561. *The Migration of Acyl Groups in* o-*Aminophenols. Part III.*

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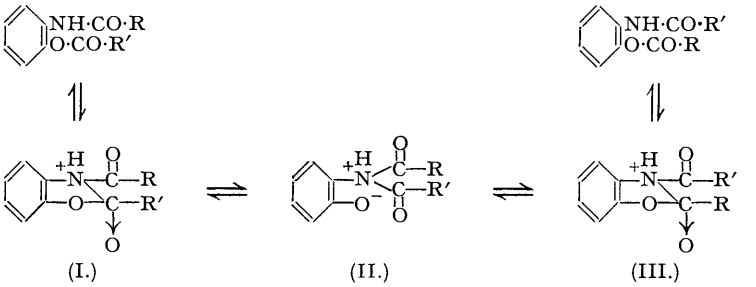
In confirmation and extension of the views advanced earlier, acyl migrations are not encountered in triacylated *o*-aminophenols or in acylated *N*-alkyl-*o*-aminophenols. The use of optically active acyl groups is described. These proved fruitless because the rotations of the products were low.

The theory advanced in Part II (*J.*, 1931, 2962) that the migration of acyl groups in *o*-aminophenols involves intermediates of types (I), (II), and (III) left undefined the function (if any) of the hydrogen atom on the nitrogen. In the present investigation it has been ascertained that

the hydrogen atom plays an essential part. First, the mixed triacyl compounds (IV)—(VII) were prepared and it was found that no interchange of the acyl groups took place on heating



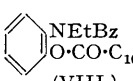
(I.) (II.) (III.)

these compounds (contrast the now well-authenticated thermal interchange in isomeric diacylated *o*-aminophenols; Le Rosen and Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 2705). On

(IV.) R = R′ = Bz; R″ = Ac. (VI.) R = R′ = Ac; R″ = Bz.
(V.) R = R″ = Bz; R′ = Ac. (VII.) R = R″ = Ac; R′ = Bz.

hydrolysis each of these compounds gave *o*-benzamidophenol. Secondly, it has been shown that migrations will not occur in mixed diacyl derivatives of *o*-alkylaminophenols such as (VIII). It appears, therefore, that the attainment of phase (II) probably depends on the simultaneous elimination of a hydrogen ion.

The conversion of a diacylated *o*-aminophenol into a monoacyl derivative is, on the present view, comparable with the hydrolysis of a diacylated aniline. The literature on this point is scanty, but the results of Wheeler and his co-workers (*Amer. Chem. J.*, 1896, **18**, 381, 540, 695; 1903, **30**, 24) on the hydrolysis of diacylated anilines strictly parallel those of Raiford (*J. Amer. Chem. Soc.*, 1924, **46**, 2305; 1925, **47**, 1111) and Pollard and Forsee (*J. Amer. Pharm. Assoc.*, 1935, **24**, 363) on related diacyl-*o*-aminophenols.



(VIII.)

The ring intermediate (I) is five-membered. In acylated 8-amino-1-naphthol (Raiford and Clarke, *J. Amer. Chem. Soc.*, 1926, **48**, 483) it would be six-membered. It appeared of interest to examine acylated 2-amino-2′-hydroxydiphenyls, for here the postulated intermediate would involve a seven-membered ring. Unfortunately we failed to obtain the required aminophenol.

Useful information concerning the interchange of isomeric diacylated *o*-aminophenols might be obtained by employing an optically active acyl group, if the rotation differed markedly according to whether it was attached to nitrogen or oxygen. Accordingly use was made of (—)-1-ethyl-*n*-hexoyl chloride to obtain a number of mixed diacylated *o*-aminophenols. Unfortunately these derivatives had such small rotatory powers that they were useless for this purpose.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

O-Benzoyl-NN-diacetyl-o-aminophenol.—*o*-Benzamidophenyl benzoate (4 g.) was heated under reflux with acetic anhydride (30 c.c.) and concentrated sulphuric acid (2 drops) during 3 hours. The resultant solution was poured into water giving a light-brown oil which solidified when nearly neutralised with sodium carbonate solution, cooled and scratched. After crystallisation from ethanol (charcoal) it formed colourless crystals, m. p. 106—107° (2·2 g.) (Found: N, 4·8. $C_{17}H_{15}O_4N$ requires N, 4·7%).

The orientation of this triacyl compound was established by comparison with its isomer. Hydrolysis by sodium hydroxide solution afforded *o*-benzamidophenol. The thermal stability of the triacyl compound was established by heating it at 150° for 1 hour; it was recovered unchanged.

NN-Dibenzoyl-O-acetyl-o-aminophenol.—To *o*-benzamidophenyl acetate (10 g.) in pyridine was added benzoyl chloride (7 g.), and the solution was set aside for 90 hours at room temperature. The *product* obtained on pouring the mixture into dilute hydrochloric acid and powdered ice was collected, washed, dried, and crystallised from toluene (charcoal). It formed rhombic prisms, m. p. 141—142° (6·1 g.) (Found: N, 4·0. $C_{22}H_{17}O_4N$ requires N, 3·9%). When mixed with *o*-benzamidophenyl acetate (133—134°) it melted at 121—126°.

The alkaline hydrolysis of this triacyl compound gave *o*-benzamidophenol. Its thermal stability was established by heating it at 200° for 2 hours; it was recovered unchanged.

ON-Dibenzoyl-N-acetyl-o-aminophenol.—*o*-Acetamidophenyl benzoate (5 g.) was dissolved in pyridine, benzoyl chloride (3·3 g.) added, and the mixture set aside for 90 hours at room temperature in a stoppered flask. The yellow gum obtained by stirring the product into dilute hydrochloric acid was dried. Crystallised from ethanol (charcoal) this triacyl *derivative* formed wedge-shaped plates, m. p.

81·5—82·5° (3·1 g.) (Found: N, 4·0. $C_{17}H_{15}O_4N$ requires N, 4·7%). Alkaline hydrolysis of the compound gave *o*-benzamidophenol. It was recovered unchanged when heated at 150—160° for 1 hour.

N-*Benzoyl*-ON-*diacetyl*-o-*aminophenol*.—*o*-Acetamidophenyl acetate (7 g.) was dissolved in pyridine, benzoyl chloride (7 g.) added, and the mixture set aside for 4 weeks at room temperature in a stoppered flask. The oil obtained by stirring the mixture into dilute hydrochloric acid was dissolved in ether, and the ethereal solution washed with, successively, sodium carbonate solution, dilute hydrochloric acid, and water. After drying (Na_2SO_4), the ether was removed. The residual light-brown oil solidified when kept for 4 months. It was then ground with ethanol (10 c.c.) and collected, giving 4·8 g. of white crystals, m. p. *ca.* 70°. Crystallised from carbon tetrachloride this *compound* forms stout prisms, m. p. 80—81° (Found: N, 4·8. $C_{17}H_{15}O_4N$ requires N, 4·7%). Alkaline hydrolysis gave *o*-benzamidophenol. Thermal stability was established by heating the compound at 130—140° for 1 hour; it was recovered unchanged.

o-*Alkylaminophenols*.—The only method described in the literature for the preparation of *o*-alkylaminophenols is that of Ransom (*Amer. Chem. J.*, 1900, **23**, 1), a most tedious process affording small yields and workable only on a small scale. The following syntheses of *o*-methyl- and *o*-ethyl-aminophenol were adopted.

o-*Methylaminophenol*. 20 G. of benz-1 : 3-oxazol-2-one (Sandmeyer, *Ber.*, 1886, **19**, 2655) were dissolved in 200 c.c. of sodium hydroxide solution and shaken with 42 c.c. of methyl sulphate (nearly 3 times the theoretical quantity), added in several lots. When a sufficient excess had been added the 3-methylbenz-1 : 3-oxazol-2-one coagulated suddenly, giving a useful indication of completion.

The white solid product was then heated under reflux with 80 c.c. of 20% sodium hydroxide solution for 1 hour. The brown oil formed quickly dissolved and a faint odour of methylamine was perceived. The solution was cooled with powdered ice, and excess of concentrated hydrochloric acid added (a white precipitate which first formed redissolved). The solution was made alkaline with sodium carbonate solution, and the *o*-methylaminophenol immediately collected and dried at room temperature *in vacuo*, giving 12·2 g. of light-brown plates which became bluish-black at 80—85°, melting at 92—95° (62% overall yield). Without further purification it gave the *N*-benzoyl derivative, m. p. 160—161°, and *N*-acetyl derivative, m. p. 152—153°.

o-*Ethylaminophenol*. A well-stirred solution of benz-1 : 3-oxazol-2-one (10 g.) in 10% sodium hydroxide solution (100 c.c.) was heated with ethyl sulphate (30 c.c.), in a boiling water-bath during 3 hours. The 3-ethylbenz-1 : 3-oxazol-2-one was extracted from the cooled product with ether, and the solvent removed, to give a brown oil. To this was added sodium hydroxide (30 g.) in water (60 c.c.) and the mixture heated under reflux for 1 hour; after addition of a further 20 c.c. of water, boiling was continued for a further 5 hours. The solution was cooled, extracted with ether (which was discarded), treated with powdered ice, and made acid with concentrated hydrochloric acid. After filtration, the solution was made alkaline with sodium carbonate solution, and the brown plates separating were immediately filtered off, washed with water, and dried *in vacuo* at room temperature. Yield, 6·35 g. (63% theory). A small quantity could be crystallised rapidly from benzene without too much decomposition: the dark mother-liquors were washed away with light petroleum, to yield *o*-ethylaminophenol as flat white needles with a pleasant citrous, phenolic odour. It became greenish black at 103°, melting slowly up to 112°. The crude material above was used for preparation of derivatives.

N-*Benzoyl*-O-*acetyl*-o-*methylaminophenol*.—This *compound* was obtained by the action of acetic anhydride on a pyridine solution of *o*-benzomethylamidophenol. It crystallised from light petroleum (b. p. 40—60°) in beautiful, long, thick needles, m. p. 55—57° (Found: C, 71·1; H, 5·7. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6%). Alkaline hydrolysis of this diacyl compound afforded *o*-benzomethylamidophenol. Its thermal stability was demonstrated by heating it at 80—100° for 2 hours; it was recovered unchanged.

O-*Benzoyl*-N-*acetyl*-o-*methylaminophenol*, prepared by benzoylation of *o*-acetomethylamidophenol in sodium hydroxide solution (Schotten–Baumann), crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 95·5—96° (Found: C, 71·8; H, 5·7. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6%). Alkaline hydrolysis afforded *o*-acetomethylamidophenol. Its thermal stability was demonstrated by heating it at 130—140° for 2 hours: it was recovered unchanged.

o-1-*Naphthomethylamidophenol*, prepared by the interaction of 1-naphthoyl chloride and *o*-methylaminophenol in pyridine, crystallised from methanol in minute crystals, m. p. 183—184° (Found: N, 5·1. $C_{18}H_{15}O_2N$ requires N, 5·1%).

ON-*Di*-1-*naphthoyl*-o-*methylaminophenol*, obtained from 1-naphthoyl chloride and *o*-1-naphthomethylamidophenol in pyridine, crystallised from methanol in small crystals, m. p. 119—120° (Found: C, 80·7; H, 4·9. $C_{29}H_{21}O_3N$ requires C, 80·7; H, 4·9%). It is hydrolysed normally, giving the *N*-monoacyl compound from which it was obtained.

N-*Benzoyl*-O-1-*naphthoyl*-o-*methylaminophenol*, obtained by the action of 1-naphthoyl chloride on a pyridine solution of *o*-benzomethylamidophenol and crystallised from ethanol, had m. p. 103° (Found: C, 78·4; H, 5·1. $C_{25}H_{19}O_3N$ requires C, 78·5; H, 5·0%). Alkaline hydrolysis of this compound gave *o*-benzomethylamidophenol. Its thermal stability was shown by heating it at 130—140° for 1 hour; it was recovered unchanged.

O-1-*Naphthoyl*-N-*acetyl*-o-*methylaminophenol*, obtained similarly from 1-naphthoyl chloride and *o*-acetomethylamidophenol in pyridine, crystallised from a little benzene in minute crystals, m. p. 118—119° (Found: C, 75·4; H, 5·5. $C_{20}H_{17}O_3N$ requires C, 75·0; H, 5·3%). Alkaline hydrolysis gave *o*-acetomethylamidophenol and 1-naphthoic acid. Its stability was demonstrated by heating it at 130—140° for 1 hour; it was recovered unchanged.

N-1-*Naphthoyl*-O-*acetyl*-o-*methylaminophenol*, prepared from *o*-1-naphthomethylamidophenol in pyridine, in a boiling water-bath (½ hour), crystallised slowly from ethanol in minute crystals, m. p. 99° (mixed with *O*-1-naphthoyl-*N*-acetyl-*o*-methylaminophenol (118—119°) it melted at 88—92°) (Found: C, 75·6; H, 5·5. $C_{20}H_{17}O_3N$ requires C, 75·6; H, 5·3%). Alkaline hydrolysis gave *o*-1-naphthomethylamidophenol. Heated at 120—130° for 1 hour, it was recovered unchanged.

o-*Acetoethylamidophenol* was prepared by the action of acetic anhydride upon *o*-ethylaminophenol.

It crystallised from 20% acetic acid in minute crystals, m. p. 131° (Found : C, 66·6; H, 7·1. $C_{10}H_{13}O_2N$ requires C, 66·8; H, 7·2%).

o-*Benzoethylamidophenol*.—*o*-Ethylaminophenol, in sodium hydroxide solution, was shaken with benzoyl chloride (2 mols.), and the gummy brown liquid separating was heated under reflux with excess of sodium hydroxide solution until it had dissolved. The o-*benzoethylamidophenol* was precipitated with acid, collected, washed with sodium carbonate solution and then with water, and dried. It crystallised from dilute ethanol in light-brown plates, m. p. 164° (Found : C, 75·0; H, 6·4. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·2%).

N-*Benzoyl*-O-1-*naphthoyl*-o-*ethylaminophenol*, obtained by the action of 1-naphthoyl chloride on a pyridine solution of *o*-benzoethylamidophenol, crystallised from ethanol in small, stout prisms, m. p. 154° (Found : C, 78·9; H, 5·6. $C_{26}H_{21}O_3N$ requires C, 79·1; H, 5·4%). Alkaline hydrolysis gave *o*-benzoethylamidophenol and 1-naphthoic acid. It was thermally stable.

o-1-*Naphthoethylamidophenol*, prepared from the amine and 1-naphthoyl chloride in pyridine, crystallised from ethanol in stout prisms, m. p. 237—238° (Found : C, 78·6; H, 6·0. $C_{19}H_{17}O_2N$ requires C, 78·4; H, 5·9%). An attempt to benzoylate this compound in pyridine solution failed, whilst under Schotten–Baumann conditions a light-yellow oil resulted which did not crystallise.

L(−)-1-*Ethyl*-n-*hexoyl Chloride*.—This was prepared by the action of thionyl chloride on L(−)-1-ethyl-*n*-hexoic acid, b. p. 113—114°/8 mm., $[\alpha]_{5461}^{20}$ −9·9° (Kenyon and Platt, *J.*, 1939, 633) in 99% yield. It forms a colourless, oily liquid with an odour reminiscent of rhubarb, b. p. 75°/21 mm., *d* 0·952, $[\alpha]_{5461}^{20}$ −3·47°.

L(−)-o-1-*Ethyl*-n-*hexoamidophenol*, prepared by the action of the above acid chloride on a pyridine solution of *o*-aminophenol, crystallised from carbon tetrachloride in prismatic needles, m. p. 89—89·5°, $[\alpha]_{5461}^{20}$ −5·6° (*c*, 1·25 in ethanol) (Found : N, 5·8. $C_{14}H_{21}O_2N$ requires N, 6·0%).

L(+)-N-*Benzoyl*-O-1-*ethyl*-n-*hexoyl*-o-*aminophenol*, prepared by the interaction of L(−)-1-ethyl-*n*-hexoyl chloride with o-benzamidophenol in pyridine, crystallised from light petroleum (b. p. 60—80°) in long cream-coloured needles, m. p. 71·5—72° $[\alpha]_{5461}^{20}$ +3·07° (*c*, 7·5 in carbon tetrachloride) (Found : N, 4·1. $C_{21}H_{25}O_2N$ requires N, 4·1%). The alkaline hydrolysis gave L(−)-1-ethyl-*n*-hexoamidophenol and benzoic acid. Its thermal stability was shown by heating it at 130—140° for 2 hours; it was recovered unchanged.

L(+)-O-*Benzoyl*-N-1-*ethyl*-n-*hexoyl*-o-*aminophenol*, prepared from L(−)-1-ethyl-*n*-hexoamidophenol and benzoyl chloride in pyridine, crystallised from light petroleum (b. p. 60—80°) in long needles, m. p. 109°, $[\alpha]_{5461}^{20}$ +9·2° (*c*, 5; carbon tetrachloride) (Found : N, 4·2. $C_{21}H_{25}O_3N$ requires N, 4·1%). The alkaline hydrolysis gave L(−)-*o*-1-ethyl-*n*-hexoamidophenol and benzoic acid. It was thermally stable.

L(+)-O-1-*Naphthoyl*-N-1′-*ethyl*-n-*hexoyl*-o-*aminophenol*, similarly obtained and crystallised, formed long needles, m. p. 101—102°, $[\alpha]_{5461}^{20}$ +6·67° (*c*, 1·5; carbon tetrachloride) (Found : N, 3·7. $C_{25}H_{27}O_3N$ requires N, 3·6%). Alkaline hydrolysis gave L(−)-*o*-1-ethyl-*n*-hexoamidophenol and 1-naphthoic acid. It was thermally stable.

L(+)-N-1-*naphthoyl*-O-1′-*ethyl*-n-*hexoyl*-o-*aminophenol*, obtained from ethyl-*n*-butylacetyl chloride and *o*-1-naphthoamidophenol in pyridine, crystallised from light petroleum (b. p. 60—80°) in long needles, m. p. 98—99°, $[\alpha]_{5461}^{20}$ +2·0° (*c*, 2·5 in carbon tetrachloride) (Found : N, 3·6. $C_{25}H_{27}O_3N$ requires N, 3·6%). Alkaline hydrolysis gave L(−)-*o*-1-ethyl-*n*-hexoylamidophenol. It was thermally stable.

Diphenyl Derivatives.—Several routes were examined for the preparation of 2-amino-2′-hydroxydiphenyl. (*a*) 2-Nitro-2′-aminodiphenyl was prepared by the method of Briggs (Thesis, London, 1947); the yield did not encourage further progress. (*b*) The mixed Ullmann reaction between *o*-iodoanisole and *o*-iodonitrobenzene gave the two symmetrical compounds as the only products isolable in a pure condition. (*c*) *o*-Iodophenol (*Org. Synth.*, Coll. Vol. **1**, 326), benzoylated in pyridine, gave *o*-iodophenyl benzoate, b. p. 213—214/20 mm., m. p. 31—33°. The mixed Ullmann reaction between this and *o*-iodonitrobenzene gave 2 : 2′-dinitrodiphenyl as the only identified product.

2-*Amino*-2′-*hydroxy*-1 : 1′-*dinaphthylmethane*.—With material prepared according to Corley and Blount (*J. Amer. Chem. Soc.*, 1947, **69**, 755) some difficulty was experienced in obtaining acyl derivatives. It was concluded that the isomerisation of the Mannich base was incomplete. The product was therefore heated to 150° during ½ hour to complete the rearrangement, whereafter no difficulty was experienced in introducing acyl groups.

2-*Acetamido*-2′-*benzoyloxy*-1 : 1′-*dinaphthylmethane*, prepared by the action of benzoyl chloride upon a pyridine solution of 2-acetamido-2′-hydroxy-1 : 1′-dinaphthylmethane, and crystallised from toluene, had m. p. 181—182·5° (Found : N, 3·0. $C_{30}H_{23}O_3N$ requires N, 3·1%). Hydrolysis by alcoholic potassium hydroxide gave the original *N*-monoacyl derivative. The diacyl compound was thermally stable, being recovered unchanged after being heated at 200° for 2 hours.

2-*Benzamido*-2′-*hydroxy*-1 : 1′-*dinaphthylmethane*, prepared in pyridine, was crystallised from toluene, then from acetone–water, and finally from ethylene glycol, to give a woolly mass of needles, which darkened and shrank at 220° and finally melted at 235—236° (Found : N, 3·1. $C_{28}H_{21}O_2N$ requires N, 3·4%).

2-*Benzamido*-2′-*acetoxy*-1 : 1′-*dinaphthylmethane*. The *N*-benzoyl derivative was boiled with acetic anhydride for 15 minutes, whereafter, on cooling and scratching, the diacyl *derivative* crystallised. After 3 recrystallisatives from toluene it formed a crystalline powder, m. p. 185 186° (Found : N, 3·3. $C_{20}H_{23}O_3N$ requires N, 3·1%). Hydrolysis of this compound with ethanolic potassium hydroxide gave the original *N*-monoacyl derivative. The thermal stability of the diacyl compound was shown by heating it at 200° for 2 hours; it was recovered unchanged.

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