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ULTRAVIOLET ABSORPTION OF PARA-AMINOBENZOIC ESTERS IN WATER SOLUTION

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RECEIVED JULY 28, 1928 PUBLISHED FEBRUARY 5, 1929

Para-aminobenzoic acid and its esters are ordinarily classed among the benzenoid compounds; their water solutions would then be expected to exhibit selective absorption in the ultraviolet with a moderate persistence referable in part to the benzene nucleus, in part to such persistence as might be ascribed to the amino group and to the carboxyl group. Without exception the eight substances which form the main part of this study possess a selective persistence of a much higher order, comparable to that of the quinonoids. The purpose of the study is to establish this fact and to explain it, at least in part. The eight substances are *p*-aminobenzoic acid, its methyl, ethyl, *n*-propyl and *n*-butyl esters, butyn, procaine and tutocaine. In the course of the discussion the data for several other substances were required and were therefore included; these are dimethyl-*p*-aminobenzoic acid, aniline and two of its salts, benzoic acid, *p*-hydroxybenzoic acid, guanidine, nitroguanidine and aminonitroguanidine. Since a number of the substances included were local anesthetics, it seemed worth while to add stovaine and alypin, in order to furnish a basis which might be of value in their identification. In the case of butyn, procaine and tutocaine, the free bases as well as the salts were measured. All solutions were water solutions, and in order to avoid the use of any other solvents, a water solution of benzene was prepared and its absorption measured. By ultraviolet we mean the region between the visible and 2100 Å.

Previous Investigations

Methyl, ethyl, *n*-propyl and *n*-butyl *p*-aminobenzoates, butyn and butyn base, procaine base, tutocaine and tutocaine base, dimethyl *p*-aminobenzoic acid, guanidine, nitroguanidine, aminonitroguanidine and alypin have not been measured previously, as far as we have been able to find, in any solvent.

Procaine, under the name novocaine, and stovaine have been studied by Brustier;[1] the measurements are reported in terms of logarithms of thickness of solution against wave lengths. A Baly tube was used.

Para-aminobenzoic acid was said by Magini to have a strong absorption band between 300 and 240 mμ which on dilution is drawn together at 260 mμ.[2]

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[1] Brustier, *Bull. soc. chim.*, (4) 39, 1527 (1926).

[2] Quoted from Kayser, "Handbuch der Spectroscopie," S. Hirzel, Leipzig, 1905, Vol. III, p. 474.

Aniline in alcohol solutions was originally studied by Hartley[3] while aniline in alcohol with and without hydrogen chloride was studied by Baly and Collie.[4] Benzoic acid and *p*-hydroxybenzoic acid have been measured recently, with high accuracy, but in a solution of hexane with 10% ether.[5]

None of these measurements fitted exactly into our scheme, either because extinction coefficients are not given, or a comparison spectrum for each solution spectrum was not used, or the curve is incomplete, or the solvent was not water, and we have therefore made our own measurements and included them in this report.

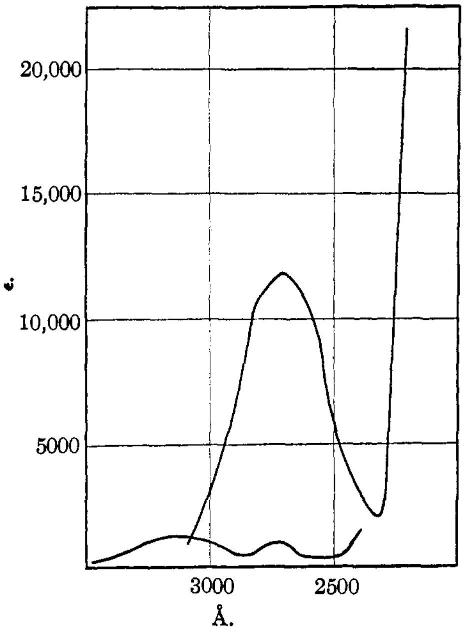

Fig. 1.—Upper curve; *p*-aminobenzoic acid; lower curve, dimethyl-*p*-aminobenzoic acid. Note: Under the curve represents absorption above, transparency.

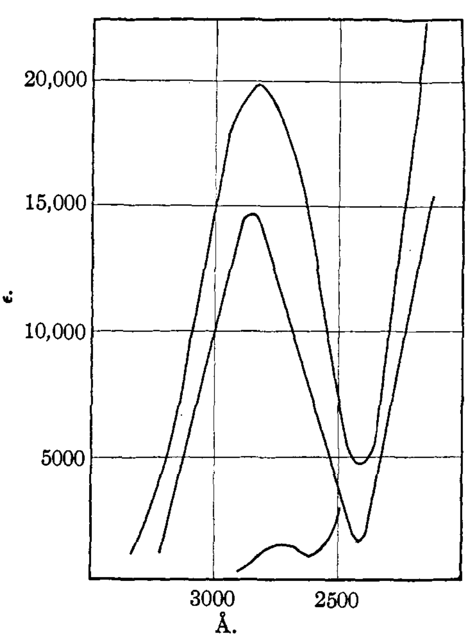

Fig. 2.—Upper curve, methyl-*p*-aminobenzoate; middle curve, ethyl-*p*-aminobenzoate (benzocaine); lower curve, alypin.

Procedure

The procedure was essentially the same as given in a previous publication, to which the reader is referred.[6]

The Schwarzschild constant in $\log t_1/t_0 = k \log I_0/I_{\text{tr}}$, the expression which links the fractions of whole revolutions of the sectors to the in-

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[3] Hartley and Huntington, *Phil. Trans. Roy Soc.*, **170**, i, 257 (1879), quoted from Baly and Collie's paper below.

[4] Baly and Collie, *J. Chem. Soc.*, **87**, 1332 (1905).

[5] Castille and Klingstedt, *Compt. rend.*, **176**, 749–750 (1923).

[6] Riegel and Reinhard, THIS JOURNAL, **48**, 1334 (1926).

tensities, was again taken as 1; a recent paper confirms previous workers in setting this constant equal to 1, and establishes that the experimental error in the use of the Hilger sector photometer need not exceed ±2%.[7]

One departure from the previous disposition was made in that the light of the comparison spectrum was allowed to pass through a blank cell containing the same lot of solvent as the solution cell. We were led to do this because of the possible reduction in intensity which the light through the solution cell might suffer by solvent absorption, while that of the comparison spectrum would not suffer the corresponding loss. The statements regarding absorption by water are conflicting. Miller[8] states that water is "ausgezeichnet durchlässig" for the ultraviolet, confirmed by Soret, Hartley, Nichols and others. Kreusler[9] gives figures which show that freshly distilled water kept in Jena glass has very little absorption except for the region of 2000 Å. and shorter waves, but that for distilled

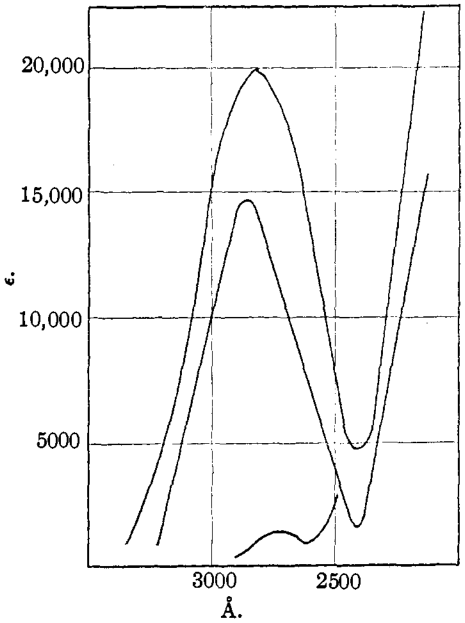

Fig. 3.—Upper curve, propyl *p*-aminobenzoate (propesine); middle curve, *n*-butyl/*p*-aminobenzoate (butesine); lower curve, stovaine.

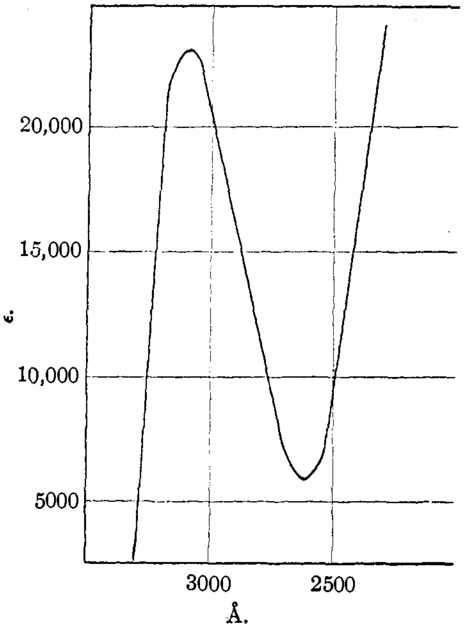

Fig. 4.—Butyn.

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[7] Baly, Morton and Riding, "The Measurement of Absorptive Power," *Proc. Roy. Soc. London*, **113A**, 709 (1927).

[8] Quoted from Kayser, "Handbuch der Spectroscopie," S. Hirzel, Leipzig, **1905**, Vol. III, p. 390.

[9] Ref. 8, p. 394.

water one-half day old, kept in common glass, the absorption was near 10%. The complete series was run first without the solvent cell for the comparison spectrum, and then repeated with the cell, and observing the caution of keeping the water in pyrex flasks. While the difference in persistence values is not great, there is a difference which makes the latter procedure imperative.[10] Only the values for the measurements with the solvent cell in place are given in this paper. All solutions were at room temperature.

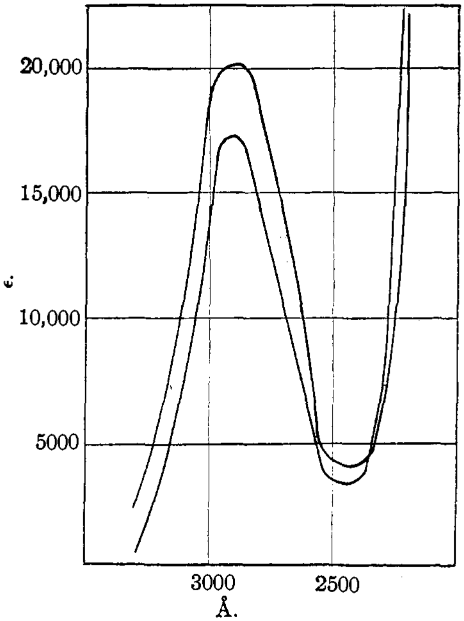

Fig. 5.—Upper curve, procaine; lower curve; tutocaine.

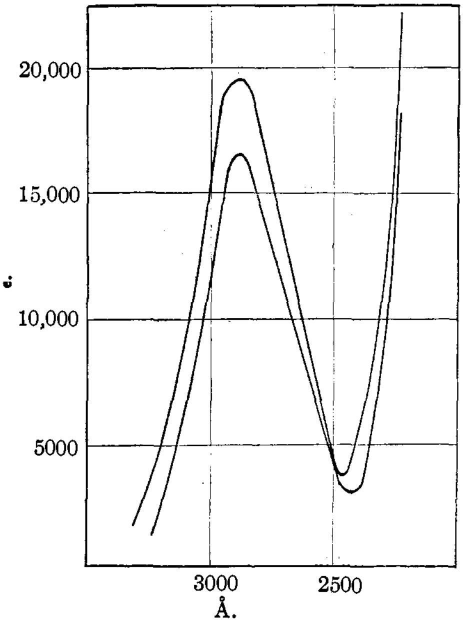

Fig. 6.—Upper curve, procaine base; lower curve, tutocaine base.

Discussion

The absorption curves of the p-aminobenzoic esters and of the free acid are clearly similar and their selective persistence is of the same order of magnitude. The values for selective persistence have been brought together in Table I; they are scaled from the original curve on millimeter paper and represent the numerical difference between the extinction coefficient for the head of the band, which is also the absolute persistence, and the extinction coefficient at the trough, where the transparency is about to cease. As will be seen from the last value in the table, the selective persistence of N-methyl-γ-pyridone, a quinonoid, is surpassed by three of the p-aminobenzoic esters and approached by the other three,

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[10] We are indebted to Dr. Shapiro of the Department of Physics, Cornell University, for this timely criticism.

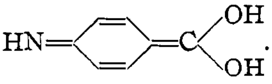
TABLE I

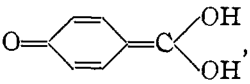
ABSOLUTE PERSISTENCES AND SELECTIVE PERSISTENCES (WATER SOLUTIONS)

Compound	Head of band, Å.	Absolute persistence	Selective persistence
p-Aminobenzoic acid	2710	11800	9700
Methyl *p*-aminobenzoate	2830	18500	13300
Ethyl *p*-aminobenzoate (benzocaine)	2850	14400	13400
Propyl *p*-aminobenzoate (propesine)	2830	19900	15100
Butyl *p*-aminobenzoate (butesine)	2850	14700	13100
Butyn	2865	19100	17100
Butyn base	2860	16700	14600
Procaine	2890	20000	15900
Procaine base	2900	19500	15700
Tutocaine	2900	17200	13700
Tutocaine base	2890	16600	13400
Dimethyl-*p*-aminobenzoic acid	2740	1000	550
Dimethyl-*p*-aminobenzoic acid	3130	1300	800
Aniline	2780	1430	810
Aniline hydrochloride	2815	230	110
Aniline hydrobromide	2735	320	100
Benzoic acid	2715	1030	340
p-Hydroxybenzoic acid	2500	17300	13900
Guanidine carbonate	..	...	none
Nitroguanidine	2630	14000	9700
Aminonitroguanidine	2650	16700	10700
Stovaine	2730	1300	350
Alypin	2750	1100	400
Benzene in water	2590	105	51
Benzene in water	2530	132	77
Benzene in water	2470	112	55
Benzene in water	2425	73	16
Benzene in water	2365	45	8
N-methyl-γ-pyridone[a] (for comparison)	2600	16700	15500

[a] THIS JOURNAL, 48, 1342 (1926).

as well as by the free acid. This suggests that for each of these substances most of the molecules are in the hemiquinoid form indicated by the formula



Such a view is confirmed by the low absorptive power of dimethyl-*p*-aminobenzoic acid, whose selective absorption is only 5.6% of that of the average of the first 11 items in the table, all with the *p*-aminobenzoic structure. The methyl group is generally assumed to migrate with great reluctance if at all. The absorption for aniline alone, added to that for benzoic acid alone, is insufficient to account for the selective persistence of the *p*-aminobenzoic compounds. *p*-Hydroxybenzoic acid, on the other hand, has a selective persistence about equaling the average of that of the *p*-aminobenzoic substances; like the latter, *p*-hydroxybenzoic acid may be written in hemiquinoid form, , which would explain its high persistence.

Mere para position does endow the molecule with a selective persistence of the magnitude possessed by the *p*-amino compounds; for example, *p*-xylene in alcohol has its maximum persistence at 2740 Å., namely 256, while *p*-cymene in alcohol has its best selective persistence at the band 2730 Å., measuring 540. The latter is the greatest persistence of *p*-substituted alkyl benzenes which we have measured.[11] It is evident that mere para position does not account for the high selective persistences reported.

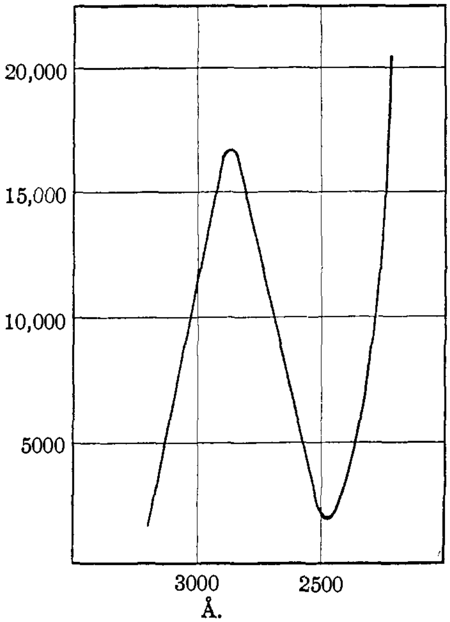


Fig. 7.—Butyn base.

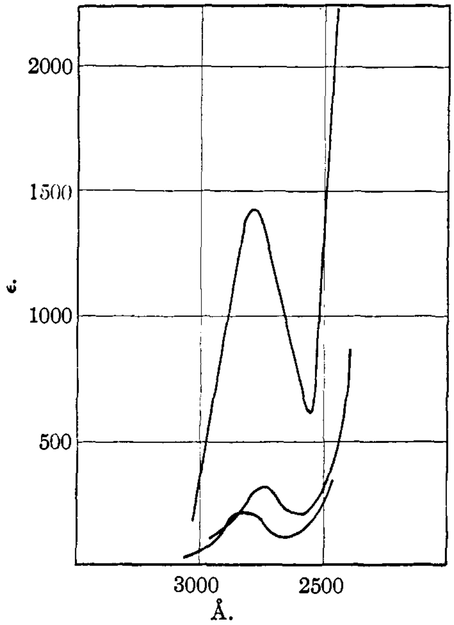


Fig. 8.—Upper curve, aniline; middle curve, aniline hydrochloride; lower curve, aniline hydrobromide.

It was expected that the free base would differ from the respective hydrochlorides or sulfates in a regular manner, but as may be seen from the table, butyn base has a selective persistence considerably lower than butyn, while procaine base has one about equal to that of procaine, and tutocaine base also has essentially the same selective persistence as tutocaine. In the case of aniline, both the hydrochloride and the hydrobromide have a selective persistence about $^1/_8$ of that possessed by the free base.

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[11] These results will be embodied in a subsequent paper.

That selective absorption is not limited to ring structures is well shown by the absorption curves for nitroguanidine and aminonitroguanidine. These two substances have not only considerable selective persistence but their curves are similar in shape to that of the *p*-aminobenzoic compounds. Guanidine carbonate has no selective absorption, so that the selective absorption of its two derivatives must be due to the nitro group and to the disturbance in the stability of the molecule caused by its introduction. Stovaine and alypin have only inconsiderable selective persistence; their molecules contain no grouping susceptible to a hemiquinoid or quinonoid rearrangement. Benzene in water has only slight selective persistence.

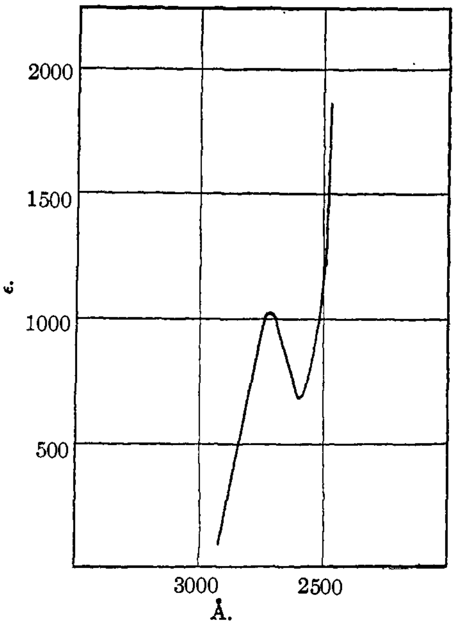

Fig. 9.—Benzoic acid.

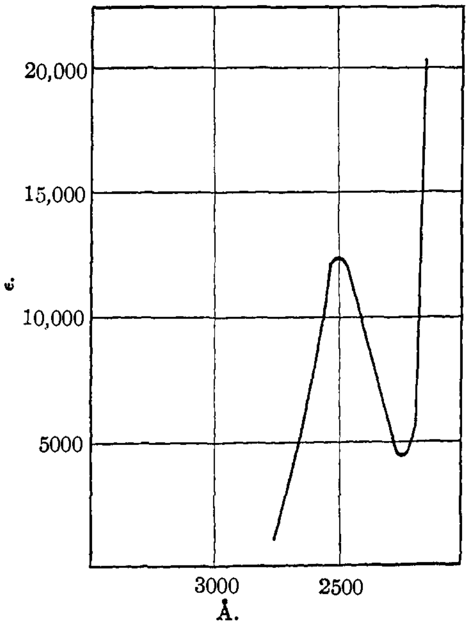

Fig. 10.—*p*-Hydroxybenzoic acid.

Cocaine in the form of hydrochloride in water solution has been measured by Castille,[12] while cocaine base in alcohol had been studied some time before that by Henri.[13] We repeated the study of the salt, using cocaine sulfate in water solution, obtaining values in agreement with those of Castille. The base dissolved in water was also measured; the curve is not unlike that for the alcohol solution. From our results a band at 2725 Å. has absolute persistence 1400, selective persistence 600; while a second band at 2310 Å. has absolute persistence 13,300 with a selective persistence undetermined because the trough of this band lies below 2100 Å.

[12] Castille, *Bull. acad. royal med. Belg.* [5], **5**, 193–200 (1925); see also ref. 1.

[13] Gompel and Henri, *Compt. rend.*, **156**, 1541 (1913).

The head of the band for the *p*-aminobenzoic esters is well toward the red from the position of the head for the free acid, in agreement with the rule of Hartley. The position of the heads of the bands for the several esters with respect to each other does not show absolute agreement with the rule.

Materials

p-Aminobenzoic acid, a by-product in the manufacture of benzoic acid by the nitration of toluene, was recrystallized twice, and the absorption spectrum determined on this sample; m. p. 186° ("International Critical Tables," 187°).

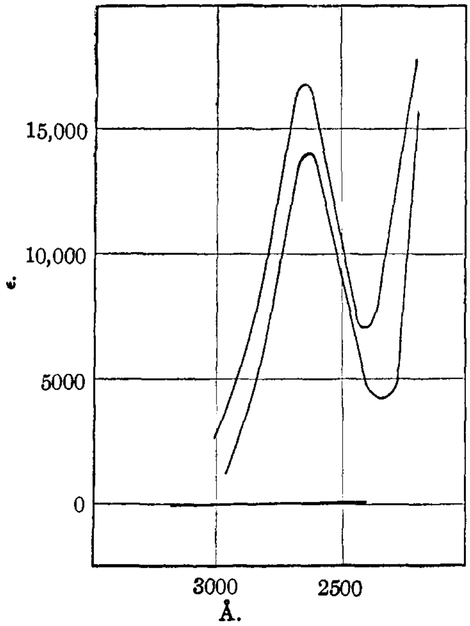

Fig. 11.—Upper curve, aminonitroguanidine; middle curve, nitroguanidine; lower curve, guanidine carbonate.

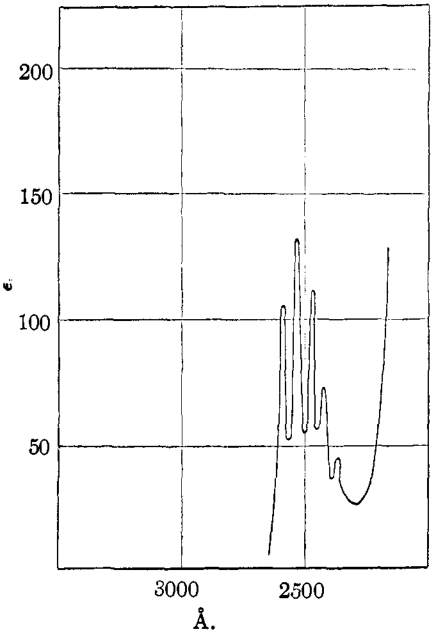

Fig. 12.—Benzene in water.

Methyl *p*-aminobenzoate was made from the acid by esterification with methyl alcohol in the presence of sulfuric acid; after refluxing for five hours the excess methyl alcohol was removed by distillation. The residual liquid was cooled and neutralized while ice-cold with caustic. A somewhat colored, sweet-smelling precipitate of the ester was formed; it was filtered off, washed with water and recrystallized from alcohol several times. The melting point was 112° ("International Critical Tables," 112°).

Ethyl p-aminobenzoate was the pharmaceutical benzocaine, recrystallized, with melting point 90° ("International Critical Tables," 91°).

n-Propyl *p*-aminobenzoate was made from the acid by esterification with *n*-propyl alcohol by the same procedure as for the methyl ester. The melting point was 75° ("International Critical Tables," 74–75°).

Butyn, procaine, tutocaine, stovaine and alypin were the pharmaceutical products; they were all recrystallized at least once and their several constants were found to agree with the literature values. The free bases for butyn, procaine and tutocaine were prepared from the salts by treating with ammonia, drying the oil first formed and, after it had hardened, crystallizing. Tutocaine base leaves the oil stage with great difficulty; we were able, however, to use a special sample prepared for this work by the Winthrop Chemical Company, consisting of well-formed crystals with melting point 98–99°. The procaine base melted at 60°, the butyn base at 33°.

Dimethyl *p*-aminobenzoic acid was made from Michler's ketone by mixing it with soda lime and heating the mixture in a retort to 350°; after the dimethylaniline had distilled off, the residue was treated with hot water and acidified with dilute acetic acid. This method is one of the two proposed by Bischoff;[14] the second one involves closed tubes. Both were tried, and the first was found to be very much superior. The crude product was recrystallized twice from 50% alcohol, giving white needles of melting point 235°, essentially the Beilstein value.

Nitroguanidine was made by dissolving guanidine nitrate in cold sulfuric acid and pouring the solution slowly into cold water;[15] long, needle-shaped crystals separate and these were recrystallized; melting point 230° ("International Critical Tables," 231°).

Aminonitroguanidine was supplied by Mr. John F. Williams of the Graduate Department, who prepared it, with Mr. Ross Phillips, for the first time.[16] The substance decomposes with explosive violence at 185°.

The remaining substances are well known and were prepared or purified by standard methods; each was tested for its physical constants, and these agreed with literature values.

Summary

1. The ultraviolet absorption of the water solutions of *p*-aminobenzoic acid and of seven of its esters has been determined.

2. In order to assist in the discussion, the ultraviolet absorption of several other substances was also determined. These substances are dimethyl-*p*-aminobenzoic acid, aniline and two of its salts, benzoic acid, *p*-hydroxybenzoic acid, guanidine, nitroguanidine, aminonitroguanidine, stovaine, alypin, benzene and the free bases of butyn, procaine and tutocaine, all in water solution.

3. The selective absorption of the *p*-aminobenzoic compounds averages 14,100, with the extremes 9700 and 15,900, while that for benzene in water solution is less than 100; hence the considerable absorption of the *p*-aminobenzoic compounds is not due to the benzenoid nucleus, but rather to a hemiquinoid state. This conclusion is confirmed by a consideration of the selective absorption of the substances listed in 2.

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[14] Bischoff, *Ber.*, 22, 341 (1889).

[15] Tenney L. Davis, THIS JOURNAL, **44**, 868 (1922).

[16] Phillips and Williams, *ibid.*, **50**, 2465 (1928).