naphthalic anhydride, 80 g. of phosphorus pentachloride and 75 cc. of phosphorus oxychloride were refluxed for twenty hours in an oil-bath, the oxychloride and excess pentachloride removed under diminished pressure and the sirupy, light brown acid chloride[14] mixed, immediately, with 40 g. of phenol. After the vigorous reaction had subsided the mixture was heated for two hours at 140–150°. The product was washed with dilute alkali, with water and then recrystallized from alcohol: m. p. 150–151°.

*Anal.* Calcd. for $C_{24}H_{16}O_4$: C, 78.23; H, 4.38. Found: C, 78.39; H, 4.41.

A mixture of 4 g. of diphenyl naphthalate, 5 g. of aluminum chloride and 20 cc. of carbon disulfide was heated on a steam-bath until the carbon disulfide had been removed and the solid residue heated for twenty-five minutes in an oil-bath at 155–160°. The mixture was treated with dilute hydrochloric acid and the product then digested with 10% sodium hydroxide solution. The solid precipitate, obtained upon acidification of the alkaline solution, was digested with sodium bicarbonate solution and the insoluble portion recrystallized from dilute alcohol; yield of phthalein 1.6 g.; m. p. 264–266°.

## Summary

It has been shown that the diphenyl ester of isophthalic acid is converted by aluminum chloride into 3-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone; from diphenyl terephthalate and aluminum chloride there was obtained 4-(4″-hydroxybenzoyl)-4′-hydroxybenzophenone.

Phenolnaphthalein was prepared from diphenyl naphthalate and aluminum chloride and from the hitherto unknown 8-(4′-hydroxybenzoyl)-1-naphthoic acid and phenol.

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[14] Mason [*J. Chem. Soc.*, **125**, 2117 (1924)] obtained this acid chloride in crystalline form and Davies and Leeper [*ibid.*, 1125 (1927)] were able to distil the material.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# The Separation and Identification of Amines with 3-Nitrophthalic Anhydride

BY JOHN W. ALEXANDER AND S. M. MCELVAIN

While numerous reagents are available for the preparation of derivatives of the three classes of amines, only two, nitrous acid and aryl sulfonyl chlorides, have been used to any considerable extent as a means of separating the different types of amines from each other when they occur in a mixture. Nitrous acid has the disadvantage of destroying completely the identity of the primary amine, often with the formation of a rearranged product. Aryl sulfonyl chlorides have proved to be quite useful on account of the fact that the sulfonamides of the primary amines are generally soluble in aqueous alkali and, consequently, can be separated from the alkali-insoluble sulfonamide of the secondary amine. However, this reagent fails when primary amines of the type $C_6H_5(CH_2)_nNH_2$ are involved because the sulfonamides of these amines are alkali-insoluble.[1] Also, certain ortho-substituted amines, such as *o*-nitroaniline,[2] can be made to react with aryl sulfonyl chlorides only with considerable difficulty. Finally, recovery of the amines from the sulfonamides is inconvenient, if not difficult, in that hydrolysis of the latter types requires that the reaction be carried out in a sealed tube.

In his textbook of qualitative organic analysis, Kamm[3] mentions the use of phthalic anhydride as a means of separating the three types of amines. So far as we are aware, there is no other reference in the literature to the general use of this reagent for the separation and identification of amines.[4] In a private communication to one of us Dr. Kamm stated that he had worked on the phthalic anhydride procedure several years ago while at the University of Illinois but had had little time to use it in practical laboratory work. The use of this reagent depends upon the fact that it does not react with tertiary amines but forms phthalamic acids with both primary and secondary amines. These derivatives are separated by heat which converts the phthalamic acid of the primary amine (I) into an alkali-insoluble N-substituted phthalimide (III) but leaves the phthalamic acid derived from the secondary amine (II) unchanged, and, therefore, alkali soluble.

Attempts to utilize phthalic anhydride for the separation and identification of amines in this Laboratory revealed the following facts: (a)

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[1] Carothers, Bickford and Hurwitz, THIS JOURNAL, **49**, 2908 (1927).

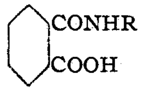
[2] *Cf.* Amundsen, *ibid.*, **59**, 1466 (1937).

[3] Kamm, "Qualitative Organic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1932, p. 69.

[4] A few patents [*C. A.*, **22**, 3417 (1928); **23**, 846, 1137 (1929); **28**, 3418 (1934)] covering the separation of certain amines with phthalic anhydride have been issued. Porai-Koshitz in a paper [*C. A.*, **29**, 131 (1935)] describes a rather large scale separation of aniline, methylaniline and dimethylaniline with this reagent.

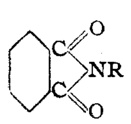
the phthalamic acids derived from the secondary amines that were studied were non-crystalline resins, (b) the temperature that was found necessary to convert the phthalamic acid of the primary amine to the N-substituted phthalimide caused some of the secondary amine derivatives to be changed into a diamide (IV) which separated as an alkali-insoluble product along with the phthalimide.[5] Succinic anhydride was found to give the desired crystalline amidic acids with the secondary amines, but these acids were converted more readily into the diamides by heat than were the corresponding derivatives from phthalic anhydride.[5b]

This paper reports the results which have been obtained with 3-nitrophthalic anhydride as a reagent for the separation and identification of amines. This anhydride has proved to be quite satisfactory as it gives crystalline derivatives with secondary amines and produces primary amine derivatives that may be converted into the phthalimides at a temperature (145°) that leaves the phthalamic acids derived from the secondary amines unchanged. With such tertiary amines as dimethylaniline, however, 3-nitrophthalic anhydride causes a violent reaction at the temperature necessary to form the phthalimide. Oxides of nitrogen are evolved and a charred mass remains as a residue. For this reason it is necessary to carry out the reaction of an amine mixture that contains such a tertiary type with 3-nitrophthalic anhydride in a solvent such as carbon tetrachloride and to separate the phthalamic acids from any tertiary amine before these acids are further heated. 3-Nitrophthalic anhydride under these conditions reacts readily and completely with *o*-substituted anilines such as *o*-nitraniline and the resulting phthalamic acids are smoothly converted by heating into the phthalimides.

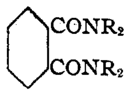


I

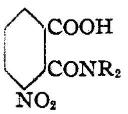
II



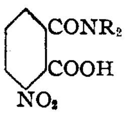
III



IV



V



VI

It is evident that there is the possibility of forming two different nitrophthalamic acids (V and VI) by the action of 3-nitrophthalic anhydride on a secondary amine. However, in no case was more than one acid obtained from this reaction. The structure V is assigned to these derivatives on the assumption that a secondary amine would react in the same way with the anhydride as does ammonia. Chapman and Stephens[6] showed that the phthalamic acid formed from ammonia and 3-nitrophthalic anhydride could be degraded through the Hofmann reaction to 3-nitroanthranilic acid. We have confirmed this observation and have carried the characterization one step further by converting the nitroanthranilic acid to *m*-nitrobenzoic acid by the diazo reaction.

The imides that are derived from the primary amines are hydrolyzed readily by 5% sodium hydroxide solution, even at room temperature. In this alkaline solution the hydrolysis goes only as far as the phthalamic acids. These acids as well as those derived from the secondary amines, on account of their stability to alkali, may be titrated, and thereby be made to reveal the molecular weight of the amine from which they were made. The phthalamic acids, however, are quite susceptible to acid hydrolysis and readily yield the amines when warmed with 10% hydrochloric acid for a few minutes. For this reason care is necessary in precipitating the phthalamic acid from alkaline solution to avoid high local concentrations of acid.

The melting points and analyses of a number of the imides derived from primary amines and of a few phthalamic acids from secondary amines are listed in the table.

## Experimental

**The Separation of a Mixture of Amines with 3-Nitrophthalic Anhydride.**—A 3–4 g. portion of the mixture of amines together with 8–10 g. of 3-nitrophthalic anhydride[7] is added to 25 cc. of carbon tetrachloride. This mixture is refluxed gently for fifteen minutes; it is not necessary that all of the solids go into solution in the carbon tetrachloride. After this time 30 cc. of 10% sodium hydroxide solution is added, followed by shaking and gentle heating until no solids remain. The carbon tetrachloride layer is separated, and the alkaline solution extracted with a 20-cc. portion of ether. The carbon tetrachloride and ether extract are mixed and the solvents removed by careful distillation. If no oily residue remains, no tertiary amine is present. If a residue remains, it may be purified by steam distillation.

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[5] (a) R. S. Pacl, University of Wisconsin M.S. Thesis, 1933; (b) J. W. Alexander, University of Wisconsin B.S. Thesis, 1935.

[6] Chapman and Stephens, *J. Chem. Soc.*, **127**, 1791 (1925).

[7] "Organic Syntheses," John Wiley and Sons, Inc., New York, 1931, Coll. Vol. I, p. 402.

VARIOUS N-SUBSTITUTED 3-NITROPHTHALIMIDES DERIVED FROM PRIMARY AMINES

| N-Substituent | Formula | M. p., °C. (uncorr.) | Analyses, % N Found | Analyses, % N Calcd. |
|---|---|---|---|---|
| Isoamyl | $C_{13}H_{14}N_2O_4$ | 89–90 | 10.40 | 10.69 |
| Phenyl[a] | $C_{14}H_8N_2O_4$ | 137–138 | 10.44 | 10.45 |
| Benzyl[a] | $C_{15}H_{10}N_2O_4$ | 142–143 | 9.68 | 9.93 |
| *m*-Bromophenyl | $C_{14}H_7BrN_2O_4$ | 186–187 | 8.26 | 8.09 |
| *p*-Bromophenyl | $C_{14}H_7BrN_2O_4$ | 201–202 | 8.09 | 8.09 |
| *o*-Chlorophenyl | $C_{14}H_7ClN_2O_4$ | 135–136 | 9.53 | 9.27 |
| *m*-Chlorophenyl | $C_{14}H_7ClN_2O_4$ | 171–173 | 9.11 | 9.27 |
| *p*-Chlorophenyl | $C_{14}H_7ClN_2O_4$ | 198–199 | 9.30 | 9.27 |
| *o*-Ethoxyphenyl | $C_{16}H_{12}N_2O_5$ | 163–164 | 8.96 | 8.97 |
| *p*-Ethoxyphenyl | $C_{16}H_{12}N_2O_5$ | 172–173 | 8.83 | 8.97 |
| *o*-Methoxyphenyl | $C_{15}H_{10}N_2O_5$ | 184–186 | 9.18 | 9.39 |
| *m*-Methoxyphenyl | $C_{15}H_{10}N_2O_5$ | 157–158 | 9.26 | 9.39 |
| *p*-Methoxyphenyl | $C_{15}H_{10}N_2O_5$ | 196–197 | 9.35 | 9.29 |
| *o*-Nitrophenyl[a] | $C_{14}H_7N_3O_6$ | 170–171 | 13.27 | 13.42 |
| *m*-Nitrophenyl[a] | $C_{14}H_7N_3O_6$ | 218–219 | 13.26 | 13.42 |
| *p*-Nitrophenyl[a] | $C_{14}H_7N_3O_6$ | 254–255 | 13.28 | 13.42 |
| *o*-Tolyl[a] | $C_{15}H_{10}N_2O_4$ | 149–151 | 9.62 | 9.93 |
| *m*-Tolyl[a] | $C_{15}H_{10}N_2O_4$ | 129–130 | 9.75 | 9.93 |
| *p*-Tolyl[a] | $C_{15}H_{10}N_2O_4$ | 155–156 | 9.87 | 9.93 |
| α-Naphthyl | $C_{18}H_{10}N_2O_4$ | 222–223 | 9.08 | 8.80 |
| β-Naphthyl | $C_{18}H_{10}N_2O_4$ | 211–212 | 9.00 | 8.80 |

[a] These compounds have been reported by Bogert and Boroschek, THIS JOURNAL, **23**, 748 (1901).

VARIOUS N,N-DISUBSTITUTED NITROPHTHALAMIC ACIDS, $C_6H_3(COOH)(CONR_1R_2)(NO_2)(1,2,3)$ DERIVED FROM SECONDARY AMINES

| $R_1$ is | $R_2$ is | | | | |
|---|---|---|---|---|---|
| Benzyl | Phenyl | $C_{21}H_{16}N_2O_5$ | 211–212 | 7.37 | 7.44 |
| Butyl | Phenyl | $C_{18}H_{18}N_2O_5$ | 204–206 | 8.11 | 8.19 |
| Ethyl | Phenyl | $C_{16}H_{14}N_2O_5$ | 203–204 | 8.63 | 8.92 |
| Methyl | Phenyl | $C_{15}H_{12}N_2O_5$ | 192–194 | 9.28 | 9.33 |
| Propyl | Phenyl | $C_{17}H_{16}N_2O_5$ | 222–225 | 8.21 | 8.54 |

To the alkaline solution of the salts of the phthalamic acids, contained in a beaker, sufficient of a 10% solution of hydrochloric acid to form the free acids is added slowly and with constant stirring. Since these acids have a tendency to form supersaturated solutions, the acid solution should be stirred vigorously until the precipitation of the phthalamic acids is complete. The precipitated solid, which may be gummy at this point, is filtered off, transferred to a small Erlenmeyer flask, and heated for thirty minutes in an oil-bath at 145°. After the first five minutes of heating, about 0.5 g. of the 3-nitrophthalic anhydride is added to the material being heated and mixed-in with a stirring rod. After heating for another twenty-five minutes, the molten reaction mixture is poured into a small mortar and allowed to solidify. Generally it is advantageous to grind the resulting hard resinous mass to a fine powder before treating it with 50 cc. of a saturated sodium bicarbonate solution to dissolve out the phthalamic acid derived from the secondary amine and any excess of 3-nitrophthalic anhydride. The reaction product which remains in the reaction flask is treated with 5 cc. of acetone and gently warmed. This amount of acetone may not dissolve all of the product remaining in the reaction flask but it loosens it sufficiently to allow it to be transferred to the sodium bicarbonate solution. The imide of the primary amine is filtered off from the bicarbonate solution and recrystallized from alcohol or an alcohol–acetone mixture. The phthalamic acid is precipitated with 10% hydrochloric acid with constant stirring as described above. This derivative may be crystallized from an alcohol–water mixture, and after drying may be titrated with standard alkali.

The primary amine may be recovered from the imide by refluxing it in 10% aqueous sodium hydroxide until all of the solid has gone into solution. This hydrolysis produces the salt of the phthalamic acid which is then hydrolyzed to the primary amine by making the alkaline solution distinctly acid with hydrochloric acid and refluxing for an additional fifteen minutes. The secondary amine may be recovered by the hydrolysis of the phthalamic acid in a similar manner with dilute hydrochloric acid.

If it is desired to prepare the N-substituted phthalimide from an individual primary amine, this readily may be accomplished by heating the amine with 3-nitrophthalic anhydride at 170° for five to ten minutes. If the preparation of a phthalamic acid derivative of an individual secondary amine is desired, it may be carried out simply by heating the secondary amine with 3-nitrophthalic anhydride at 145° for a few minutes. Higher reaction temperatures cause oxidation of the secondary amine.

## Summary

A procedure for the separation of a mixture of amines with 3-nitrophthalic anhydride is described. The melting points and analyses of a number of N-substituted 3-nitrophthalimides and N,N-disubstituted nitrophthalamic acids are listed.

MADISON, WISCONSIN RECEIVED JUNE 16, 1938