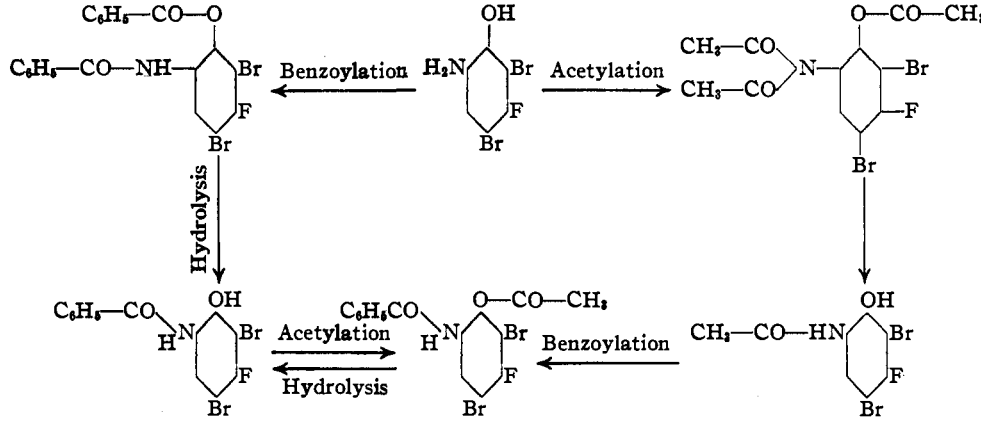

Fig. 1.—The migration of acyl in 2,4-dibromo-3-fluoro-6-aminophenol.

In the present work two isomeric derivatives of *o*-aminophenol, *viz.*, 2-amino-3-fluoro-4,6-dibromophenol and 2,4-dibromo-3-fluoro-6-aminophenol, were studied. These compounds were prepared from the related nitrophenols.[7] The occurrence of acyl migration constitutes further proof of the correctness of the structures previously assigned to these nitrophenols. In each case the mixed benzoyl-acetyl derivative seemed to be the same, regardless of the order of introduction. Hydrolysis showed the benzoyl group attached to nitrogen in all cases. Although the occurrence of some of the other mixed acyl derivative cannot be entirely excluded, since recovery was never quantitative, it is certain that migration occurred in these cases.

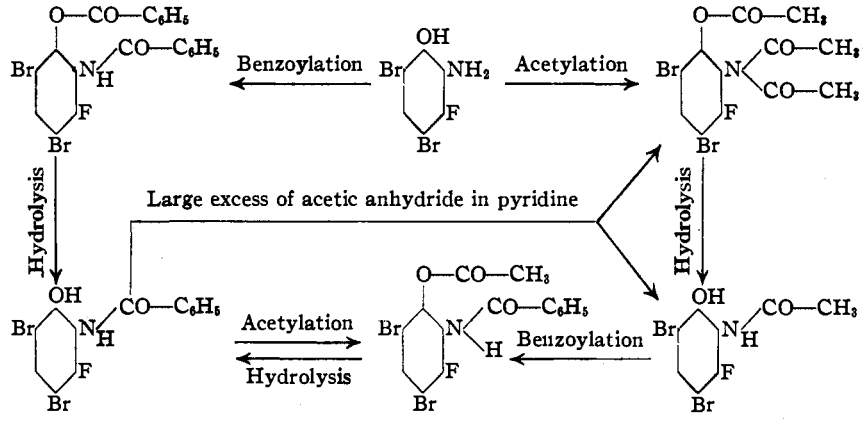

Fig. 2.—The migration of acyl in 2-amino-3-fluoro-4,6-dibromophenol.

Both the 2- and 6-aminodibromofluorophenols easily formed a triacetyl derivative.

The monobenzoyl derivative of 2-amino-3-fluoro-4,6-dibromophenol showed an unusual melting point behavior. It melted at 178°, then solidified and melted again at 195°. On cooling and redetermination of the melting point the higher value was found, however, if the cooled material was dissolved in ligroin–benzene and recrystallized, the melting point at 178° was observed. Apparently two crystal forms are involved.

A new case of the replacement of an acyl group was discovered during the attempted preparation of the acetyl derivative of 2-benzoylamino-3-fluoro-4,6-dibromophenol by treatment with a large excess of acetic anhydride in pyridine. Instead of the expected acetyl derivative of 2-benzoylamino-3-fluoro-4,6-dibromophenol the compound obtained was a diacetyl compound

(1) From a thesis submitted by Arthur L. LeRosen in partial fulfillment of the requirements for the degree of Doctor of Philosophy to the Graduate College of the State University of Iowa, June, 1940.

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(4) L. C. Raiford and J. R. Couture, THIS JOURNAL, **46**, 2305 (1924); **44**, 1792 (1922).

(5) L. C. Raiford, *ibid.*, **41**, 2068 (1919).

(6) L. C. Raiford and H. P. Lankelma, *ibid.*, **47**, 1111 (1925).

(7) L. C. Raiford and A. L. LeRosen, *ibid.*, **66**, 1872 (1944).

TABLE I

CHARACTERISTICS OF 2-AMINO-3-FLUORO-4,6-DIBROMOPHENOL AND SOME OF ITS ACYLATED DERIVATIVES

Derivatives	Formula	Solvent	Crystal form[a]	M. p., °C. (uncor.)	Yield, %	Halogen content (not including fluorine) Calcd.	Found
2-Amino-3-fluoro-4,6-dibromophenol	$C_6H_4ONBr_2F$	Pet. ether (b. p. 110°)	Plates or needles	143 dec.	55	56.09	55.95
Hydrochloride	$C_6H_5ONClBr_2F$	.....	Needles	...	..	60.76	61.06
Hydrochloride monohydrate	$C_6H_5ONClBr_2H_2O$	Dil. HCl	Needles	...	96	57.54	57.83
Triacetyl	$C_{12}H_{10}O_4NBr_2F$	75% alc.	Granules–	124	82	38.90	38.81
N-Acetyl	$C_8H_6O_2NBr_2F$	Benzene	Fibrous needles	190	95	48.87	48.49
Dibenzoyl[b]	$C_{20}H_{12}O_3NBr_2F$	Ether–pet. ether–dioxane	Granules	173	66	32.41	32.11
N-Benzoyl	$C_{13}H_8O_2NBr_2F$	Benzene	Fibrous needles	178–195[c]	93	41.08	40.85
Acetylated N-benzoyl	$C_{15}H_{10}O_3NBr_2F$	Ether–pet. ether	Granules	152[d]	..	37.07	37.23
Benzoylated N-acetyl	$C_{15}H_{10}O_3NBr_2F$	Ether–pet. ether	Needles	152[d]	..	37.07	37.30

[a] All crystals were colorless. [b] The crude product was placed in a warm mixture of equal volumes of ether and petroleum ether insufficient to dissolve it completely, then dioxane was added to complete the solution. The product separated after treatment with charcoal and cooling. [c] This compound melts at 178° then solidifies and melts again at 195°. [d] A mixture of the two mixed acyl derivatives melted at 152°.

TABLE II

CHARACTERISTICS OF 6-AMINO-3-FLUORO-2,4-DIBROMOPHENOL AND SOME OF ITS ACYLATED DERIVATIVES

Derivative	Formula	Solvent	Crystal form[a]	M. p., °C. (uncor.)	Yield, %	Halogen content (not including fluorine) Calcd.	Found
6-Amino-3-fluoro-2,4-dibromophenol	$C_6H_4ONBr_2F$	Pet. ether	Leaflets	148	..	56.09	55.87
Hydrochloride	$C_6H_5ONClBr_2F$	Dil. HCl	Needles	...	92	60.76[b]	60.65[b]
Triacetyl	$C_{12}H_{10}O_4NBr_2F$	75% Methyl alc.	Needles	105	59	38.90	38.81
N-Acetyl	$C_8H_6O_2NBr_2F$	75% Methyl alc.	Needles	166	98	48.87	48.62
Dibenzoyl	$C_{20}H_{12}O_3NBr_2F$	Benzene–pet. ether	Needles	181	78	32.45	31.69
N-Benzoyl	$C_{13}H_8O_2NBr_2F$	Methyl alc., water	Platelets	195	98	41.08	40.95
Acetylated N-benzoyl	$C_{15}H_{10}O_3NBr_2F$	Ether-pet. ether	Granules	180[c]	98	37.07	36 62
Benzoylated N-acetyl	$C_{15}H_{10}O_3NBr_2F$	Ether-pet. ether	Granules	179[c]	88	37.07	37.03

[a] All compounds were colorless. [b] This value is for bromine and chlorine. [c] A mixture of the two mixed-acyl derivatives melted at 180°.

while some of the monoacetyl compound separated from the diluted reaction mixture. When a longer time was allowed for the reaction to proceed, the corresponding triacetyl derivative was formed, and the mixture deposited a small amount of the monoacetyl derivative.

The reactions occurring in this study are indicated in Figs. 1 and 2.

Experimental

Methods and Materials.—The crystal forms, melting point yields and analyses of the compounds prepared in this work are given in Tables I and II. The aminophenols used were prepared by reducing the corresponding nitrophenols, previously described,[7] with stannous chloride in hydrochloric acid. The *p*-aminophenol was also prepared. Acylations were carried out using either acetic or benzoic anhydride in pyridine. For the hydrolysis of these compounds sodium hydroxide in 75% methyl alcohol was used.

2,6-Dibromo-3-fluoro-4-aminophenol.—This compound was obtained in 93% yield from the corresponding nitrophenol. Crystallization from petroleum ether (b. p. 60–70°) gave colorless leaflets, m. p. 175°.

Anal. Calcd. for $C_6H_4ONBr_2F$: Br, 56.09. Found: Br, 55.76.

Replacement of the Benzoyl Group by Acetyl during the Acetylation of 2-Benzoylamino-3-fluoro-4,6-dibromophenol.—Attempts to prepare the acetyl derivatives of 2-benzoylamino-3-fluoro-4,6-dibromophenol by treatment with a moderate excess of acetic anhydride in pyridine gave products of indefinite melting point. The analysis for bromine did not agree with that calculated for the expected product. This behavior suggested that the introduction of the second acyl might be irregular. In order to test this assumption 1.38 g. of the benzoylaminophenol was treated with a large excess (15 ml.) of acetic anhydride in 10 ml. of pyridine. The mixture was warmed gently and then poured into water. An oil appeared and was dissolved in ether and dried over sodium sulfate. Most of the ether was evaporated and petroleum ether was added to the residual solution. This solution was stirred and cooled until small colorless granules formed. The solvent was decanted and the crystals were washed with petroleum ether. After recrystallization from a benzene–petroleum ether mixture, they melted at 167°. The yield was 34%. Analysis indicated that the compound was a diacetyl derivative during the preparation of which the benzo group had been lost.

Anal. Calcd. for $C_{10}H_8O_3NBr_2F$: Br, 43.31. Found Br, 42.81.

A sample of the above compound, 0.177 g., was hydrolyzed with 1 ml. of 6 *N* sodium hydroxide, water was added and the solution was acidified with phosphoric acid. The separated solid was collected and was found to melt at 191°. It did not depress the melting point (191°) of an authentic sample of 2-acetylamino-3-fluoro-4,6-dibromophenol. The filtrate from the acidified hydrolysis mixture was diluted with a large volume of water and was distilled as long as acid passed over. After correcting for a blank, 0.486 millimole of acetic acid were found in the distillate The value calculated for 0.177 g. of diacetyl compound was 0.481 millimole.

On cooling, the mother liquor from the diacetyl compound deposited 0.30 g. of colorless needles (yield 26%), melting at 189° after recrystallization from benzene, and showing no melting point depression when mixed with pure 2-acetylamino-3-fluoro-4,6-dibromophenol.

A repetition of this experiment in which the reaction mixture was set aside for twelve hours gave the triacetyl derivative (m. p. and mixed m. p. 125°), which on hydrolysis yielded the monoacetyl derivative. In this case also a second minor fraction consisting of the monoacetyl compound was obtained and identified.

Summary

When both acetyl and benzoyl groups were introduced into either 2-amino-3-fluoro-4,6-dibromophenol or 2,4-dibromo-3-fluoro-6-aminophenol, only one mixed acyl derivative was isolated, regardless of the sequence of introduction. On hydrolysis the benzoyl group was found on the nitrogen.

Acetylation of 2-benzoylamino-3-fluoro-4,6-dibromophenol with a large excess of acetic anhydride in pyridine caused the replacement of the benzoyl group by acetyl.

BATON ROUGE, LA. RECEIVED SEPTEMBER 11, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

The Preparation of Riboflavin.[1] III. The Synthesis of Alloxazines and Isoalloxazines

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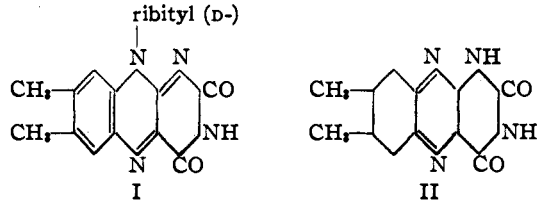
During the past ten years, isoalloxazines have assumed importance because riboflavin, I, is a member of this class of compounds.



The only known, general synthesis of isoalloxazines involves the reaction of mono-N-substituted *o*-phenylenediamines with alloxan in acidic media.[4]

Kuhn and Cook,[5] in a search for other syntheses, found none of wide application and concluded that the reaction between ortho phenylenediamines and alloxan constitutes the only general method for making alloxazines (related to II) and isoalloxazines. Among the many routes unsuccessfully investigated by Kuhn and Cook was the reaction between ortho phenylenediamine and 5-bromobarbituric acid which according to them did not yield alloxazine. Contrary to this report we found that the reaction between halogenated barbituric acids and derivatives of *o*-phenylenediamine is a general method for preparing alloxazines and isoalloxazines. With the reagents employed by Kuhn and Cook, the yield of alloxazine is poor and the product difficult to isolate. This fact is not entirely unexpected as the halogen in 5-bromobarbituric acid is "positive"[6] and would, therefore, bring about oxidation and/or bromination of the diamine. The chlorobarbituric acids, 5-chloro- and 5,5-dichlorobarbituric acids, however, are better suited for reaction with ortho phenylenediamines as the chlorine atoms are "less positive".[7] It was also found that the nature of the diamine is important. Alkylated *o*-phenylenediamines behave better in the reaction with the halobarbituric acids than does ortho phenylenediamine itself. Thus, 4,5-dimethyl-*o*-phenylenediamine and 5,5′-dichlorobarbituric acid form 6,7-dimethylalloxazine, II, in almost quantitative yield whereas *o*-phenylenediamine under the same conditions is converted to alloxazine in 20% yield.

The condensation is best carried out in pyridine; the use of methanol and acetic acid as solvents gives unsatisfactory yields. With pyridine a striking color change occurs. A deep blue color is formed at the beginning and, as the reaction proceeds the mixture becomes orange-red. In most instances the product separates from the reaction mixture on cooling. With the appropriate diamines and the chlorobarbituric acids, we prepared alloxazine, 6,7-dimethylalloxazine, riboflavin, tetraacetylriboflavin, 1-araboflavin, 6,7-dimethyl-9-benzylisoalloxazine and 6,7-dimethyl-9-methylisoalloxazine.[8]

Although riboflavin is formed in excellent yields from the diamine III and 5,5′-dichlorobarbituric

(1) For other publications in this series, see Ladenburg, Tishler and Wellman, THIS JOURNAL, **66**, 1217 (1944); Tishler, Wendler, Ladenburg and Wellman, *ibid.*, **66**, 1328 (1944).

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(3) Present address: Wyeth, Inc., Philadelphia, Pennsylvania.

(4) Kuhn, Reinemund and Weygand, *Ber.*, **67**, 1460 (1934); Kuhn and Weygand, *ibid.*, **67**, 1939 (1934). Karrer, Salomon, Schopp and Schlitter, *Helv. Chim. Acta*, **17**, 1165 (1934). For a more complete bibliography, see H. R. Rosenberg, "Chemistry and Physiology of the Vitamins," Interscience Publishers, Inc., New York, N. Y., 1942, pp. 163-170.

(5) Kuhn and Cook, *Ber.*, **70**, 761 (1937).

(6) Hirst and Macbeth, *J. Chem. Soc.*, **121**, 904, 2169 (1921); Macbeth, *ibid.*, **121**, 116 (1921); Cox, Macbeth and Pennycuick, *ibid.*, 1870 (1931).

(7) The difference in nature of the halogen in 5-bromo- and 5-chlorobarbituric acids is manifested by the behavior of these compounds in acetone. Whereas the latter is resistant to change in warm acetone, the former rapidly brominates acetone and is converted to barbituric acid.

(8) Tishler and Wellman, U. S. Patent 2,261,608.