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AN INTRAMOLECULAR EXCHANGE REACTION OF N,N-DIMETHYLCARBAMOYLSALICYLIC ACID

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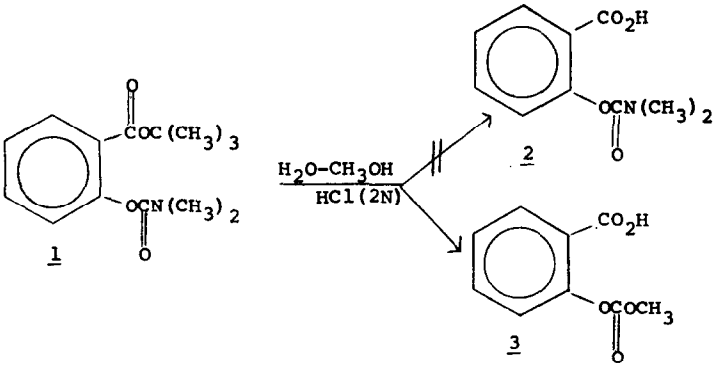
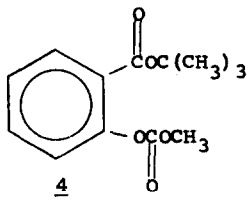
An unusual reaction occurs when one attempts to prepare N,N-dimethylcarbamoylsalicylic acid, (2), by acid hydrolysis of t-butyl N,N-dimethylcarbamoylsalicylate[1], (1), in a methanol-water solution. Carbomethoxysalicylic acid, (3), is the only product formed (12%) in the mixture after four days at 35°C, the remainder being starting material. The presence



of this carbonate was observed after two days of hydrolysis by the appearance of an infrared carbonyl band at 1770 cm^{-1}.[2] Compound 3 and an authentic sample of carbomethoxysalicylic acid, synthesized independently by the treatment of salicylic acid with methyl chloroformate,[3] show identical G.L.C. retentio times.[4] Also, melting points, infrared spectra and elemental analyses are identical.

Efforts to hasten the hydrolysis by increasing temperature or acid concentration result in formation of salicylic acid. The transformation does not occur in either anhydrous or aqueou methanol. This suggests that the reaction is initiated by acid catalysis.

The sequence of events in this hydrolysis-exchange reaction was further explored to determine if ester hydrolysis occurs ex clusively before methanol exchange with the carbamate group. t Butyl carbomethoxysalicylate, (4), would be the intermediate fo if exchange takes place prior to hydrolysis. Compound 4 was pr pared from sodium t-butyl salicylate and methyl chloroformate b could not be detected in the hydrolysis reaction mixture when a quots were withdrawn and analyzed by G.L.C. and infrared althou 4 is stable under these conditions. Thus the acid-catalysis re quirement and sequence of the reaction suggests that ester hydrolysis is the primary step and is necessary before exchange c be achieved.



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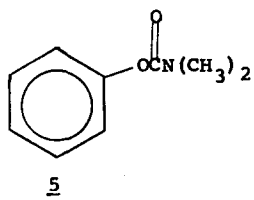

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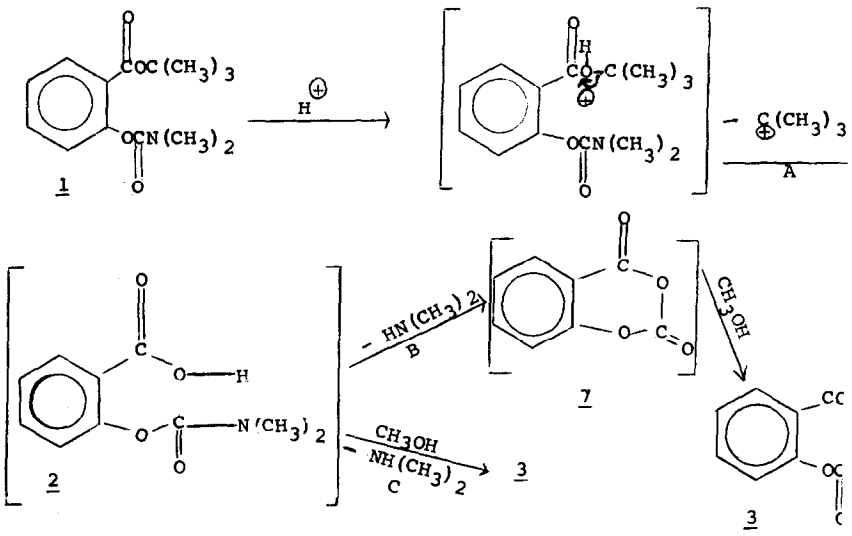
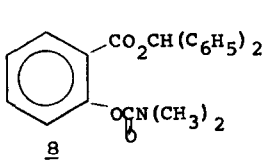
The next study was to ascertain whether this type of exchange reaction is general for phenylcarbamates. Accordingly, N,N-dimethylphenylcarbamate[5], (5), was synthesized from phenol and N,N-dimethylcarbamoyl chloride and subjected to the same hydrolysis procedure as 1. No trace of phenylmethyl carbonate was formed, and 5 remained unaltered. Therefore, it appears that the exchange is not general and is probably indirectly assisted, with regard to 1, by the ortho carboxylic acid group generated upon ester hydrolysis.

Some possible mechanisms for this novel hydrolysis-exchange reaction are outlined as follows:



Step A involves protonation of 1 and alkyl-oxygen cleavage to give intermediate 2 which can be converted to carbomethoxysalicylic acid, (3), via paths B or C.[7] Path B may proceed by intramolecular protonation of the dimethylamino portion of the carbamate by the ortho carboxylic acid to form anhydro-O-carboxysalicylic acid, (7), which can react further with methanol to form 3. Path C can occur by an intramolecular protonation and loss of dimethyl amine with simultaneous attack of methanol on the carbonyl carbon of the carbamate group.

To test these alternatives, compounds 2 and 7 were prepared. Hydrogenolysis of benzhydryl N,N-dimethylcarbamoylsalicylate, (8), affords a high yield (83.8%) of 2.[8,9] The anhydride, (7), was prepared by the method of Davies from dried disodium salicylate and phosgene in anhydrous toluene.[10]



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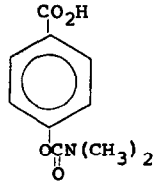

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When 2 was treated with methanol-water and acid or methanol-water at 35°C. an average of 30% carbonate, (3), was formed in only four hours, along with salicylic acid (17%). As acid is not required, intramolecular protonation appears likely. With methanol alone, little, if any, carbonate formed. This slowdown in methanol may be due to the lowered polarity of the solution.

Under identical conditions as above, treatment of 7, in either methanol or in methanol-water and acid, resulted in quantitative conversion to 3.[11] Therefore, path B or C is feasible even though intermediate 7 was not observed by G.L.C. or infrared. The anhydride may possibly react at a more rapid rate than it is formed. Also, in proceeding from t-butyl N,N-dimethylcarbamoylsalicylate, (1), to 3, we could not distinguish 2 by G.L.C. or infrared either, perhaps for the very same reason.

Convincing evidence for the intramolecularity of this exchange and its independence of external protons is the failure of p-N,N-dimethylcarbamoylhydroxybenzoic acid, (9), to undergo any reaction in methanol-water and acid or methanol-water within four hours in contrast to its ortho isomer, (2).

Further efforts to elucidate this mechanism are in progress.

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