Calculated for $C_{18}H_{16}ON_3$: N, 14.43
Found: N, 14.34.

Under like conditions, α-naphthalidomethyleneacetoacet-α-naphthalide gave the *α-naphthalide of 1-phenyl-5-methylpyrazole-4-carboxylic acid*, white needles from alcohol, melting at 168°. Analysis:

Calculated for $C_{21}H_{17}ON_3$: N, 12.85.
Found: N, 12.88.

The *β-naphthalide of 1-phenyl-5-methylpyrazole-4-carboxylic acid* crystallizes from alcohol in white needles which melt at 170°. Analysis:

Calculated for $C_{21}H_{17}ON_3$: N, 12.85.
Found: N, 12.91.

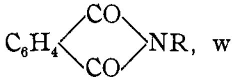
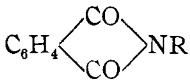
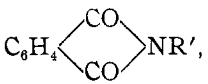
These pyrazole derivatives are all colorless compounds with melting points ten to thirty degrees higher than the corresponding isomeric colored pyrazolones.

WASHBURN COLLEGE, TOPEKA, KANSAS.

INTRAMOLECULAR REARRANGEMENT OF PHTHALAMIDIC ACIDS. IV.

BY J. BISHOP TINGLE AND B. F. PARLETT BRENTON.

Received August 4, 1909.

The previous papers on this subject by the senior author and his collaborators[1] have shown that secondary and tertiary amines, if they are not too negative, convert phthalamidic acids, $RNHCOC_6H_4CO_2H$, into imides,  $C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle NR$, whereas primary amines, $R'NH_2$, give rise to one or more of the following products: the amidic acid, $R'NHCOC_6H_4CO_2H$, the imides,  $C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle NR$ or  $C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle NR'$, or the amides, $RNHCOC_6H_4CONHR'$ and $C_6H_4(CONHR')_2$. In all cases, of course, the primary product of the reaction is an ammonium salt.

In the present communication we describe the results which we have obtained by a more extended study of the above reaction. On account of the rather curious and unexpected observations described by Bishop Tingle and Rolker,[2] our attention was first directed towards the behavior of phthal-*m*-nitrophenylamidic acid, $O_2NC_6H_4NHCOC_6H_4CO_2H$, and we have investigated its interaction with a considerable number of amines of various classes. We obtained *normal salts* from butylamine, isobutylamine, isoamylamine, benzylamine, benzylethylamine and dibenzylamine; all of these salts, when heated above their melting points, evolved the amine and gave phthal-*m*-nitrophenylimide. With ammonia, di-

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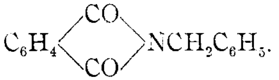
[1] Bishop Tingle and Cram, *Am. Chem. J.*, **37**, 596 (1907); Bishop Tingle and Lovelace, *Ibid.*, **38**, 642 (1907); Bishop Tingle and Rolker, THIS JOURNAL, **30**, 1882 (1908).

[2] *Loc. cit.*

amylamine and dibenzylamine we were unable to isolate any salt. These experiments and others, described below, were made in the hope of preparing unsymmetrical diamides, $RNHCOC_6H_4CONHR'$. Bishop Tingle and Rolker[1] had obtained phthalphenyl-*p*-tolyldiamide in the course of their rearrangement experiments. We failed to find in the literature any description of these unsymmetrical diamides as a class and no general method appears to be known for their preparation, although one or two members have, perhaps, been produced incidentally, as it were. We have found that, in certain cases, these diamides may be obtained by fusion of the substituted ammonium salt of a phthalamidic acid. Unfortunately the method, although simple and easy to use, does not appear to be of general utility; its efficacy appears to depend very largely on the nature of the group R, in the compounds $RNHCOC_6H_4CO_2H$, but no doubt the amine employed exerts some influence. Our best results were obtained with benzylamine. No diamide could be isolated from phthal-*m*-nitrophenyl- or -β-naphthylamidic acids, but from the *p*-tolyl derivative we obtained the *benzylammonium salt* and from this the *diamide*, $CH_3C_6H_4NHCOC_6H_4CONHCH_2C_6H_5$. *Benzylammonium phthal-β-naphthylamidate* gave phthaldibenzylamide,

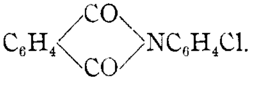
$$C_6H_4(CONHCH_2C_6H_5)_2,$$

and *dibenzylammonium phthalate* yielded phthalbenzylimide,



$$C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle NCH_2C_6H_5.$$

For employment in the further study of the influence of substituting groups in the molecule of the amine, we prepared *phthal-p-chlorphenylamidic acid*, $ClC_6H_4NHCOC_6H_4CO_2H$, which melts at 180°. It is not changed by prolonged heating with alcohol (40 per cent.). *Pyridine* and *aniline*, at 65°, and *β-naphthylamine*, at 100°, all transform it into phthal-*p*-chlorphenylimide,



$$C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle NC_6H_4Cl.$$

Our attention was now directed to the investigation of phthalamidic acids containing two like or unlike groups linked to the nitrogen atom, $RNR'COC_6H_4CO_2H$, and we have prepared the following compounds of this type: *phthaldiisobutylamidic*, *phthaldiphenylamidic* and *phthalphenyl-β-naphthylamidic acids*. The products from diamylamine, methyl-, ethyl- and amylanilines and also those from benzylmethylethyl- and from benzylethylamine were oily or tarry and unsuited for our purpose.

Phthaldiisobutylamidic acid is not changed by boiling with ethyl alcohol (40 per cent.) or with acetone. At 65°, *pyridine* failed to react with it; *aniline* produced a quantity of phthalphenylimide, some un-

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[1] *Loc. cit.*, p. 1889.

changed acid being recovered. At 100°, β-naphthylamine behaved in a similar manner, giving phthal-β-naphthylimide.

PHTHALDIPHENYLAMIDIC ACID and pyridine yield, at 100°, *dipyridinium phthalate*, $C_6H_4(CO_2NHC_5H_5)_2$, which, for comparison, was prepared from phthalic acid. It melts at 109°, and its formation from the diamidic acid is the first example of hydrolysis which we have observed during our work with amidic acids. Attempts to obtain a pyridinium hydrogen phthalate were unsuccessful. With *aniline*, the amidic acid gave phthalphenylimide which, together with phthal-β-naphthylamidic acid, was also produced by the action of *β-naphthylamine.* Bishop Tingle and Rolker have shown[1] that β-naphthylamine and phthalphenylamidic acid yield phthal-β-naphthylamidic acid, whereas aniline reacts with this latter acid with much greater difficulty, giving phthalphenylimide.[2] It would appear, therefore, that in the transformation of the diphenylamidic acid with β-naphthylamine a part of the acid is hydrolyzed to phthalphenylamidic acid which then reacts in the manner described by Bishop Tingle and Rolker.

Phthalphenyl-β-naphthylamidic acid, $C_6H_5N(C_{10}H_7)COC_6H_4CO_2H$, was prepared without difficulty on two occasions, but we were unable to obtain it subsequently, although we varied the experimental conditions rather widely. We are unable to offer any satisfactory explanation of this experience. The acid is colorless and crystalline and melts at 115°.

Experimental.

EXPERIMENTS WITH PHTHAL-*m*-NITROPHENYLAMIDIC ACID.—Supplementing the description of this compound given in an earlier paper, we have found that it is most conveniently recrystallized from ethyl alcohol (40 per cent.), from which it is deposited in prisms. At 100°, during 1.5 hours, in presence of acetone or ethyl alcohol (40 per cent.), it undergoes no change; after evaporation of the solvents the residue dissolves completely in an aqueous solution of sodium carbonate.

In the experiments described below the acid was dissolved in acetone and the base dropped in slowly, while shaking vigorously. Any precipitate which formed was removed and treated in the manner mentioned.

Alcoholic Ammonia.—The precipitate was recrystallized from acetone, after which it melted at 202°, both alone and when mixed with an equal portion of the original acid. It follows, therefore, that if any salt is produced it is extremely unstable.

Butylamine.—In equimolecular proportion a *salt,*

$$O_2NC_6H_4NHCOC_6H_4CO_2NH_3CH_2CH_2C_2H_5,$$

is formed, which crystallizes from acetone in needles, melting at 169°.

Found: N, 12.12.
Calculated: N, 11.69.

When fused this salt evolves alkaline fumes and yields phthal-*m*-nitrophenylimide.

Isobutylamine.—The *salt,* $O_2NC_6H_4NHCOC_6H_4CO_2NH_3CH_2CH(CH_3)_2$, of this base resembles that of its isomer and is deposited from acetone in needles, melting at 182°.

[1] *Loc. cit.*, p. 1886.

[2] *Ibid.*, p. 1893.

Found: N, 12.12.
Calculated: N, 11.69.

When fused the salt behaved like that of butylamine.

Isoamylamine.—The *salt*, $O_2NC_6H_4NHCOC_6H_4CO_2NH_3CH_2CH_2CH(CH_3)_2$, of this base was deposited from ethyl alcohol in tabular crystals, melting at 172°.

Found: N, 11.45.
Calculated: N, 11.26.

When fused it also yielded the *m*-nitrophenylimide.

Benzylamine.—This amine and the acid were mixed in ethyl alcohol solution (40 per cent.). The salt, $O_2NC_6H_4NHCOC_6H_4CO_2NH_3CH_2C_6H_5$, which was deposited, crystallized from acetone in colorless needles, melting at 166°.

Found: N, 10.70.
Calculated: N, 10.68.

It is evidently identical with the salt described by Bishop Tingle and Rolker.[1] When fused alkaline vapors are evolved and the *m*-nitrophenylimide is produced. Other experiments were made in which the amine and acid were heated at 100°, during 45 minutes, in presence of benzene and also of ethyl alcohol, but the only product was the same benzylammonium salt which is described above.

Diamylamine.—A precipitate was formed on adding this amine to the acid, but after purification the product consisted of the original acid.

Benzylethylamine.—The *salt*, $O_2NC_6H_4NHCOC_6H_4CO_2NH_2(C_2H_5)CH_2C_6H_5$, crystallized from chloroform in prisms, melting at 169°.

Found: N, 9.42.
Calculated: N, 9.97.

When fused the salt evolved alkaline vapors and gave the *m*-nitrophenylimide.

Dibenzylamine.—The *salt*, $O_2NC_6H_4NHCOC_6H_4CO_2NH_2(CH_2C_6H_5)_2$, crystallized from acetone in tufts, melting at 165°.

Found: N, 9.03.
Calculated: N, 8.73.

When fused the salt yielded the *m*-nitrophenylimide.

Tribenzylamine failed to react with phthal-*m*-nitrophenylamidic acid.

EXPERIMENTS WITH PHTHAL-*p*-TOLYLAMIDIC ACID.—The *benzylammonium salt*, $CH_3C_6H_4NHCOC_6H_4CO_2NH_3CH_2C_6H_5$, was prepared in chloroform solution. It crystallized from toluene in needles, melting at 168°.

Found: N, 8.25.
Calculated: N, 7.73.

When fused the salt evolved alkaline vapors; the residue, after being crystallized from benzene, melted at 153°. Analysis indicated that it consisted of the *unsymmetrical diamide*, $CH_3C_6H_4NHCOC_6H_4CONHCH_2C_6H_5$.

Found: N, 8.33.
Calculated: N, 8.14.

Phthaldibenzylamide melts at 174°.

In order to show how markedly a change in the experimental conditions affects the results, we mixed the acid and benzylamine, in the same proportions as used in the preparation of the salt (1 : 1 mol.), added benzene and heated the liquid on a boiling water bath during 45 minutes. The residue was washed with dilute hydrochloric acid and then digested with an aqueous solution of sodium bicarbonate, which removed a quantity of the original acid. The portion insoluble in the carbonate solu-

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[1] *Loc. cit.*, p. 1890.

tion consisted of phthal-*p*-tolylimide (m. p. 201°), showing that, under these conditions, the benzylamine reacts with the acid like the amines studied by Bishop Tingle and Rolker.[1]

Experiments with Phthal-β-naphthylamidic Acid.—Benzylamine was added to the acid in acetone solution and the resulting precipitate was recrystallized from ethyl alcohol. The first portion consisted of needles, melting at 174°. This proved to be phthaldibenzylamide, $C_6H_4(CONHCH_2C_6H_5)_2$, the melting point of which has been given previously as 178°.[2]

Found: N, 8.47.
Calculated: N, 8.14.

The alcoholic mother-liquor, after evaporation, deposited prismatic crystals, melting at 165°. These proved to be the *benzylammonium salt*,

$$C_{10}H_7NHCOC_6H_4CO_2NH_3CH_2C_6H_5.$$

When warmed with an aqueous solution of sodium carbonate it evolves benzylamine.

Found: N, 7.12.
Calculated: N, 7.03.

These results show that salt formation precedes the production of the diamides, as well as that of the imides.

The acid was heated on a boiling water bath, during 45 minutes, in benzene solution, with benzylamine. The product of the reaction was worked up in the manner described in connection with the similar experiment with phthal-*p*-tolylamidic acid; the only substance which could be isolated was the original phthal-β-naphthylamidic acid. Under similar conditions, with a larger proportion of benzylamine (2 : 1 instead of 1 : 1 mols.), a quantity of the benzylammonium salt (see above), m. p. 165°, was obtained.

Experiments with Phthalic Acid.—In acetone solution, benzylamine forms the *diammonium salt*, $C_6H_4(CO_2NH_3CH_2C_6H_5)_2$, irrespective of the proportions (1 : 1 or 2 : 1 mols.) of base and acid employed. It crystallizes from acetone in needles, melting at 185°.

Found: N, 7.65.
Calculated: N, 7.37.

When evaporated to dryness, the mother-liquor deposits, in both cases, *phthalbenzylimide* (m. p. 116°).

Experiments with Phthal-*p*-chlorphenylamidic Acid.—This *acid*,

$$ClC_6H_4NHCOC_6H_4CO_2H,$$

has not been described hitherto. It was prepared by heating phthalic anhydride and *p*-chloraniline, a little gasoline (b. p. 100–120°) being added. The resulting imide was hydrolyzed by means of sodium hydroxide, in aqueous solution, and the acid precipitated with concentrated hydrochloric acid. The amidic acid was purified by dissolving it in aqueous sodium hydroxide and boiling the solution with animal charcoal. It melts at 180°, is readily soluble in sodium carbonate solution, acetone, or ethyl alcohol, more sparingly in toluene.

Found: N, 4.91.
Calculated: N, 5.10.

When boiled with ethyl alcohol (40 per cent.), during 45 minutes, the acid is not transformed to the imide. The experiments with the amines mentioned below were carried out in the manner described by Bishop Tingle and Rolker[1], the mixture of

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[1] *Loc. cit.*

[2] Bishop Tingle and Lovelace, *Loc. cit.*

amine and acid being heated at 65°, during 35 minutes. The products were separated by means of dilute hydrochloric acid and an aqueous solution of sodium carbonate.

Pyridine gives the *p*-chlorphenylimide (12.5 per cent.) and unchanged acid.

Aniline gave the same products, but the reaction was, apparently, less rapid, therefore the time of heating was prolonged to over 70 minutes.

β-Naphthylamine is without action on the acid at 65°, but at 100°, under the conditions mentioned above, the *p*-chlorphenylimide is produced.

Up to this point our transformation experiments had been carried out with phthalamidic acids of the general formula, $RNHCOC_6H_4CO_2H$; we now turned our attention to the disubstituted acids, $RNR'COC_6H_4CO_2H$, where R and R′ represent similar or dissimilar groups. Very few acids of this type appear to have been described in the literature. Unless otherwise stated, our compounds were prepared according to the general method described by Bishop Tingle and Rolker.

EXPERIMENTS WITH PHTHALDIISOBUTYLAMIDIC ACID.—This *acid*,

$$[(CH_3)_2CHCH_2]_2NCOC_6H_4CO_2H,$$

after purification by means of its *sodium salt*, was deposited from benzene as a colorless, crystalline powder, melting at 153°. It dissolves readily in aqueous sodium carbonate solution, benzene, or toluene, but is less soluble in acetone, or ethyl alcohol (40 per cent.).

Found: N, 5.44.
Calculated: N, 5.05.

The acid was recovered unchanged after being heated with benzene, during 1.5 hours, on a boiling water bath, consequently this substance was used as a solvent.

At 65°, during 35 minutes, *pyridine* fails to produce any transformation of the acid.

Aniline, under similar conditions, yields a quantity of phthalphenylimide, together with unchanged acid.

With *β-naphthylamine* the results were not very definite, but at 100°, the products are phthal-β-naphthylimide and the original acid.

PHTHALDIAMYLAMIDIC ACID.—Attempts to prepare this compound were not very successful. The product from phthalic anhydride and diamylamine was dissolved in a hot, aqueous solution of sodium carbonate. From this hydrochloric acid precipitated a colorless, amorphous solid and a yellow tar. We failed to obtain any crystalline derivative from either of these materials.

METHYLANILINE AND PHTHALIC ACID.—We carried out a number of experiments with these substances, but the only product which we could isolate was the diamide, $C_6H_4[(CON(CH_3)C_6H_5)]_2$.

ETHYLANILINE AND PHTHALIC ACID gave results similar to those obtained with methylaniline, and the products from AMYLANILINE were amorphous.

DIPHENYLAMINE AND PHTHALIC ACID.—We prepared phthaldiphenylamidic acid, $(C_6H_5)_2NCOC_6H_4CO_2H$, by the simplified method described in an earlier paper. After purification by means of the sodium salt, our product melted at 151° instead of 147–8°, as given in the literature. The acid is slightly soluble in benzene and in toluene, more readily in acetone, and it is not changed by heating at 100°, during 1.5 hours, in presence of toluene. It reacts with amines in the following manner. When heated with *pyridine*, on a boiling water bath, during 35 minutes, *dipyridinium phthalate*,

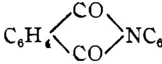
$$C_6H_4(CO_2NHC_5H_5)_2,$$

was produced. It forms colorless crystals, melting at 109°.

Found: N, 8.02.
Calculated: N, 8.63.

A specimen was prepared for comparison from phthalic acid and pyridine, in benzene solution. The same product resulted when the acid and amine were mixed in the molecular ratios 1 : 1 and 1 : 2. On the other hand, we found that dry pyridine and dry phthalic anhydride fail to react at the ordinary temperature, consequently it follows that the water necessary for the decomposition of the diphenylamidic acid must have been contained in the materials employed, or must have been absorbed from the atmosphere. We isolated and identified the diphenylamine which was liberated by pyridine from the amidic acid.

Aniline, under conditions similar to those described for pyridine, transformed phthaldiphenylamidic acid into phthalphenylimide,



$C_6H_4{<}^{CO}_{CO}{>}NC_6H_5$. The experiments with *β-naphthylamine* were made in toluene solution, under conditions otherwise similar. The products were phthalphenylimide and phthal-β-naphthylamidic acid. These results are discussed in the theoretical part of this paper.

PHENYL-β-NAPHTHYLAMINE AND PHTHALIC ACID.—These substances were allowed to react under conditions which, so far as we know, were in all respects similar to those employed with diphenylamine (see above). The resulting *phthalphenyl-β-naphthylamidic acid*, $C_6H_5N(C_{10}H_7)COC_6H_4CO_2H$, was purified by means of its sodium salt and recrystallized from ethyl alcohol (40 per cent.). We obtained minute, colorless crystals, melting at 115°. It dissolves readily in benzene, toluene, acetone, ethyl alcohol and in an aqueous solution of sodium carbonate.

Found: N, 3.61.
Calculated: N, 3.81.

After the preparation of two rather small specimens of this acid, our further efforts to obtain it were fruitless, although we varied the experimental conditions rather widely as regards the time of heating, the temperature and the presence or absence of a solvent. At present we are unable to offer any entirely satisfactory explanation of this result.

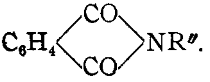
BENZYLMETHYLAMINE AND PHTHALIC ACID.—These substances reacted vigorously when they were mixed, and on heating water was evolved and also vapors having an odor of bitter almonds. No crystalline product could be isolated in spite of many efforts. Similar results were obtained with BENZYLETHYLAMINE.

The investigation of the action of amines on phthalic and on other dibasic acids will be continued in this laboratory during the coming academic year.

Summary.

1. We have prepared a number of phthalamidic acids of the general formula, $RNR'COC_6H_4CO_2H$, in which R and R′ may represent either similar or dissimilar groups.

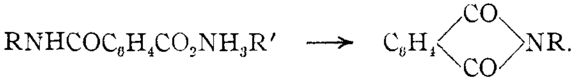
2. A study of the action of amines on these secondary amidic acids shows that the amidic acid may be hydrolyzed to phthalic acid, or that the group in the amine, $R''NH_2$, replaces R or R′ in the amidic acid, $RNR'COC_6H_4CO_2H$, giving $R''NHCOC_6H_4CO_2H$. This latter may then transform into the imide,



$C_6H_4{<}^{CO}_{CO}{>}NR''$.

3. A number of salts of amines and phthalamidic acids have been prepared.

4. Some of these salts when heated above their melting points evolve the amine and water and yield the imide,



$$RNHCOC_6H_4CO_2NH_3R' \longrightarrow C_6H_4\left\langle\begin{matrix}CO\\ \\CO\end{matrix}\right\rangle NR.$$

5. The remaining salts, when heated, form unsymmetrical phthaldiamides, $RNHCOC_6H_4CONHR'$, or the symmetrical compounds in which R is derived from the ammonium complex, thus,

$$R'NHCOC_6H_4CO_2NH_3R \longrightarrow C_6H_4(CONHR)_2.$$

Dibenzylammonium phthalate gave phthalbenzylimide.

6. The action of a number of amines on phthal-*p*-chlorphenylamidic acid has been studied; they lead to the formation of the *p*-chlorphenylimide.

After the manuscript of this paper had been prepared, our attention was called to a communication by Shigeru Komatsu, on the "Amine Salts of Phthalamic, Phenylphthalamic, and Phenylsuccinamic Acids."[1] His work was carried out in Prof. M. Kuhara's laboratory, the problem being to show that salts of amines and of the acids mentioned could exist. Komatsu mentions the paper of Bishop Tingle and Lovelace, but, unfortunately for himself, has remained in ignorance of the later work on the subject. Had he been better informed he would have been aware that *his* problem was solved by Bishop Tingle and Rolker more than a year ago. A slight acquaintance with more recent literature would also have saved Mr. Komatsu from being guilty of the discourtesy of intruding on a field of work concerning which the senior author has published four papers in the space of two years. In each of these papers a request was made for the subject to be reserved; it was mentioned that work was proceeding and special stress was laid on the question of the formation of ammonium salts of amines and the amidic acids which were under investigation.

McMaster University, Toronto, Canada,
July, 1909.

[Division of Pharmacology, Hygienic Laboratory, U. S. Public Health and Marine-Hospital Service, Washington, D. C.]

SOLUBILITIES OF THE SALICYLATES OF THE UNITED STATES PHARMACOPOEIA IN AQUEOUS ALCOHOL SOLUTIONS AT 25°.

By Atherton Seidell.

Received June 1, 1909.

The following results upon the salicylates of the United States Pharmacopoeia are a part of an extended series of determinations which are now

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[1] *Mem. Col. Sci. and Eng., Kyoto*, 1, 431.