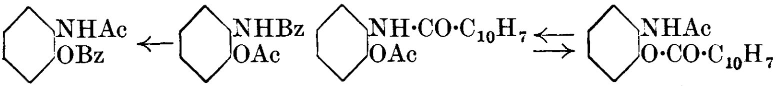
CCCCX.—*The Migration of Acyl Groups in* o-*Aminophenols. Part II.*

By Frank Bell.

Many examples are known of the migration of an acyl group during the preparation and also the hydrolysis of diacyl-*o*-aminophenols. For instance, Nelson and Rothrock have shown (*J. Amer. Chem. Soc.*, 1929, **51**, 2761) that 2-valeramidophenyl benzoate on hydrolysis gives 2-benzamidophenol, and Raiford and Lankelma (*ibid.*, 1925, **47**, 1111) have shown that 3-chloro-5-acetamido-*p*-cresol with α-naphthoyl chloride gives 3-chloro-5-α-naphthamido-*p*-tolyl acetate. It is now found that migration of acyl can occur whilst two acyl groups are present in the molecule.

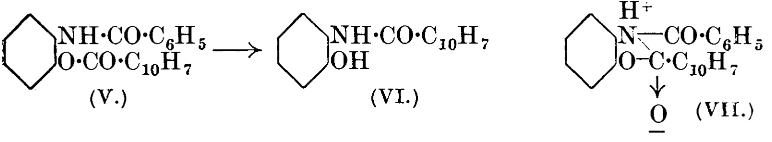
Contrary to the statement of Raiford (*ibid.*, 1919, **41**, 2068), acetylation of 2-benzamidophenol was found to give a compound different from that obtained by the benzoylation of 2-acetamidophenol. Both compounds had ill-defined melting points, which varied according to the method of crystallisation and the rate of heating from 133° to 140°, but mixtures of the two always gave clear melts below 120°. The liquids obtained on melting were singularly reluctant to crystallise on cooling and these observations suggested that some change was taking place. Both substances were therefore maintained in the molten state for some time and the viscous masses so obtained were crystallised from alcohol. Only the original material was isolated from 2-*acetamidophenyl benzoate* (I), but 2-*benzamidophenyl acetate* (II) was largely converted into the former substance.



(I.) (II.) (III.) (IV.)

Treatment of 2-acetamidophenol with α-naphthoyl chloride gave a compound different from that obtained by the acetylation of 2-α-naphthamidophenol (contrast Raiford and Greider, *ibid.*, 1924, **46**, 430) and with this pair of substances a different type of behaviour was observed. When 2-acetamidophenyl α-naphthoate (IV) was maintained above its melting point for an hour it was largely transformed into 2-α-naphthamidophenyl acetate (III), but this in turn could be partly converted into 2-acetamidophenyl α-naphthoate (compare Nelson and Davis, *ibid.*, 1926, **48**, 1677, for an apparent equilibrium between 2-propionamidophenyl acetate and 2-acetamidophenyl propionate).

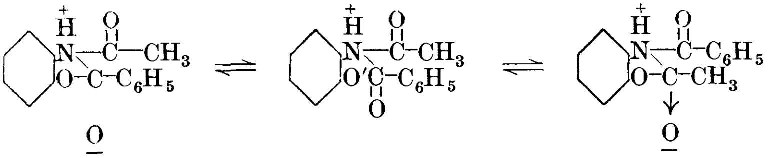
2-α-Naphthamidophenyl benzoate was quite different from 2-benzamidophenyl α-naphthoate (contrast Raiford and Greider, *loc. cit.*) and both were recovered unchanged after remaining in the molten condition for one hour. On the other hand, both gave 2-α-naphthamidophenol (VI) on hydrolysis (Part I; J., 1930, 1986), which suggests that alkaline conditions are very favourable for isomeric change.

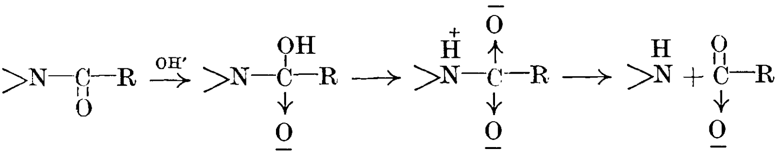


(V.) (VI.) (VII.)

If, as was recently suggested (this vol., p. 2346), hydrolytic migration involves the intermediate formation of a compound of the benzoxazole type (VII), migration is not so much determined by the ortho-position of the amino- and hydroxyl-groups as by their arrangement in space. Raiford and Clarke (*J. Amer. Chem. Soc.*, 1926, **48**, 483) have established that migration of acyl can take place in 8-amino-1-naphthol, but it would not be expected to occur in a normal *m*-aminophenol. It is now found that 3-acetamidophenyl benzoate on hydrolysis gives 3-acetamidophenol, no migration occurring.

Even a cursory survey of the large amount of experimental work on acyl migrations in *o*-aminophenols indicates immediately that we are dealing with a finely balanced system, subject to considerable disturbance with only a small change in the chemical constitution of the molecule. If it is tentatively granted that the interchange of 2-acetamidophenyl benzoate (I) and 2-benzamidophenyl acetate (II) involves the intermediates (VIII), (IX), and (X), the failure to obtain any simple generalisation is readily understood. Formation of the benzoxazoles (VIII) and (X) will be partly determined by the positive character of the amino-hydrogen atom and partly by the tendency of the *O*-carbonyl group to undergo polarisation in the way indicated. For easy interchange of the isomeric pair the radical of the *N*-acyl group should be an electron sink, whilst that of the *O*-acyl group should be an electron source. Clearly the changes will be promoted by alkaline conditions. If (IX) is the formula of the diacyl compound at the moment of hydrolysis, it appears that this process may involve the following stages : addition of hydroxyl ion, attraction of hydrogen ion to the nitrogen, and severance. Both of the initial processes are favoured by an electron-donating R, so that of the two acyl groups attached to the nitrogen that derived from the acid of lower dissociation constant should sever first. In other


(VIII.) (IX.) (X.)



$$>N-\underset{O}{\overset{\|}{C}}-R \xrightarrow{OH'} >N-\underset{\substack{\downarrow\\ \underline{O}}}{\overset{OH}{C}}-R \longrightarrow >\overset{\substack{+\\ H}}{N}-\underset{\substack{\downarrow\\ \underline{O}}}{\overset{\substack{\overline{O}\\ \uparrow}}{C}}-R \longrightarrow >\overset{H}{N}+\underset{\substack{\downarrow\\ \underline{O}}}{\overset{\substack{O\\ \|}}{C}}-R$$

words, the acyl group derived from the acid of high dissociation constant should be found attached to the nitrogen. To summarise, if the two acyl groups are of comparable character, ready interchange of the isomeric pair would be anticipated and on hydrolysis the more acidic group should be found attached to the nitrogen. On the other hand, if the groups are of very different electrical character, the isomeride in which the electron sink is attached to the oxygen will tend to exist to the exclusion of that in which it is attached to the nitrogen, and consequently on hydrolysis the less acidic group will be found attached to the nitrogen atom. This appears to agree with experimental facts, as the following table compiled from the results of Raiford and Couture (*ibid.*, 1924, **46**, 2305) and Raiford and Lankelma (*loc. cit.*) shows. In the first column are the pairs of radicals introduced into the *o*-aminophenol, in the second the dissociation constants of the acids corresponding to the acyl radicals, and in the third the acyl group attached to the nitrogen atom after hydrolysis of the diacylated phenol with dilute alkali solution. In the first five pairs one member contains a nitro-group whilst the other contains no electron sink comparable with this. Hydrolysis, therefore, leaves the less acidic group attached to nitrogen. In the second five pairs the groupings are of a comparable type (in spite of being derived from acids of widely different dissociation constants in three cases) and consequently hydrolysis results in the production of an *N*-acylaminophenol corresponding to the stronger acid. Admittedly this theory is provisional in nature, but it may provide a much needed guide to further experiment.

Radicals R·CO.	Diss. const. of $R\cdot CO_2H$ ($\times 10^5$).	Radical on N after hydrolysis.
p-Chlorobenzoyl	9·9	*p*-Chlorobenzoyl*
p-Nitrobenzoyl	40	
Acetyl	1·8	Acetyl*
p-Nitrobenzoyl	40	
Benzoyl	7·2	Benzoyl*
p-Nitrobenzoyl	40	
Benzoyl	7·2	Benzoyl
3 : 5-Dinitrobenzoyl	160	
Acetyl	1·8	Mixture*
m-Nitrobenzoyl	34·5	
Acetyl	1·8	α-Naphthoyl
α-Naphthoyl	20	
p-Toluoyl	4·4	Phenylacetyl
Phenylacetyl	5·2	
p-Nitrobenzoyl	40	*o*-Nitrobenzoyl
o-Nitrobenzoyl	700	
α-Naphthoyl	20	α-Naphthoyl
β-Naphthoyl	6·8	
p-Chlorobenzoyl	9·9	*o*-Chlorobenzoyl
o-Chlorobenzoyl	135	

* Using 4 : 6-dibromo-2-aminophenol; the other results were obtained with 3-chloro-5-amino-*p*-cresol.

EXPERIMENTAL.

2-*Acetamidophenyl benzoate*, prepared by the interaction of 2-acetamidophenol and benzoyl chloride in pyridine or sodium hydroxide solution, crystallised from acetic acid, alcohol, or benzene in needles, m. p. *ca.* 140° (Found: C, 70·7; H, 5·3. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1%. All analyses were made by Dr.-Ing. A. Schoeller of Berlin). A solution of this compound in xylene was boiled for 3 hours. On cooling, there separated needles, m. p. 132—135°, depressed by admixture with 2-benzamidophenyl acetate. 5·7 G. were heated at 150° for 2 hours. The residual gum when crystallised from alcohol gave the following crops: 2·1 g., m. p. 125—127°; 0·5 g., m. p. 122—127°; 1·5 g., m. p. 105—120°; 1·3 g., m. p. 85—100°. The last two after recrystallisation from alcohol had m. p. 122—127°, and all crops then gave a depression in m. p. with 2-benzamidophenyl acetate and an elevation with 2-acetamidophenyl benzoate. Clearly the formation of 2-benzamidophenyl acetate in small percentage is not precluded, but its isolation was not achieved in this experiment or in subsequent repetitions.

2-Acetamidophenyl benzoate dissolved rapidly in warm aqueous sodium hydroxide and on addition of hydrochloric acid impure 2-benzamidophenol was precipitated.

2-*Benzamidophenyl acetate*, prepared by the reaction of 2-benzamidophenol with acetyl chloride in pyridine solution or, better, with acetic anhydride on the steam-bath with subsequent removal of the excess of the reagent in a vacuum, crystallised from acetic acid, alcohol, or benzene in needles, m. p. *ca.* 140° (Found: C, 70·6; H, 5·1%). A solution of this compound in xylene was boiled for 2 hours. On cooling, there separated needles, m. p. 130—138°, depressed by admixture with 2-acetamidophenyl benzoate. 4·7 G. were heated at 150° for 2 hours and the residual gum was crystallised from acetic acid. The first crop, m. p. 125—127°, was 2-benzamidophenyl acetate, but the second (m. p. 110—129°) and third (m. p. 113—119°) crops were recrystallised from alcohol, 1·4 g. of material, m. p. 125—127° (raised on admixture with 2-acetamidophenyl benzoate), then being obtained. In another experiment the residual gum was crystallised from alcohol. The first crop had m. p. *ca.* 115°, raised by admixture with either 2-benzamidophenyl acetate or 2-acetamidophenyl benzoate, but the second crop, m. p. 124—128°, had m. p. 129—132° and m. p. 112—115° when mixed with 2-acetamidophenyl benzoate and 2-benzamidophenyl acetate, respectively.

Hydrolysis of 2-benzamidophenyl acetate with aqueous sodium hydroxide gave impure 2-benzamidophenol.

5·6 G. of 2-α-naphthamidophenyl acetate (J., 1930, 1986) were heated at 160° for 1 hour and the viscous residue was dissolved in acetic acid. On cooling, there separated needles (2·2 g.), m. p. 143—145°, raised on admixture with 2-α-naphthamidophenyl acetate. The filtrate on dilution with water gave a crop (2·7 g.), m. p. 120—126°, which after recrystallisation from acetic acid had m. p. 128—130° (below 120° in admixture with the original substance: slightly raised by addition of 2-acetamidophenyl α-naphthoate).

2-Acetamidophenyl α-naphthoate (*ibid.*, p. 1986), after being treated as described above, gave 2·5 g. of the original material, and then crops with very low melting points owing to partial hydrolysis on dilution with water. 5 G. were heated at 150° for 1 hour and the residual gum was dissolved in alcohol. The first crop (4 g., m. p. 124—128°) consisted of 2-acetamidophenyl α-naphthoate, but the second (0·4 g., m. p. 136—140°) showed a depression in m. p. on admixture with the initial material but a slight rise with 2-α-naphthamidophenyl acetate.

2-α-Naphthamidophenyl benzoate (*ibid.*, p. 1986. Found: C, 74·5; H, 5·1. Calc.: C, 74·7; H, 4·9%) (5 g.) was heated at 180—190° for 1 hour. The residue was warmed with alcohol and allowed to cool. 2-α-Naphthamidophenyl benzoate (4·8 g., m. p. 173—176°) separated, and a further crop of the same material was obtained on evaporation of the alcohol.

2-Benzamidophenyl α-naphthoate was obtained from 2-benzamidophenol in almost quantitative yield (*ibid.*, p. 1986; contrast Raiford and Greider, *loc. cit.*). 4·5 G. were heated at 170—180° for 1 hour and the residue was boiled with alcohol. The first crop (3·9 g., m. p. 158—166°) consisted of 2-benzamidophenyl α-naphthoate, and a further quantity was obtained on evaporation of the alcoholic mother-liquor.

A solution of 3-acetamidophenol and benzoyl chloride (1 mol.) in pyridine was after 12 hours poured into water, and the precipitate was collected, triturated with *N*/10-sodium hydroxide, dried, and crystallised from benzene. 3-*Acetamidophenyl benzoate* was obtained in plates, m. p. 140° (Found: C, 70·4; H, 5·1. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1%). It dissolved rapidly in warm sodium hydroxide solution to give 3-acetamidophenol.

3-*Acetamidophenyl α-naphthoate*, prisms, m. p. 153° (Found: C, 74·7; H, 4·9. $C_{19}H_{15}O_3N$ requires C, 74·7; H, 4·9%), and 3-*acetamidophenyl β-naphthoate*, needles, m. p. 141° (Found: C, 74·7; H, 4·9%), were prepared by the same process. Both dissolved rather slowly in warm sodium hydroxide solution and gave 3-aminophenol.

In conclusion, the author wishes to express his thanks to the Dyestuffs Research Group of Imperial Chemical Industries, Ltd., for a grant.

BATTERSEA POLYTECHNIC, S.W. 11. [*Received, September 3rd*, 1931.]