TABLE II

THERAPEUTIC INDICES

Compounds	Toxicity to rats, M. L. D. in mg. per kg.	Bactericidal dilutions *B. typhosus*	Bactericidal dilutions *Staph. Aureus*	Index *B. Typhosus*	Index *Staph. Aureus*
o-$CH_3HgSC_6H_4COONa$	40	1–2000	1–4000	0.533	0.80
o-$C_2H_5HgSC_6H_4COONa$	50	1–3000	1–4000	1.0	1.0
o-$C_5H_{11}HgSC_6H_4COONa$	60	1–2000	1–3000	0.80	0.90
o-$C_6H_5HgSC_6H_4COONa$	15	1–1000	1–1000	.10	.075
p-$C_2H_5HgSC_6H_4COONa$	100	1–1000	1–1000	.667	.50
p-$C_2H_5HgSC_6H_4CH_2COONa$	100	1–1000	1–2000	.667	1.0
$C_2H_5HgSCH(COONa)CH_2CH_3$	80	1–1000	1–1000	.533	0.40
p-$C_2H_5HgSC_6H_4SO_3Na$	25	1–1000	1–1000	.167	.125

cidal values were sufficiently low to indicate the influence of the aryl group on toxicity and its probable low index.

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Summary

1. Nine new organo-mercury compounds have been prepared.
2. In water solution their sodium salts are desirable germicides.
3. A therapeutic index indicates that an alkaryl combination is the most stable and germicidal type.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF PURDUE UNIVERSITY]

ACYL DERIVATIVES OF ORTHO-AMINOPHENOL. VI

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When diacyl derivatives of *o*-aminophenol were prepared in the past by the usual methods, it was found in most 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 position of the acyl groups of the molecule can be 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 identical diacyls mentioned above were found to saponify to yield identical products, as would be expected.

The formation of identical rather than isomeric products on reversing the order of acylation indicates that during acylation a rearrangement must have occurred in one of the two cases. It has been found that certain

acyl groups have more power than others to bring about this migration, weight and acidity of the group being considered to have the predominating influence in their obtaining a position in the more basic amino group in preference to the phenol group.

Previous work on this subject by Ransom,[1] Ransom and Nelson,[2] Nelson and others,[3] and Raiford and others[4] is discussed in the literature.

In view of the experimental evidence that relative acidity and weight of the acyl groups play some role in these rearrangements, this investigation was an attempt to determine the effects of these factors when one of the acyl groups was a constant throughout the experiments. Phenylacetyl chloride was used as one of the acylating agents in the preparation of all diacyl derivatives of *o*-aminophenol in these experiments. The selection of the phenylacetyl group afforded the use of lighter and heavier acyl groups and acyl groups derived from weaker and stronger acids.

When *o*-phenylacetylaminophenol was acylated with acetyl chloride, a diacyl melting at 101–102° was produced, while the acylation of *o*-acetylaminophenol with phenylacetyl chloride gave a diacyl melting at 99–100°. A mixture of these two diacyls melted at 76–79°, showing the two to be different. Saponification of each of these diacyls produced only *o*-phenylacetylaminophenol, indicating that in the latter case migration of the phenylacetyl group from the oxygen to the nitrogen must have occurred. Similar results were obtained with diacyls containing the propionyl and chloroacetyl groups. The saponification of these isomers involved rearrangements in which the phenylacetyl group replaced the lighter and less acidic acetyl and propionyl groups and the lighter and more acidic chloroacetyl group.

o-Phenylacetylaminophenol acylated with *n*-butyryl chloride gave *o*-phenylacetylaminophenyl *n*-butyrate, which yielded *o*-phenylacetylaminophenol on saponification. Acylation of *o*-*n*-butyrylaminophenol with phenylacetyl chloride produced *o*-*n*-butyrylaminophenyl phenylacetate. Saponification of this diacyl gave *o*-*n*-butyrylaminophenol. A rearrangement did not occur in either case. In the first case the phenylacetyl group, which is the heavier and more acidic group, is attached while in the second case the lighter and less acidic *n*-butyryl group is attached to the nitrogen. Similar results were obtained with diacyls containing the benzoyl group, which is lighter and more acidic than the phenylacetyl group.

Acylation of *o*-phenylacetylaminophenol with *n*-valeric anhydride gave

[1] Ransom, *Am. Chem. J.*, **23**, 1 (1900).

[2] Ransom and Nelson, THIS JOURNAL, **36**, 390 (1914).

[3] (a) Nelson and others, *ibid.*, **48**, 1677 (1926); (b) **48**, 1680 (1926); (c) **49**, 3129 (1927); (d) **50**, 919 (1928); (e) **51**, 2761 (1929).

[4] (a) Raiford and others, *ibid.*, **41**, 2068 (1919); (b) **44**, 1792 (1922); (c) **45**, 469 (1923); (d) **45**, 1728 (1923); (e) **46**, 430 (1924); (f) **46**, 2051 (1924); (g) **46**, 2246 (1924); (h) **46**, 2305 (1924); (i) **47**, 1111 (1925); (j) **47**, 1454 (1925); (k) **48**, 483 (1926).

o-phenylacetylaminophenyl *n*-valerate. Saponification of this diacyl produced crystals melting from 94–99° which when mixed with *o*-phenylacetylaminophenol (m. p. 149–150°) melted from 102–120°. When mixed with *o*-*n*-valerylaminophenol (m. p. 78.5–79.5°), the mixture melted from 72–75°. Mixtures of the two possible pure monoacyls were made; such a mixture of approximately 65% *o*-phenylacetylaminophenol and 35% *o*-*n*-valerylaminophenol melted from 93–98°. Some of the saponification product was added to this mixture of the pure monoacyls and the resulting mixture melted through practically the same range. Evidently the saponification product was about 65% *o*-phenylacetylaminophenol and 35% *o*-*n*-valerylaminophenol, showing that a partial rearrangement occurred. When *o*-*n*-valerylaminophenol was acylated with phenylacetyl chloride, *o*-*n*-valerylaminophenyl phenylacetate was produced. Saponification of this diacyl gave only *o*-*n*-valerylaminophenol, a rearrangement did not occur and the lighter and less acidic valeryl group was attached to the nitrogen atom.

When *o*-phenylacetylaminophenol was acylated with isovaleryl chloride, *o*-phenylacetylaminophenyl isovalerate was formed, while the introduction of the acyl groups in reverse order gave the isomeric diacyl *o*-isovalerylaminophenyl phenylacetate. Saponification of each of these diacyls produced *o*-isovalerylaminophenol. In the first case the isovaleryl radical, which is the lighter and less acidic radical, migrated from the oxygen to the nitrogen.

Acylation of *o*-phenylacetylaminophenol with *m*-chlorobenzoyl chloride gave *o*-phenylacetylaminophenyl *m*-chlorobenzoate. Introduction of the acyl group in reverse order gave *o*-(*m*-chlorobenzoylamino)-phenyl phenylacetate. Each of these diacyls gave *m*-chlorobenzoylaminophenol on saponification. A migration of the *m*-chlorobenzoyl group, which is the heavier and more acidic radical, from the oxygen to the nitrogen occurred during saponification of the first diacyl.

The acylation of *o*-(*m*-bromobenzoylamino)-phenol with phenylacetyl chloride produced *o*-(*m*-bromobenzoylamino)-phenyl phenylacetate. On saponification this diacyl gave *o*-(*m*-bromobenzoylamino)-phenol. Attempts to prepare this diacyl or its isomer by introducing the acyls in reverse order were unsuccessful.

When *o*-phenylacetylaminophenol was acylated with methyl chlorocarbonate, the same diacyl was produced as when methyl *o*-hydroxycarbanilate was acylated with phenylacetyl chloride. Saponification of this diacyl yielded a mixture of approximately 50% of each of the two possible monoacyls. A partial rearrangement occurred during saponification or the diacyl was an equilibrium mixture of the two possible diacyls. The latter does not seem probable, as the diacyl melted at 105–106°.

When *o*-phenylacetylaminophenol was acylated with ethyl chlorocarbon-

ate, the same diacyl was obtained as when ethyl *o*-hydroxycarbanilate was acylated with phenylacetyl chloride. Saponification gave ethyl *o*-hydroxycarbanilate, showing the carboethoxy group to be attached to the nitrogen.

Acylation of *o*-phenylacetylaminophenol with isobutyl chlorocarbonate gave the same diacyl as when isobutyl *o*-hydroxycarbanilate was acylated with phenylacetyl chloride. Saponification showed the isocarbobutoxy group attached to the nitrogen.

Experimental

All monoacyls were prepared by the method of Groenvik[5] using *o*-aminophenol and the acid chloride. Their properties are summarized in Table I.

TABLE I

PROPERTIES OF MONOACYLS

Phenol	Formula	M. p., °C.	Yield, %	Analyses, N, % Calcd.	Found
o-Phenylacetylamino-	$HOC_6H_4NHCOCH_2C_6H_5$	149–150	60	6.16	6.21
o-*n*-Butyrylamino-	$HOC_6H_4NHCOC_3H_7$	80–81	58	7.81	7.62
o-(*m*-Bromobenzoylamino)-	$HOC_6H_4NHCOC_6H_4Br$	180	60	4.79	4.86
o-(*m*-Chlorobenzoylamino)-	$HOC_6H_4NHCOC_6H_4Cl$	156–158	52	5.64	5.51

The other monoacyls used, which have been described previously, were made by the same method.

***o*-Phenylacetylaminophenyl Acetate** ($C_6H_5CH_2CONHC_6H_4OCOCH_3$).—To 3 g. of *o*-phenylacetylaminophenol a slight excess (1.4 g.) of acetyl chloride was added. After the addition of a drop of sulfuric acid, the mixture was stirred and heated on the water-bath for thirty minutes. A purplish-black oil formed which solidified when cold water was added. The solid was finely ground and washed with warm water. It was then dissolved in hot dilute alcohol, filtered and crystallized as flesh-colored, light flaky crystals. Repeated crystallizations gave crystals melting at 101–102°.

About 1 g. of this compound was saponified in the equivalent quantity of 10% potassium hydroxide. After complete solution resulted, the solution was acidified with dilute hydrochloric acid. A yellowish-brown precipitate formed which was washed with warm water and crystallized from dilute alcohol. These crystals melted at 147.5–148.5° and when mixed with *o*-phenylacetylaminophenol (m. p. 148–149°) melted at 148–149°, showing them to be identical.

***o*-Acetylaminophenyl Phenylacetate** ($CH_3CONHC_6H_4OCOCH_2C_6H_5$).—A slight excess (3.2 g.) of phenylacetyl chloride was added to 3 g. of *o*-acetylaminophenol. A drop of sulfuric acid was added, the mixture stirred and heated on the water-bath for thirty minutes. A dark blue oil formed which solidified on addition of cold water. The solid was ground fine, washed with warm water and dissolved in hot dilute alcohol. On cooling it crystallized as pinkish-brown flakes. After four crystallizations the melting point was constant at 99–100°. Some of these crystals were mixed with the diacyl made in the reverse order and the mixture melted from 76–79°, showing the two to be different.

This diacyl was saponified in the same manner as the preceding one and yielded *o*-phenylacetylaminophenol. A rearrangement must have occurred during saponification.

[5] Groenvik, *Bull. soc. chim.*, [2] **25**, 173 (1876).

TABLE II

DIACYL DERIVATIVES OF *o*-AMINOPHENOL

	Name	Formula
1	*o*-Phenylacetylaminophenyl acetate	$C_6H_5CH_2CONHC_6H_4OCOCH_3$
2	*o*-Acetylaminophenyl phenylacetate	$CH_3CONHC_6H_4OCOCH_2C_6H_5$
3	*o*-Phenylacetylaminophenyl propionate	$C_6H_5CH_2CONHC_6H_4OCOC_2H_5$
4	*o*-Propionylaminophenyl phenylacetate	$C_2H_5CONHC_6H_4OCOCH_2C_6H_5$
5	*o*-Phenylacetylaminophenyl butyrate	$C_6H_5CH_2CONHC_6H_4OCOC_3H_7$
6	*o*-*n*-Butyrylaminophenyl phenylacetate	$C_3H_7CONHC_6H_4OCOCH_2C_6H_5$
7	*o*-Phenylacetylaminophenyl valerate	$C_6H_5CH_2CONHC_6H_4OCOC_4H_9$
8	*o*-*n*-Valerylaminophenyl phenylacetate	$C_4H_9CONHC_6H_4OCOCH_2C_6H_5$
9	*o*-Phenylacetylaminophenyl isovalerate	$C_6H_5CH_2CONHC_6H_4OCOC_4H_9$
10	*o*-Isovalerylaminophenyl phenylacetate	$C_4H_9CONHC_6H_4OCOCH_2C_6H_5$
11	*o*-Phenylacetylaminophenyl monochloroacetate	$C_6H_5CH_2CONHC_6H_4OCOCH_2Cl$
12	*o*-Monochloroacetylaminophenyl phenylacetate	$ClCH_2CONHC_6H_4OCOCH_2C_6H_5$
13	*o*-Phenylacetylaminophenyl benzoate	$C_6H_5CH_2CONHC_6H_4OCOC_6H_5$
14	*o*-Benzoylaminophenyl phenylacetate	$C_6H_5CONHC_6H_4OCOCH_2C_6H_5$
15	*o*-Phenylacetylaminophenyl *m*-chlorobenzoate	$C_6H_5CH_2CONHC_6H_4OCOC_6H_4Cl$
16	*o*-(*m*-Chlorobenzoylamino)phenyl phenylacetate	$ClC_6H_4CONHC_6H_4OCOCH_2C_6H_5$
17	*o*-Phenylacetylaminophenyl *m*-bromobenzoate	$C_6H_5CH_2CONHC_6H_4OCOC_6H_4Br$
18	*o*-(*m*-Bromobenzoylamino)phenyl phenylacetate	$BrC_6H_4CONHC_6H_4OCOCH_2C_6H_5$
19	Phenylacetate of methyl *o*-hydroxycarbanilate	$C_6H_5CH_2COOC_6H_4NHCOOCH_3$
20	Phenylacetate of ethyl *o*-hydroxycarbanilate	$C_6H_5CH_2COOC_6H_4NHCOOC_2H_5$
21	Phenylacetate of isobutyl *o*-hydroxycarbanilate	$C_6H_5CH_2COOC_6H_4NHCOOC_4H_9$

	M. p., °C.	Yield, %	Analyses, N, % Calcd.	Found	Saponification product
1	101–102	60	5.20	5.50	$C_6H_5CH_2CONHC_6H_4OH$
2	99–100	45	5.20	5.40	$C_6H_5CH_2CONHC_6H_4OH$
3	98–99	40	4.94	4.74	$C_6H_5CH_2CONHC_6H_4OH$
4	71–72	35	4.94	4.76	$C_6H_5CH_2CONHC_6H_4OH$
5	91–92	40	4.71	4.52	$C_6H_5CH_2CONHC_6H_4OH$
6	46–48	40	4.71	4.57	$C_3H_7CONHC_6H_4OH$
7	80–82	50	4.50	4.60	65% $C_6H_5CH_2CONHC_6H_4OH$ 35% $C_4H_9CONHC_6H_4OH$
8	71–72	40	4.50	4.39	$C_4H_9CONHC_6H_4OH$
9	87–88	50	4.50	4.31	Iso-$C_4H_9CONHC_6H_4OH$
10	56–57	55	4.50	4.28	Iso-$C_4H_9CONHC_6H_4OH$
11	106–107	50	4.61	4.86	$C_6H_5CH_2CONHC_6H_4OH$
12	113–114	55	4.61	4.82	$C_6H_5CH_2CONHC_6H_4OH$
13	110–111	60	4.23	4.08	$C_6H_5CH_2CONHC_6H_4OH$
14	108–109	75	4.23	4.10	$C_6H_5CONHC_6H_4OH$
15	146–148	65	3.82	3.64	$ClC_6H_4CONHC_6H_4OH$
16	150–152	55	3.82	3.92	$ClC_6H_4CONHC_6H_4OH$
17	Several attempts failed to produce this compound				
18	157–159	55	3.41	3.48	$BrC_6H_4CONHC_6H_4OH$
19	105–106	60	4.91	4.85	50% $C_6H_5CH_2CONHC_6H_4OH$ 50% $CH_3OCONHC_6H_4OH$
20	62–63	40	4.68	4.58	$C_2H_5OCONHC_6H_4OH$
21	72–73	53	4.28	4.25	Iso-$C_4H_9OCONHC_6H_4OH$

All diacyl derivatives of *o*-aminophenol except the phenylacetates of methyl, ethyl and isobutyl *o*-hydroxycarbanilate were made by the method described above using

the monoacyl, the acid chloride and a drop of sulfuric acid, which is a modification of the method of Jacobs, Heidelberger and Rolf or by the method of Jacobs, Heidelberger and Rolf[6] using the monoacyl, the acid anhydride and a drop of sulfuric acid. The *o*-hydroxycarbanilates were made by the Schotten–Baumann reaction. The properties of all of these diacyls are summarized in Table II.

The melting points in the cases of three pairs of isomers listed above as 1, 2, 13, 14, 15 and 16 might indicate the possibility that in each case they were identical substances in an impure state, but the facts that each substance appeared to be homogeneous and the melting points of the mixtures were decidedly lower lead to the conclusion that they were isomers.

Mixed melting point of 1 and 2.....	76–79°
Mixed melting point of 13 and 14.....	80–90°
Mixed melting point of 15 and 16.....	128–135°

Summary

A study of the diacyl derivatives of *o*-aminophenol, when one of the acyl groups was always the phenylacetyl radical, has been made. The phenylacetyl group was checked against the acetyl, propionyl, butyryl, valeryl, isovaleryl, monochloroacetyl, benzoyl, *m*-chlorobenzoyl, *m*-bromobenzoyl, carbomethoxy, carboethoxy and isocarbobutoxy groups.

When both acylating agents were of the type (ClCOR), isomeric diacyls were obtained depending on the order of introduction of the acyl groups. In five cases out of eight complete rearrangement occurred during saponification, one case showed partial rearrangement and in two cases rearrangement did not occur.

Apparently relative acidity and weight are not the controlling factors in this type of rearrangement. Where complete rearrangement did occur the nitrogen atom was shown to be attached to the heavier and more acidic group in three cases, to the heavier and less acidic in one case and to the lighter and less acidic in another. Although there were differences in weight and acidity of the acyl groups, one case showed only partial rearrangement and two cases showed no migration of the acyl groups even during saponification.

Where one of the acylating agents was an alkyl chlorocarbonate (ClCOOR), the same diacyl derivative was obtained regardless of the order of introduction of the groups. Saponification of these diacyls gave a mixture of the two possible monoacyls in one case and showed no migration of the groups in the other two cases. In the last two cases the phenylacetyl group was removed by saponification, showing it to be attached to the oxygen in the diacyls.

New mono and diacyl derivatives of *o*-aminophenol have been made and studied.

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[6] Jacobs, Heidelberger and Rolf, THIS JOURNAL, **41**, 458 (1919).