[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BROOKLYN COLLEGE]

The Acid Anhydride Character of Aspirin

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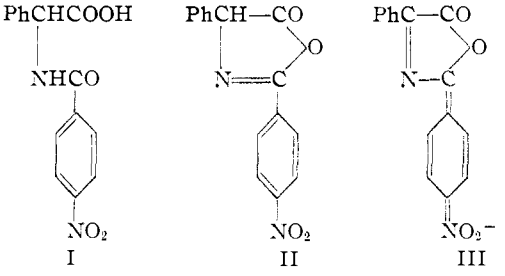
Aspirin, in pyridine solution, converts α-(*p*-nitrobenzoyl)-amino-α-toluic acid (I) to the corresponding azlactone II. This behavior is characteristic of acyclic acid anhydrides and may be accounted for by assuming an equilibrium between aspirin and salicyloylacetic anhydride (VII). Such an hypothesis offers an explanation for several unusual properties of aspirin previously known as well as for its marked acetylating action and, in particular, for the mixed benzoylating and salicyloylating action of benzoylsalicylic acid.

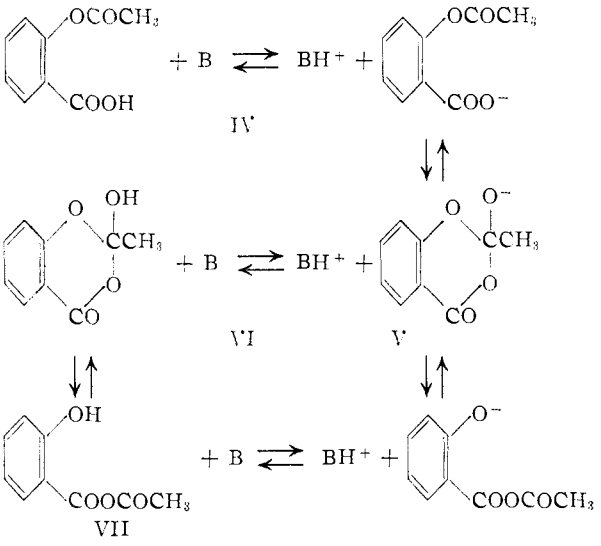
A useful test for acyclic carboxylic acid anhydrides depends upon the conversion of α-(*p*-nitrobenzoyl)-amino-α-toluic acid (I) to the corresponding azlactone II. The occurrence of this reaction is readily recognized since, in the pyridine medium employed, the azlactone displays its blue anion III.[1]



I II III

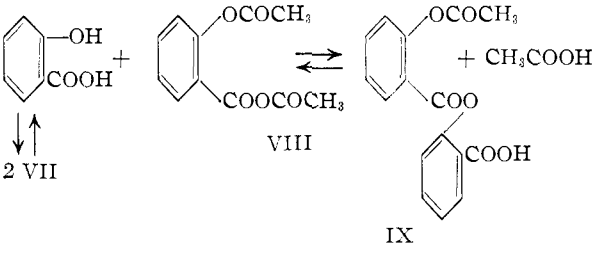
In the course of applying this test to the detection of the anhydrides formed in the pyrolysis of monocarboxylic acids[2] it was observed that aspirin gives a test for anhydride even before it is subjected to pyrolysis. A number of other unusual properties of aspirin appear in the literature. Thus, when heated at 135° it undergoes facile change yielding polysalicylide (a polyester of salicylic acid) and acetic acid together with small amounts of salicylic acid and *acetic anhydride*.[3] In pyridine solution at room temperature it is slowly converted to acetyldiplosal IX.[4] Its rate of hydrolysis in aqueous solution[5] is independent of *p*H in the range 5–8 and is much higher than might be expected. The last-mentioned property has been explained[6] by the assumption that acetylsalicylate ion (IV) rearranges (presumably in a rate-controlling step) to structure V which is then rapidly converted to salicylic and acetic "acids" by water.

It may be predicted that structure V represents a stronger base than structure IV and hence that in the *p*H range mentioned, V will be largely converted to its conjugate acid VI or to the isomeric salicyloylacetic anhydride (VII). This hypothesis of a base-catalyzed isomerization of aspirin to salicyloylacetic anhydride led to the study of acetylations and dehydrations by means of aspirin



IV VI V VII

reported in this paper. It may also serve to explain the previously known behavior of aspirin. For instance, its conversion to acetyldiplosal (IX) may be viewed as follows. Two molecules of VII may yield salicylic acid and acetylsalicyloylacetic anhydride (VIII) and this pair of substances may revert to two molecules of VII or to acetic acid and acetyldiplosal (IX).



2 VII VIII IX

Closely related to the postulated rearrangement of aspirin to salicyloylacetic anhydride is the known base-catalyzed rearrangement of *o*-acetoxybenzamide (X) to N-acetylsalicylamide (XI).[7] Certain N-acylsalicylamides undergo the reverse reaction when heated with glacial acetic acid.[7,8] The mechanism which has been proposed[7] for this isomerization involves a bicyclic structure analogous to VI, but this is inadequate to explain the fact that the isomeric compounds, XII and XIV, both yield XIII on treatment with bases. This phenomenon is readily accounted for by assuming a rearrangement similar to that proposed above for

(1) D. Davidson, *Anal. Chem.*, in press; compare P. Karrer and R. Keller, *Helv. Chim. Acta*, **26**, 50 (1943), and J. L. O'Brien and C. Niemann, THIS JOURNAL, **72**, 5348 (1950).

(2) D. Davidson and P. Newman, THIS JOURNAL, **74**, 1515 (1952).

(3)(a) R. Anschütz, *Ber.*, **52**, 1875 (1919). The occurrence of acetic anhydride is not mentioned in the more recent work of (b) W. Baker, W. D. Ollis and T. S. Zeally, *J. Chem. Soc.*, 201 (1951), but has been confirmed in the present work.

(4) German Patents 236,196 and 237,211; *Friedländer*, **10**, 1115, 1117 (1903).

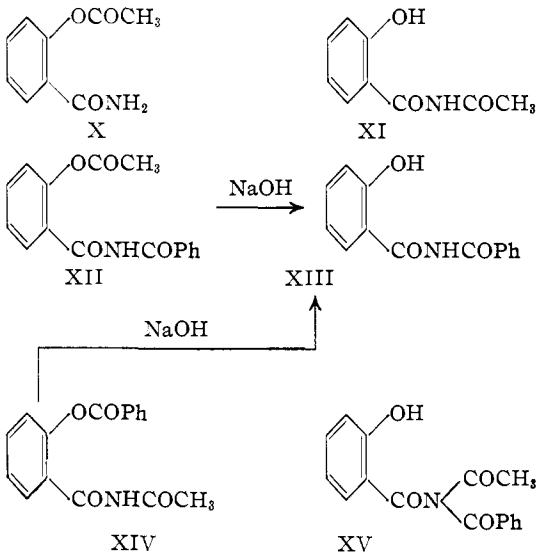
(5) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950).

(6) J. D. Chanley, E. M. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952).

(7) J. McConnan and A. W. Titherley, *J. Chem. Soc.*, **89**, 1318 (1906).

(8) R. Anschütz, *Ann.*, **442**, 18 (1925).

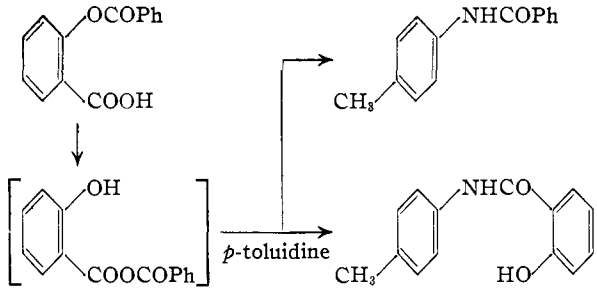
aspirin. This would involve the common intermediate, XV. Significantly enough, while tribenzoylsalicylamide has been prepared, N,N-dibenzoylsalicylamide has *not* been, presumably because of its ready rearrangement to 2-benzoyloxy-N-benzoylbenzamide.



The *m*- and *p*-isomers of aspirin do not respond to the azlactone test for anhydrides mentioned in the first paragraph and neither do phenyl salicylate (salol), acetylsalol, acetylsalicylaldehyde diacetate and numerous other esters.

Further evidence of the anhydride character of aspirin was sought in its reaction with oxalic acid. Acetic anhydride has been shown to react with oxalic acid at room temperature, particularly in pyridine solution, to yield a mixture of carbon monoxide and carbon dioxide.[9] While the half-life of the reaction between acetic anhydride and oxalic acid in pyridine at room temperature under the conditions given below is about two minutes, the corresponding half-life for aspirin is 165 minutes. In the same period of time *p*-acetoxybenzoic acid gives little or no gas. The final yield of gas obtained from aspirin corresponded to 80% of theory. This figure suggests that the dehydrating action of aspirin (on α-(*p*-nitrobenzoyl)-amino-α-toluic acid, for instance) is not due to a minor impurity but to the aspirin itself.

Aspirin in pyridine reacts rapidly with primary aromatic amines with the evolution of heat. Good yields of *p*-acetotoluide, for example, are obtained both at room temperature and at 100°. β-Naphthol reacts slowly at room temperature but completely within ten minutes at 100°. The results indicate that aspirin is essentially an acetylating agent. It was of interest, therefore, to test an analog of aspirin, *i.e.*, benzoylsalicylic acid, in which case the postulated isomeric anhydride, salicyloylbenzoic anhydride, might be more likely to undergo scission in the two theoretically possible ways. In accordance with this expectation, it was found that benzoylsalicylic acid reacted with *p*-toluidine in pyridine at 100° to form a mixture of *p*-benzotoluide and *p*-salicylotoluide in the molecular ratio of 11:1.



Experimental

The Azlactone Test for Anhydrides.—To 1 ml. of a 3% solution of α-(*p*-nitrobenzoyl)-amino-α-toluic acid[10] in pyridine add one drop or 30 mg. of the test substance. A deep blue color develops in a few seconds and then gradually fades. Acids as strong as salicylic acid inhibit the test but this difficulty may be overcome by adding a few drops of triethylamine.

Positive tests are obtained with aspirin and with benzoylsalicylic acid. Negative tests are given by *m*-acetoxybenzoic acid,[11] *p*-acetoxybenzoic acid,[11] salol, acetylsalol, acetylsalicylaldehyde diacetate, ethyl trichloroacetate and methyl oxalate.

Reactions with Oxalic Acid.—The apparatus consisted of a 4 × 1/2″ test-tube attached to a gas buret containing water saturated with carbon dioxide. A shaker similar to that used in the Parr hydrogenator permitted the test-tube to be shaken. The charge consisted of 0.20 g. of anhydrous oxalic acid, 1.0 ml. of dry pyridine and 0.001 mole of test substance. The reaction of oxalic acid with acetic anhydride at room temperature was half complete in less than two minutes. Aspirin gave an 80% yield of gas the half-life of the reaction being 165 minutes. In this length of time *p*-acetoxybenzoic acid gave little or no gas.[11]

The Pyrolysis of Aspirin.—Eighteen grams (0.1 mole) of aspirin was pyrolyzed in vacuum in an air-bath at 200° according to the recent directions of Baker and co-workers.[8b] The acetic acid–acetic anhydride distillate weighed 4.7 g. (theory, for acetic acid, 6.0 g.). This was treated with 1.0 g. of *p*-toluidine (considerable heat was evolved) and after a few minutes the mixture was made basic to litmus with 2 *M* sodium hydroxide and filtered. This yielded 0.440 g. (0.0064 mole) of aceto-*p*-toluide, m.p. 149°. A control experiment with glacial acetic acid showed that no aceto-*p*-toluide was formed from acetic acid under these conditions.

The Reaction of Aspirin with *p*-Toluidine. A. Unheated.—To 1.80 g. (0.010 mole) of aspirin contained in an insulated 6 × 3/4″ test-tube was added a solution of 1.70 g. (0.015 mole) of *p*-toluidine in 2 ml. of pyridine. The temperature of the stirred solution first fell as the aspirin dissolved and then rose within eight minutes to 59° while a precipitate appeared. After an hour, 10 ml. of water was added, the mixture chilled in ice-water and then filtered. The crystals (P_1) were washed with five ml. of ice-water and the filtrate and washings combined (F_1). P_1 was then washed successively with 10 ml. of ice-water, 5 ml. of 0.4 *M* sodium hydroxide (F_2) and 10 ml. of ice-water. It weighed 1.27 g. Acidification of F_1 with concd. hydrochloric acid gave a precipitate (P_2) weighing 1.27 g. F_2 gave no precipitate when acidified with glacial acetic acid. P_2 was treated with 20 ml. of *M* sodium bicarbonate. This left 0.072 g. of undissolved material (P_3). Acidification of the bicarbonate filtrate gave 1.08 g. (78%) of salicylic acid, m. p. 159°. P_3 was washed with 2.5 ml. of 0.4 *M* sodium hydroxide, but acidification of the filtrate (F_3) with glacial acetic acid gave no precipitate. The total yield of aceto-*p*-toluide (P_1 + P_3) was 1.34 g. or 90%. This melted at 149°. Recrystallization from methanol gave a product, m. p. 151°, which was not improved by further recrystallization. When the melt resolidified it sometimes remelted at the same point

(9) (a) H. H. Krause, *Ber.*, **52**, 426 (1919); (b) E. A. Whitford, THIS JOURNAL, **47**, 2934 (1925); (c) C. K. Rosenblum and J. H. Walton, *ibid.*, **52**, 3366 (1930).

(10) A. W. Ingersoll and R. Adams, THIS JOURNAL, **44**, 2930 (1922).

(11) More recent observations by Mr. David Rhum in this laboratory have shown that at 100° both *m*- and *p*-acetoxybenzoic acids react slowly with oxalic acid. At this temperature faint azlactone tests also are given.

and sometimes at 146°. This behavior was also shown by an authentic sample of aceto-*p*-toluide.

B. At 100°.—Similar results were obtained when aspirin was treated with a hot solution of *p*-toluidine in pyridine and the mixture heated in a boiling water-bath for 10 minutes. The one difference was that F_3 yielded three mg. (0.13%) of salicyclo-*p*-toluide, m.p. 156° (mixed m.p. 157°). This gave no colored complex with aqueous ferric chloride but gave a purple complex with aqueous *methanolic* ferric chloride.

An authentic sample of salicylo-*p*-toluide was prepared by the simpler version of the salol method.[12] The crude product melted at 156°. After recrystallization from ethanol it melted at 158°.

The Reaction of Aspirin with β-Naphthol.—To 1.80 g. (0.010 mole) mixed with 1.01 g. (0.0070 mole) of β-naphthol was added 2 ml. of pyridine. The resulting solution was heated for 10 minutes at 100° and cooled. The addition of 10 ml. of water caused the separation of an oil which soon solidified. The solid was filtered, washed twice with 5-ml. portions of water and air-dried. The product weighed 1.23 g., and melted at 69°. The combination of the wash waters with the original filtrate caused a further precipitation of 0.036 g. of product making the total 1.28 g. or 98% of theory. Recrystallization from aqueous methanol gave a product melting at 71° which exhibited no depression of the m.p. when mixed with authentic β-naphthyl acetate.

At room temperature the reaction between aspirin and β-naphthol was only slightly exothermic and remained incomplete after an hour.

The Reaction of Benzoylsalicylic Acid with *p*-Toluidine.—To 2.42 g. (0.010 mole) of benzoylsalicylic acid[13] was added a solution of 1.7 g. (0.015 mole) of *p*-toluidine in 2 ml. of pyridine. The resulting solution was heated for 10 minutes at 100° after which the mixture was cooled and 10 ml. of water added. The resulting precipitate was filtered (F_1), washed with 5 ml. of water (F_2) and then with a further 10 ml. of water. The precipitate was then ground in a mortar with 10 ml. of *M* sodium hydroxide, filtered (P_1) and washed with 5 ml. of water. The alkaline filtrate and washings were combined and treated with 1.2 ml. of glacial acetic acid. This produced a precipitate (P_2) which was filtered and washed with 10 ml. of water. F_2 was acidified with concd. hydrochloric acid. The resulting precipitate was filtered, washed with 5 ml. of water and treated with 20 ml. of *M* sodium bicarbonate solution which dissolved most of it. Filtration gave a small amount of solid which was treated like the original precipitate but with only 2 ml. of *M* sodium hydroxide (P_1' and P_2'). The filtrate was acidified with concd. hydrochloric acid (P_3).

The yield of benzo-*p*-toluide [$P_1 + P_1'$] was 1.83 + 0.015 = 1.85 g. (87%). The crude product melted at 153°. After recrystallization from methanol it melted at 158° and showed no depression when mixed with authentic benzo-*p*-toluide, m. p. 159°.

The yield of salicylo-*p*-toluide [$P_2 + P_2'$] was 0.182 + 0.008 = 0.19 g. (8%). It melted at 155°. After recrystallization from methanol it melted at 157° and showed no depression when mixed with the product prepared by the action of salol on *p*-toluidine (see above).

P_3 weighed 0.88 g. and melted at 155° indicating the possibility that it was mainly salicylic acid, admixed with a minor amount of benzoic acid.

At room temperature, the reaction of benzoylsalicylic acid with *p*-toluidine was not noticeably exothermic.

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(12) C. F. H. Allen and J. VanAllan, *Org. Syntheses*, **26**, 94 (1946).
(13) A. Einhorn, L. Rothlauf and R. Seuffert, *Ber.*, **44**, 3309 (1911).

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, UNIVERSITY OF CONNECTICUT, AND ILLINOIS INSTITUTE OF TECHNOLOGY]

Intermediates in the Reactions of Carboxylic Acid Derivatives. II. Infrared Absorption Spectra as Evidence for the Formation of Addition Compounds of Carboxylic Acid Derivatives[1,2]

BY MYRON L. BENDER

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The infrared absorption spectra of a number of esters, amides and acids have been determined. Addition to the carbonyl group of these compounds was detected by observation of the intense absorption band in the region 1600–1800 cm.$^{-1}$ assigned to the carbon–oxygen double bond. Sodium methoxide, sodium ethoxide, and to lesser extent the corresponding lithium alkoxides add to the carbonyl group of ethyl trifluoroacetate in di-*n*-butyl ether solution whereas water, ethanol and various salts do not. The addition of sodium methoxide to ethyl trifluoroacetate is reversible. The effect of successive substitution by fluorine in ethyl acetate displaces the position of equilibrium toward the addition compound. Increasing the chain length of the ester reduces the extent of addition. Sodium alkoxide adds to ethyl oxalate and partially to trifluoroacetamide. No unequivocal evidence for ortho acid formation with perfluoro acids was obtained. The addition compounds are considered to be examples of stable intermediates in base-catalyzed transesterification. The parallel effect of structure on the addition equilibria and on the rates of basic ester hydrolysis indicates that the slow step in the hydrolysis probably is the addition of hydroxide ion to the carbonyl carbon atom.

Compounds formed by addition to the carbonyl group have been postulated as intermediates in a number of reactions involving acid derivatives and carbonyl compounds. For example, the isotopic oxygen exchange of acetone[3] probably proceeds through the hydrate; the isotopic oxygen exchange of benzoic acid[4] proceeds through the hydrate of the acid (the ortho acid); the hydrolysis of ethyl benzoate under both acidic and basic catalysis proceeds through the hydrate of the ester.[1] Presumably the reverse of the latter reaction, the esterification of benzoic acid with ethanol, proceeds through an intermediate compound formed by the addition of ethanol to the carbonyl group of benzoic acid.[1]

It was considered desirable to obtain information concerning stable representatives of the addition compounds which were postulated as intermediates above. There are several examples in the literature of stable hydrates of aldehydes and ketones in which there is definite evidence that the hydrate consists of the addition of a water molecule to the carbonyl double bond. Some of these are chloral,[5] fluoral,[6] trifluoroacetone,[7] hexafluoroacetylacetone,[8]

(1) Previous paper: M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).
(2) Presented at the Chicago Meeting of the American Chemical Society, September, 1953.
(3) M. Cohen and H. C. Urey, THIS JOURNAL, **60**, 679 (1938).
(4) I. Roberts and H. C. Urey, *ibid.*, **61**, 2580 (1939).
(5) M. M. Davies, *Trans. Faraday Soc.*, **36**, 1114 (1940).
(6) H. Shechter and F. Conrad, THIS JOURNAL, **72**, 3371 (1950).
(7) A. L. Henne, M. S. Newman, L. L. Quill and R. A. Staniforth, *ibid.*, **69**, 1819 (1947).
(8) B. G. Schultz and E. M. Larsen, *ibid.*, **71**, 3250 (1949).