4-Carboxy Diphenyl (6).—The hydrolysis of 4-cyano diphenyl yielded the substance. M. p. 220° C.

4-β-Diethylamino Carbethoxy Diphenyl Hydrochloride.—This substance was obtained by refluxing sodium *p*-phenyl benzoate with diethylamino ethyl chloride and subsequently covering the base to its hydrochloride by methods mentioned above.

Analysis—Chlorine found, 10.29%.
Calculated for $C_{19}H_{24}O_2NCl$, 10.64%.

Anesthetics Tests.—The biological results have indicated that phenyl procaine is considerably more active than cocaine hydrochloride and novocaine. This fact is borne out by the following table denoting the concentrations required for equivalent duration of anesthesia by intradermal injection into guinea pigs.

TABLE I.

	Required Concentration of the Dihydrochloride.		
Duration of Anesthesia.	Phenyl Procaine.	Cocaine.	Procaine.
50 Minutes	0.73%	1.01%	2.1%
35 Minutes	0.40%	0.52%	1.0%

Phenyl procaine hydrochloride was also more active on the rabbit's cornea although it was slightly irritating.

The biological tests on compounds reported herein were made in the Biological Research Laboratories of E. R. Squibb and Sons and we gratefully acknowledge their assistance.

SUMMARY.

In a series of phenyl derivatives of procaine the most active is the hydrochloride of β-diethylamino ethyl 2-phenyl 4-amino benzoate.

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ACYL DERIVATIVES OF ORTHO-AMINOPHENOL.*

BY C. B. POLLARD AND W. T. FORSEE, JR.

When diacyl derivatives of *o*-aminophenol were prepared by the usual methods, it was found in many cases that the order of introduction of the two different acyl groups has no influence upon the formation of the diacyl, identical products being isolated from the two acylations. The formation of identical rather than isomeric products on reversing the order of acylation indicated that during acylation a rearrangement must have occurred in one of the two cases. The positions of the acyl groups of the molecule were determined by removing the group attached to the oxygen by saponification with dilute alkali, and determining from the physical constants of the remaining monoacylated product the group attached to the nitrogen. The formation of isomeric diacyls and the production of the same

* Contribution from the Chemical Laboratories, College of Pharmacy, University of Florida.

saponification product indicates that a rearrangement must have occurred during saponification.

Considerable experimental evidence has indicated that certain acyl groups have more influence than others in bringing about this migration, weight and the acidity of the groups being considered to have the predominating influence in their obtaining a position in the more basic amino group.

Previous work on this subject by Ransom (1), Ransom and Nelson (2), Nelson and others (3, 4, 5, 6, 7), Raiford and others (8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18) and Bell (19, 20) is discussed in the literature.

The work of Pollard and others (21, 22) using one particular acyl chloride as one of the acylating agents in each diacyl throughout each series of experiments, indicated that relative acidity and weight of the acyl groups are not the controlling factors in this type of rearrangement.

This investigation was carried out in order to study further the effect of these factors on rearrangement. The acylating agent, *o-n*-heptanoyl chloride, was kept constant throughout the series. This selection afforded a heavy group and one which was less acidic than any group against which it was introduced. Diacyls were prepared by introducing the heptanoyl group against the *n*-butyryl, *n*-valeryl, *n*-caproyl, phenylacetyl and hydrocinnamyl groups.

Regardless of the order of introduction, the *n*-heptanoyl and *n*-valeryl groups produced diacyls whose melting points and mixed melting points indicated that one or both of the compounds was a mixture of the two possible isomers. Saponification of each of these diacyls yielded only *o-n*-heptanoylaminophenol, indicating in one case the migration of the *n*-heptanoyl group from the oxygen to the nitrogen. Similar results were obtained with diacyls in which the acylating groups were *n*-heptanoyl and *n*-caproyl. The acylation and saponification of these isomers involved rearrangements in which the *n*-heptanoyl group replaced the lighter and more acidic *n*-valeryl and *n*-caproyl groups.

o-n-Heptanoylaminophenol acylated with *n*-butyryl chloride gave a compound which was distinctly different from that obtained by the acylation of *o-n*-butyrylaminophenol with *n*-heptanoyl chloride. However, both isomeric diacyls yielded the same saponification product, *o-n*-heptanoylaminophenol. Similar results were obtained with diacyls in which the acylating groups were *n*-heptanoyl and phenylacetyl. The saponification of these isomers involved rearrangements in which the *n*-heptanoyl group replaced the lighter and more acidic *n*-butyryl group and the heavier and more acidic phenylacetyl group.

Introduction of the *n*-heptanoyl and hydrocinnamyl groups resulted in the production of the equilibrium mixtures of the two possible diacyls regardless of the order of introduction. Saponification in each case, also gave mixtures composed of approximately 50% of each of the possible monoacyls, showing that a partial rearrangement had occurred in each case.

EXPERIMENTAL.

o-n-Heptanoylaminophenol and *o-n*-caproylaminophenol were prepared by the method of Groenvik (23) using *o*-aminophenol and the acid chloride in an anhydrous ether solution. Their properties are summarized in Table I. The other monoacyls used, which have been previously described, were made by the same method.

TABLE I.—PROPERTIES OF MONOACYLS.

	1.	2.
Name	*o-n*-Heptanoylaminophenol	*o-n*-Caproylaminophenol
Formula	$C_6H_{13}CONHC_6H_4OH$	$C_5H_{11}CONHC_6H_4OH$
M. p., ° C.	85.5–86.5	80.0–80.5
Yield, %	96.00	95.00
N, % calculated	6.33	6.76
N, % found	6.18	6.76
C, % calculated	70.56	69.51
C, % found	70.64	69.46

o-n-Heptanoylaminophenyl n-valerate ($C_6H_{13}CONHC_6H_4OCOC_4H_9$).—To 5 Gm. of *o-n*-heptanoylaminophenol was added 2.7 Gm. of *n*-valeryl chloride. After the addition of 2 drops of concentrated sulphuric acid, the mixture was heated on a water-bath for 5 hours. A yellow oil was formed. The product was washed thoroughly with hot water and, after repeated recrystallization from hot 80% alcohol and cooling in an ice salt bath, it solidified in white crystals melting at 37.5–38.5°.

About 0.5 Gm. of this compound was saponified with a small quantity of a 10% potassium hydroxide solution. After complete solution had taken place, the mixture was filtered, cooled and acidified with dilute hydrochloric acid. White crystals separated. This product was filtered, washed with water and recrystallized from dilute alcohol. A mixed melting point of this product with *o-n*-heptanoylaminophenol showed the two compounds to be identical.

Compounds listed in Table II as 2, 3, 4, 7 and 8 were prepared by this method which is a modification of that of Jacobs, Heidelberger and Rolf (24).

o-n-Heptanoylaminophenyl n-butyrate ($C_6H_{13}CONHC_6H_4OCOC_3H_7$).—A mixture of 5 Gm. of *o-n*-heptanoylaminophenol, 2.5 Gm. of *n*-butyryl chloride and 2 drops of concentrated sulphuric acid was placed in an anhydrous ether solution and refluxed on a water-bath for 2 hours. After evaporation of the ether, a pale yellow oil remained. This was thoroughly washed with hot water and, after cooling in an ice bath, the product solidified. It was recrystallized four times from hot 80% alcohol, being deposited in white crystals, m. p. 41.5–42.5°.

The compound listed in Table II as 6 was also prepared by this method. All diacyls were saponified in approximately the same manner as previously described.

o-n-Heptanoylaminophenyl hydrocinnamate ($C_6H_{13}CONHC_6H_4OCOCH_2CH_2C_6H_5$).—An excess (6 Gm.) of hydrocinnamyl chloride was added to a pyridine solution of 6.6 Gm. of *o-n*-heptanoylaminophenol. The mixture was refluxed on a water-bath for 4 hours. After allowing to stand over night, the mixture was diluted with several volumes of water. A red oil separated. This was filtered and washed thoroughly with a very dilute hydrochloric acid solution. The remaining oil was then washed with a 5% solution of ammonium carbonate. After thoroughly washing with hot water, the oily product was dissolved in a minimum quantity of hot 80% alcohol and allowed to crystallize in an ice salt bath. Red-brown crystals separated. After several such recrystallizations, a cream-colored product was deposited which melted at 47–50° C.

The compound listed in Table II as 10 was also prepared by this method which is that of Einhorn and Hollandt (25).

TABLE II.—DIACYL DERIVATIVES OF *o*-AMINOPHENOL.

	Name.	Formula.
1.	*o-n*-Heptanoylaminophenyl *n*-valerate	$C_6H_{13}CONHC_6H_4OCOC_4H_9$
2.	*o-n*-Valerylaminophenyl *n*-heptanoate	$C_4H_9CONHC_6H_4OCOC_6H_{13}$
3.	*o-n*-Heptanoylaminophenyl *n*-caproate	$C_6H_{13}CONHC_6H_4OCOC_5H_{11}$
4.	*o-n*-Caproylaminophenyl *n*-heptanoate	$C_5H_{11}CONHC_6H_4OCOC_6H_{13}$
5.	*o-n*-Heptanoylaminophenyl *n*-butyrate	$C_6H_{13}CONHC_6H_4OCOC_3H_7$
6.	*o-n*-Butyrylaminophenyl *n*-heptanoate	$C_3H_7CONHC_6H_4OCOC_6H_{13}$
7.	*o-n*-Heptanoylaminophenyl phenylacetate	$C_6H_{13}CONHC_6H_4OCOCH_2C_6H_5$
8.	*o*-Phenylacetylaminophenyl *n*-heptanoate	$C_6H_5CH_2CONHC_6H_4OCOC_6H_{13}$
9.	*o-n*-Heptanoylaminophenyl hydrocinnamate	$C_6H_{13}CONHC_6H_4OCOCH_2CH_2C_6H_5$
10.	*o*-Hydrocinnamylaminophenyl *n*-heptanoate	$C_6H_5CH_2CH_2CONHC_6H_4OCOC_6H_{13}$

	M. P., ° C.	Yield, %.	Analysis, N, %. Calcd.	Found.	Analysis, C, %. Calcd.	Found.
1.	38–39	15	4.58	4.38	70.76	70.28
2.	43.5–45	25	4.58	4.41	70.76	70.33
3.	37–38	20	4.38	4.30	71.42	71.61
4.	41–42.5	20	4.38	4.25	71.42	71.75
5.	41.5–42.5	61	4.80	4.56	70.05	70.01
6.	32.5–33.5	27	4.80	4.54	70.05	69.82
7.	69–69.5	44	4.12	3.87	74.29	74.08
8.	83–85	31	4.12	4.16	74.29	74.35
9.	47–50	62	3.96	3.73	74.74	74.85
10.	54–56.5	55	3.96	3.69	74.74	74.55

Saponification Product.

1. $C_6H_{13}CONHC_6H_4OH$
2. $C_6H_{13}CONHC_6H_4OH$
3. $C_6H_{13}CONHC_6H_4OH$
4. $C_6H_{13}CONHC_6H_4OH$
5. $C_6H_{13}CONHC_6H_4OH$
6. $C_6H_{13}CONHC_6H_4OH$
7. $C_6H_{13}CONHC_6H_4OH$
8. $C_6H_{13}CONHC_6H_4OH$
9. 50% $C_6H_{13}CONHC_6H_4OH$
   50% $C_6H_5CH_2CH_2CONHC_6H_4OH$
10. 50% $C_6H_{13}CONHC_6H_4OH$
    50% $C_6H_5CH_2CH_2CONHC_6H_4OH$

The melting points in the cases of three pairs of isomers listed in Table II as 1, 2, 3, 4, 9 and 10 might indicate that in each case they were identical substances in an impure state, but analysis and mixed melting points seem to indicate that each might be an equilibrium mixture of the two possible isomeric diacyls.

Mixed melting point of 1 and 2	38–40°
Mixed melting point of 3 and 4	37–39°
Mixed melting point of 9 and 10	50–54°

All the diacyls prepared are insoluble in water, soluble in alcohol and very soluble in ether.

SUMMARY.

A study of the diacyl derivatives of *o*-aminophenol, when one of the acyl groups was always the *n*-heptanoyl radical, has been made. The *n*-heptanoyl group was checked against the *n*-butyryl, *n*-valeryl, *n*-caproyl, phenylacetyl and hydrocinnamyl groups.

Apparently relative weight and acidity are not the controlling factors in this type of rearrangement. When complete rearrangement did occur, the nitrogen atom was shown after saponification to be attached to the heavier and less acidic group in three cases and to the lighter and less acidic group in one case. One case showed only partial rearrangement. In this case saponification products showed part of the nitrogen to be attached to the heavier and more acidic group while the remainder of the nitrogen was attached to the lighter and less acidic group.

Two monoacyls and ten diacyl derivatives of *o*-aminophenol have been prepared, isolated and studied.

Some of these compounds are being studied for antiseptic and physiological effects. The results of this investigation will be published at a later date.

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THE POTENCY OF OREGON DIGITALIS.*[1]

(A PRELIMINARY INVESTIGATION.)

BY DONALD KUO-CHIH LEE AND ERNST T. STUHR.[2]

INTRODUCTION.

The literature reveals considerable conflicting evidence relative to physiological activity of cultivated and wild growing foxglove (1, 2, 3, 4, 5, 6, 7, 8, 9) and age of the foliage (10, 11). These contradictions prompted the investigation of the native growing Oregon plants.

Foxglove grows wild throughout the Pacific slope region from Vancouver Island to California. In Oregon it is abundant along the western part of the state, but more especially in Lincoln and Coos counties.

The results here presented are from a seasonal study of wild growing Oregon digitalis, *Digitalis purpurea* L.

Procedure.—Monthly collections were made of both first- and second-year leaves during the spring and summer of 1932–1933. Tinctures were prepared in accordance with U. S. P. specifications. The fat-free preparations were placed in glass-stoppered amber-colored bottles and stored in a cool place in order to retard deterioration (12, 13, 14).

The resulting preparations were biologically assayed by the official "one-hour" frog method (15). Throughout the experiments only healthy frogs of the species *Rana pipiens* (common "grass" or "leopard" frogs) weighing 20–35 Gm. were used. Temperature was kept constant (20° C.) The degree of sensitiveness of the frogs was ascertained, using ouabain solution as a standard. Series of standardized frogs were used in assaying the respective tinctures for each particular age and month's collection of digitalis leaves.

An attempt was made to correlate physiological activity with seasonal glucosidal content by the proposed colorimetric method of Knudsen and Dresbach (16).

* An abstract based upon a thesis by Donald Kuo-Chih Lee submitted to the Graduate Faculty of the Oregon State College in partial fulfilment of the requirements for the degree of Master of Science.

[1] Scientific Section, A. PH. A., Madison meeting, 1933.

[2] Department of Pharmacology and Pharmacognosy, Oregon State College, Corvallis Ore.