TABLE I

Ester of *m*-cresol used			Temp. of reaction, °C.	*o*-Hydroxy ketone			M. p., phenylhydrazone, °C.	*p*-Hydroxy ketone		
Acyl group	Wt., g.	B. p., °C. (mm.)		Yield G.	Yield %	B. p., °C. (mm.)		Yield G.	Yield %	M. p., °C.
Propionyl	30	90–92 (5)	120–140	28	93	M. p. 43–44				
Propionyl	21	90–92 (5)	25	15	67	M. p. 43–44		Trace		
Propionyl	36	90–92 (5)	2	23.5	65	M. p. 43–44		3.5	10	117–118
Butyryl	40	89–93 (4)	120–140	30	75	112–115 (4)	97–98			
Butyryl	43	89–93 (4)	25	28	66	112–115 (4)	97–98	Trace		
Butyryl	33	89–93 (4)	2	24	72	112–115 (4)	97–98	1	3	98–99
Valeryl	30	93–95 (2)	120–140	24	80	121–125 (3)	138–139			
Valeryl	20	93–95 (2)	25	14	67	121–125 (3)	138–139			
Caproyl	68	104–105 (2)	120–140	62	91	134–135 (3)	97–97.5			
Caproyl	26	104–105 (2)	25	16	62	134–135 (3)	97–97.5			
Heptylyl	20	112–115 (2)	120–140	14	67	148 (4)	82–83			
Heptylyl	17	112–115 (2)	25	12.5	73	148 (4)	82–83			
Pelargonyl	91	156–162 (4)	120–140	68	75	175–177 (4)				

permanganate solution, it yielded methoxyterephthalic acid, m. p. 278–280°. Consequently, the caproyl group is para to the methyl. The same acid was obtained by similar treatment of 6-acetyl-*m*-cresol.

Summary

In the Fries isomerization the tendency of the fatty acid esters of *m*-cresol to change to *o*-hydroxy ketones, rather than to para, is greater than has hitherto been supposed. This tendency becomes more marked with esters of the higher acids.

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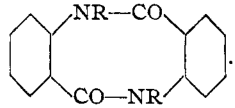
RECEIVED JUNE 27, 1933
PUBLISHED OCTOBER 6, 1933

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Anhydrides of N-Arylanthranilic Acids

BY M. GOODMAN, N. ARBITER AND GARFIELD POWELL

Introduction.—Concerning the formulas for the anhydrides of acyl anthranilic acids, of salicylic acids, and of related compounds, there is still some dispute and obscurity.[1] For example, anhydrides of unknown constitution are reported in attempted preparations of chlorides and esters of anthranilic acid,[2] and the only recognized anhydrides of anthranilic acid itself or N-alkyl or N-aryl anthranilic acids are those reported by Schroeter[1b] of the type 2M–$2H_2O$ (M is the original acid) which are formulated as 8-ring compounds  NR—CO CO—NR. It is the purpose of this communication to show that the hitherto unrecognized acyl anhydride type must be considered in dealing with dehydration products of N-

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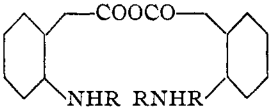
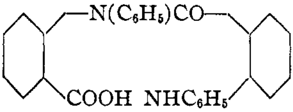
[1] (a) G. Heller and H. Lanth, *Ber.*, **52B**, 2295 (1919); (b) G. Schroeter and O. Eisleb, *Ann.*, **367**, 144 (1909); (c) R. Spallino, *Gazz. chim. ital.*, **37**, II, 151 (1907).

[2] H. Meyer, *Ann.*, **351**, 267 (1907).

aryl anthranilic acids. It seems likely that this type 

is the first product of the reaction of dehydrating agents such as benzene sulfochloride or phosphorus oxychloride on all N-aryl anthranilic acids in pyridine solution.

Theoretical.—When N-phenylanthranilic acid is treated in pyridine solution with benzene sulfochloride, a yellow compound (A) is given in almost theoretical yield. It is insoluble in alkalies or hydrochloric acid hot or cold, but treatment with glacial acetic acid or mild treatment with alcoholic alkalies leads to complete conversion into a white compound (B).

Examination of B points to the formula $2M-H_2O$ by analysis and determinations of molecular weight. It is soluble in ammonia and a sodium salt can easily be crystallized from water. It is only slowly hydrolyzed by alcoholic potash or hydrochloric acid in glacial acetic acid solution, giving rise to phenylanthranilic acid. On heating it is converted equally into acridone and phenylanthranilic acid, a reaction which, though unpredictable, serves to confirm the formula $2M-H_2O$. It can be completely hydrolyzed to N-phenylanthranilic acid but is stable to alcoholic ammonia. The only possible formula seems to be that of N-phenylanthranoylo-N-phenylanthranilic acid 

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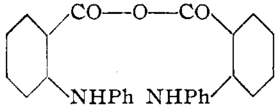
Examination of (A) also points to the formula $2M-H_2O$. On heating it behaves as does (B) and with hydrolytic agents it gives the same results, in all probability through the compound (B) into which it is so easily converted. Its solubilities resemble those of the Schroeter type of anhydride. It is completely converted with alcoholic ammonia into equal parts of phenylanthranilic amide and phenylanthranilic acid. N-Methylanthranilic acid does not give this type of compound in these conditions so the suspicion might arise that the ortho position of the N-aryl substituent is involved. This is not the case, since N-mesitylanthranilic acid gives the same type of anhydride. In the same conditions of preparation, with similar properties, a compound of the type A can also be obtained from N,N-diphenylanthranilic acid, and, as would be expected, it is not convertible into a compound of the B type but is converted immediately by alkalies or glacial acetic acid completely back to the original acid. For the yellow compound, then, the only admissible reaction formula seems to be acyl anhydride 

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Since great difficulty has been experienced in attempted syntheses of the esters and chlorides of anthranilic acid and N-substituted anthranilic acids,[2b,3] these anhydrides will be examined for further synthetic uses. Observations already made point to a general production of these A anhydrides and conversion to the peptide compound B in N-arylanthranilic acids. These compounds will be examined in relation to the Schroeter anhydrides.

Experimental

The Yellow Anhydrides (A Compounds)

1. Phenylanthranilic Anhydride.—Five grams of N-phenylanthranilic acid was dissolved in 10 cc. of pyridine. Benzene sulfochloride (1.6 cc. = 0.55 mole) was added and the flask shaken and allowed to stand for fifteen minutes. The product was stirred into 200 cc. of cold water and allowed to stand until solid; yield, 5 g., m. p. 145–148°. Repeated crystallization by solution in 15 cc. of chloroform and addition of 30 to 40 cc. of alcohol while hot gave the maximum m. p. of 152–153°, reddening at 149°. A little above the melting point the product lightens in color and appears to solidify (see decomposition by heat). This same product is obtained with *p*-toluene sulfochloride or phosphorus oxychloride, avoiding temperatures above 50° or excess of dehydrating agent. It can also be prepared by reaction in benzene solution with the same dehydrating agents in the presence of anhydrous potassium carbonate.

Anal. Calcd. for $2M-H_2O$: C, 76.43; H, 4.95. For $M-H_2O$: C, 79.9; H, 4.7. Found: C, 77.0, 76.4, 76.6; H, 4.9, 5.1, 4.3. *Mol. wt.* B. p. in benzene = 1.5 M; b. p. in alcohol = 1.8 M.

These analyses and molecular weights are paralleled by others of the same type of compound.

Decomposition by Heat.—Six grams of the anhydride was heated for four minutes at 200° in a test-tube. Melting and partial solidification took place. By collection of the whole product and treatment with dilute ammonia it was separable into 2.6 g. of ammonia-insoluble product and 2.0 g. of ammonia-soluble product (some loss of this portion occurred in recovery from alcohol and clarification through infusorial earth). The ammonia-soluble product had m. p. 179–181°. When crystallized from dilute alcohol it gave no depression of melting point with a specimen of N-phenylanthranilic acid. The ammonia-insoluble product was insoluble in cold concentrated hydrochloric acid, insoluble in alkalies, soluble in alcoholic alkalies, subliming above 310° in the same fashion as a specimen of acridone, giving fluorescent solutions.

Decomposition with Ammonia.—This yellow anhydride, on refluxing with a mixture of alcohol and aqueous ammonia for a few hours, gave evidence of a change to phenylanthranilic acid, some white compound probably of the B type, and a compound of high nitrogen content. When 3 g. of the anhydride in 50 cc. of absolute alcohol, saturated with ammonia, was heated in a bomb tube at 80–90° for two hours, a complete conversion to phenylanthranilic acid and phenylanthranilic amide was observed in the following way. The product was mixed with excess of water and the mixture boiled to remove most of the alcohol and ammonia, sodium hydroxide solution being added so that the concentration was about 4% at the end of the boiling. An insoluble residue, as well as crystals given out on cooling, had m. p. 127.5–128.5, total 1.4 g. These crystals could be recrystallized from a large volume of water or 30% alcohol, m. p. 127.5–128.5. The filtrate, on acidification, gave 1.7 g. of substance of m. p. 174–182°, and, crystallized from dilute alcohol, was shown to be almost wholly phenylanthranilic acid. The neutral product was presumed to be phenylanthranilic amide. To confirm this the amide was

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(3) L. Anschütz and Z. M. Delijski, *Ann.*, **493**, 241 (1932).

prepared as shown below, and had the same m. p. and properties as this neutral compound, giving no depression of melting point on admixture.

The preparation of the methyl ester of phenylanthranilic acid was undertaken. This is described by Schroeter[1b] as unobtainable by the use of hydrochloric acid on a mixture of acid and alcohol. He further states that the reaction of the silver salt of the acid with methyl iodide leads to sticky and uncrystallizable solids. However, the methyl ester had previously been reported[4] as an oil of b. p. 216°, 18.5 mm. Repetition of the silver salt and potassium salt method with methyl iodide led to an oil boiling at 186°, 9 mm. It seemed homogeneous but hydrolysis with alcoholic alkalies led to a recovery of about 80% of phenylanthranilic acid and about 10% of an acid of a distinct bright yellow color. Furthermore, from some specimens of the oil a solid of m. p. 58° slowly crystallized out, undoubtedly one of the pure esters. Accordingly, the preparation was undertaken by the ordinary method with gaseous hydrochloric acid. A good yield of a solid of m. p. 57–58° was obtained. This was the methyl ester, hydrolysis by solution in 5% alcoholic potassium hydroxide and refluxing for fifteen minutes (or until such time as large dilution with hot water gave no precipitate) leading to a total recovery of the original acid.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.98; H, 5.77. Found: C, 73.90; H, 5.81.

It is probable that the Schroeter product contained mixed esters and unchanged acid and that the Baeyer product was the best obtainable from the phenylanthranilic acid used by them, prepared by the method of Graebe.[5]

The methyl ester is colorless, less soluble in ethyl alcohol than the acid itself, and fairly stable to aqueous alkalies. Conversion of this ester into amide was accomplished by heating in absolute ethyl alcohol saturated with ammonia (at 10°) in a bomb tube at 120° for five hours. Even at this temperature the conversion was not complete. The product was poured into water containing potassium hydroxide, most of the alcohol and ammonia boiled off, and the insoluble amide filtered from the cold solution. Crystallized from a large volume of water, the yield was 1 g. of m. p. 127.5–129° from 9 g. of ester. Mixed with the suspected amide from the yellow anhydride, m. p. 127.5–129°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.5; H, 5.7; N, 13.2. Found: C, 73.2; H, 6.0; N, 12.91.

Phenylanthranilic amide is colorless, slightly soluble in hot water, soluble in cold concentrated hydrochloric acid.

Decomposition of the Yellow Anhydride with Acids and Alkalies.—The yellow anhydride, by solution in about ten times its weight of 95% acetic acid, and refluxing for a few minutes gives, on dilution with water while refluxing, a white compound of m. p. 200–201°, reddening at 198°, changing just above the melting point, apparently solidifying and lightening in color. The yield is the theoretical (see B).

With aqueous 2% sodium hydroxide the anhydride is apparently not changed on boiling for a few minutes. With alcoholic alkalies, however, a change occurs on solution by heating. The product is again the white compound. By heating with glacial acetic acid containing a small proportion of concentrated hydrochloric acid (1–2%) for fifteen minutes a partial change to phenylanthranilic acid occurs, demonstrated by extraction of this acid either with cold dilute ammonia or 5% sodium hydroxide solution, clarification through infusorial earth, and crystallization from dilute alcohol.

Drastic treatment with alcoholic alkalies leads to a further decomposition of the white compound into a total yield of phenylanthranilic acid. Thus 1.4 g. of the white compound (B) was refluxed for eight hours with 15 g. of potassium hydroxide in 100 cc. of 80% alcohol. On dilution with 700 cc. of water, filtration, precipitation with acetic

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(4) A. Baeyer and V. Villiger, *Ber.*, **37**, 3201 (1904).

(5) Graebe and Lagodinski, *Ann.*, **276**, 43 (1893).

acid, 1.4 g. of an acid was obtained. This acid gave no residue when taken up in 200 cc. of 7% sodium hydroxide (the B compound would come out as sodium salt) and, on recovery by acidification, an acid of m. p. 178–182° was obtained. Dissolved in alcohol, the solution clarified, and crystallized by addition of a large excess of water, the acid came out of m. p. 183–184°, yield 1.3 g., giving no depression with phenylanthranilic acid of m. p. 183–184°. Treatment of the anhydride with methyl alcohol at 100° for seven hours leads to the white compound (B) and not to esters.

2. **N,N-Diphenylanthranilic Anhydride.**—This anhydride is not so readily formed as the previous anhydride. Since high temperatures must be avoided to prevent acridone formation, or other products, it is best to accept a small yield. Seven grams of N,N-diphenylanthranilic acid was dissolved in 30 cc. of pyridine and benzene sulfochloride (1 mole = 3.5 cc.) was added. The mixture was warmed to 50° and allowed to stand at that temperature for five minutes. When the reaction mixture was poured into water the product came out as a sticky mass. The water was decanted and the mass washed with water by decantation a few times. The mass was then pressed under alcohol, the alcohol decanted, and finally taken up in a little chloroform, thrown out with warm 95% alcohol; yield 4.5 g., m. p. 143–145°. Recrystallization in the same way gave a maximum m. p. of 144.5–146° (uncorr.).

Anal. Calcd. for $2M-H_2O$: C, 81.40; H, 5.03. Found: C, 81.60, 81.24; H, 5.00, 5.20.

On heating above the melting point this anhydride also suffered a change, not investigated. It was easily hydrolyzed; 2.4 g. refluxed with 80% acetic acid for five minutes (keeping in solution by further addition of glacial acetic acid if necessary) gave a crude yield of an acid, 2.3 g., m. p. 199–202°. When this acid was taken up in cold dilute ammonia, clarified by filtration through infusorial earth, and reprecipitated, it was obtained in yield of 2.2 g., m. p. 202–203°. Mixed with N,N-diphenylanthranilic acid of m. p. 202–203°, it gave no depression of the melting point. The same result is obtained if heated for a few minutes in solution in alcoholic potassium hydroxide. That is, with gentle hydrolytic treatment there was observed no formation of a compound of the B type. In the preparation of this anhydride there are probably present some traces of N-phenylacridone, evident after hydrolytic treatment as a trace causing turbidity in the ammoniacal solution. If higher temperature was used in the preparation, sufficient of this impurity could be recovered after hydrolysis to give an m. p. of 273–275° and characteristics of N-phenylacridone which has an m. p. of 276°.

The Peptide Compounds (B)

3. **N-Phenylanthranoylo-N-phenylanthranilic Acid.**—This is prepared from the yellow anhydride, as stated, by mere solution in hot acetic acid. It can also be prepared by gentle treatment with alcoholic potash but is best crystallized from acetic acid solution, hot, by the gradual addition of hot water. Crystallization from dilute alcohol is liable to lead to a low melting (probably hydrated) form of greater solubility and so only succeeds when slowly done. Thus, if a specimen of this acid is taken up in dilute sodium hydroxide solution, precipitated with acetic acid and collected and washed, it appears on the filter paper with a slight yellow tinge. When pressed apparently dry it gives off water near 120° without melting. Also, in this form, it goes readily into solution in alcohol or benzene, but, on continued heating, comes out again absolutely colorless. It is, indeed, only slightly soluble in benzene, alcohol or chloroform, coming out of solution slowly in very small crystals, m. p. as given. Above its melting point it lightens in color, apparently solidifying, exactly as does the yellow anhydride at its lower melting point; 2 g. of this acid was held at 220° in a test-tube for three minutes. The product was crushed under dilute ammonia, giving 0.90 g. of ammonia-soluble product of m. p. 176–180° which, on crystallization from dilute alcohol, is identified as N-phenylanthra-

nilic acid. The residue of 0.95 g. was acridone. When treated with alcoholic ammonia in a bomb tube, it is unchanged at 120° for five hours (unlike the 8-ring anhydride of Schroeter). As has been previously stated, it can be completely hydrolyzed to phenylanthranilic acid.

Anal. Calcd. for $2M-H_2O$: C, 76.43; H, 4.95. Found: C, 76.85; H, 5.17. *Mol. wt.* B. p. in chloroform = 1.0 M; f. p. in acetic acid = 1.1 M; f. p. in camphor = 1.5 M.

The nearest analog of this compound is anthranoylo-N-phenylanthranilic acid described by Schroeter[1b] and prepared by the reduction of the nitro compound. In encountering the yellow anhydrides it was naturally suspected that they would correspond to the $2M-2H_2O$ compounds of Schroeter and that the white acids were formed by hydrolysis. The molecular weight determinations are curious, lower than expected and much lower than the consistently normal results by Schroeter. A possibility of unknown N-arylanthranils could not be overlooked, nor molecular combinations of previously described dehydration products of the anthranilic acids. The complexities are illustrated by a test preparation in isoquinoline, leading to a compound analyzing $2M-H_2O$ + isoquinoline, from which the isoquinoline could be recovered. One might well expect, therefore, analyses $3M-H_2O$ for other members of this series. The carbon figure is the only significant variant (by about 1%) for the different possibilities. The results given here are supported by other results with N-arylanthranilic acids to be given later.

Summary

1. An argument for the acyl anhydride formula for certain dehydration products of N-arylanthranilic acids.

2. The transformations of N-phenylanthranilic anhydride by heat to acridone, by ammonia to N-phenylanthranilic amide, by solution in certain media to (probably) N-phenylanthranoylo-N-phenylanthranilic acid.

NEW YORK CITY

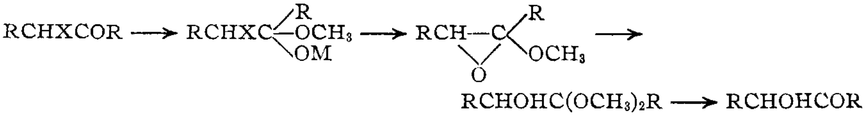
RECEIVED JUNE 27, 1933
PUBLISHED OCTOBER 6, 1933

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Reactions of Halogenated Ketones.
II. The Action of Potassium Cyanide on Desyl Chloride

BY E. P. KOHLER AND F. W. BROWN

Recent investigations have indicated that the formation of alpha hydroxy ketones from the corresponding halogen compounds occurs in a series of steps which may be represented as follows[1]



$$\mathrm{RCHXCOR} \longrightarrow \mathrm{RCHXC}\begin{matrix}\diagup \mathrm{R}\\ -\mathrm{OCH_3}\\ \diagdown \mathrm{OM}\end{matrix} \longrightarrow \underset{\diagdown\,\mathrm{O}\,\diagup}{\mathrm{RCH{-}C}}\begin{matrix}\diagup \mathrm{R}\\ \diagdown \mathrm{OCH_3}\end{matrix} \longrightarrow$$

$$\mathrm{RCHOHC(OCH_3)_2R} \longrightarrow \mathrm{RCHOHCOR}$$

In view of these and similar results it seems not improbable that the carbonyl group participates in most of the reactions of alpha halogenated

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(1) Ward, *J. Chem. Soc.*, 1541 (1929); Kohler and Addinall, THIS JOURNAL, **52**, 3728 (1930); Bergmann and Miekeley, *Ber.*, **64**, 802 (1931).