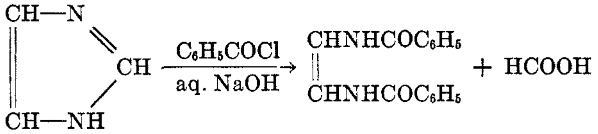
[Contribution from the Chemical Laboratory of Swarthmore College]

ETHYLENEDIAMINE. V.[1] THE ACTION OF AROMATIC ACID CHLORIDES ON 4,5-DIHYDROIMIDAZOLES IN AQUEOUS MEDIA

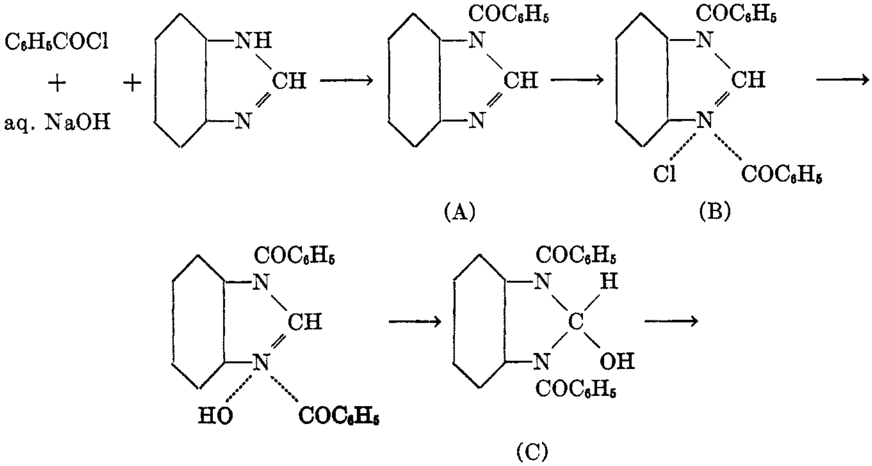
SAMUEL R. ASPINALL

Received August 4, 1941

It is known that imidazoles and benzimidazoles of simple structure, although possessing a nitrogenous ring which in general is very stable, readily undergo ring fission when subjected to a Schotten-Baumann reaction even at 0°.

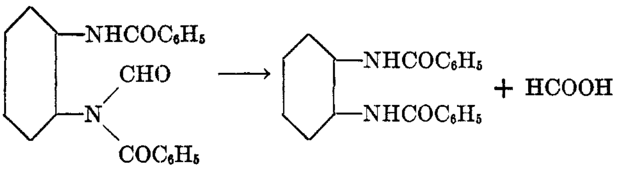


This remarkable vulnerability of a very stable ring has been the subject of many investigations. Gerngross (1) allowed benzoyl chloride to act on benzimidazole under a variety of conditions, and obtained several compounds which he showed to be intermediates and postulated the mechanism shown in formulas A–E.



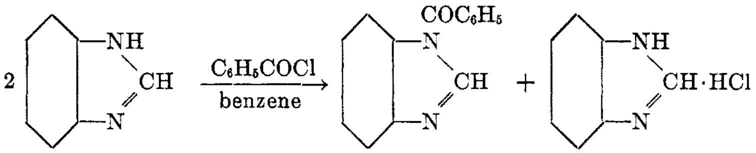
---

[1] For the fourth article of this series see *J. Am. Chem. Soc.*, **63**, 852 (1941).

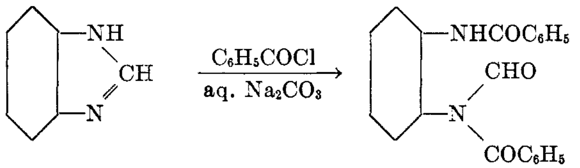


(D) (E)

Benzoylbenzimidazole (A) is obtained by treating benzimidazole in benzene solution with one-half equivalent of benzoyl chloride.



The evidence for the existence of an addition product (B) between benzoylbenzimidazole and benzoyl chloride consisted only in anomalous freezing point depression data; however, if one equivalent of water is added to a mixture of the two, 1,3-dibenzoylbenzimidazolol (C) is produced. This latter compound melts at 135–140°, and in so doing is converted into the isomeric N-benzoyl-N′-benzoylformylorthophenylenediamine (D), which solidifies and then melts at 157°. N-Benzoyl-N′-benzoylformylorthophenylenediamine also arises directly by the action of benzoyl chloride on benzimidazole in carbonate solution.



Finally, the formyl group may be eliminated by heat or alkali to give E.

While the evidence is not altogether concordant, it is generally agreed that the stability towards acylating agents increases in the order imidazoles, benzimidazoles, and naphthimidazoles (*i.e.*, acylation of the secondary nitrogen rather than ring fission is more likely to occur in that order); and that the tendency of the medium to favor fission of the ring rather than simple acylation increases in the order benzene or ether, pyridine, aqueous carbonate, and aqueous caustic. Thus imidazole can be benzoylated in benzene on the secondary nitrogen using one mole of imidazole to absorb the hydrogen chloride formed, but any other technique of acylation results in ring fission. Benzimidazole can be benzoylated in benzene or pyridine, while carbonate or caustic result in ring fission; and naphthimidazole can be benzoylated by the customary Schotten-Baumann method. Imidazoles are remarkably stable towards alkali, hence the linear amides do not arise by hydrolytic fission of the ring to a monoacyl derivative followed by acylation. Furthermore the diamides isolated were symmetrical and characteristic of the acid chloride, while the 2-carbon was found in the filtrate as an acid. It is also known that isovaleryl chloride brings about analogous results, but it has been stated that sulfonyl chlorides do not show this reaction (2).

TABLE I

REACTION PRODUCTS AND THEIR DERIVATIVES

NAME	NUMBER ON FLOWSHEET	M.P., °C. CORR.	N, %	
			Calc'd	Found[a]
2-Methyl-4,5-dihydroimidazole[b]	I	103		
2-Phenyl-4,5-dihydroimidazole[b].	I′	102		
Monoacetylethylenediamine	II			
Monobenzoylethylenediamine	II′			
N-Acetyl-N′-benzoylethylenediamine	III; VIII	180[c]	13.59	13.55
sym-Dibenzoylethylenediamine.	III′; VII; VIII′	250	[d]	
Monoacetylethylenediamine picrate	IV	175	[d]	
Monobenzoylethylenediamine picrate	IV′	216–221 (decomp.)	17.81	17.95
N-Acetyl-N′-benzenesulfonylethylenediamine	V	104	[d]	
N-Acetylbenzoyl-N′-benzoylethylenediamine	VI	115[e]		
Tribenzoylethylenediamine	VI′	104	7.52	7.60
N-Acetylbenzenesulfonyl-N′-benzenesulfonylethylenediamine	IX	122	7.33	7.33
N-Benzoylbenzenesulfonyl-N′-benzenesulfonylethylenediamine	IX′	162	6.31	6.25
sym-Dibenzenesulfonylethylenediamine	X	171	[d]	

[a] Analytical results are the averages of two Kjeldahl determinations, neither of which differs from the theoretical by more than 0.15%.

[b] Prepared according to Hill and Aspinall, *J. Am. Chem. Soc.*, **61**, 822 (1939).

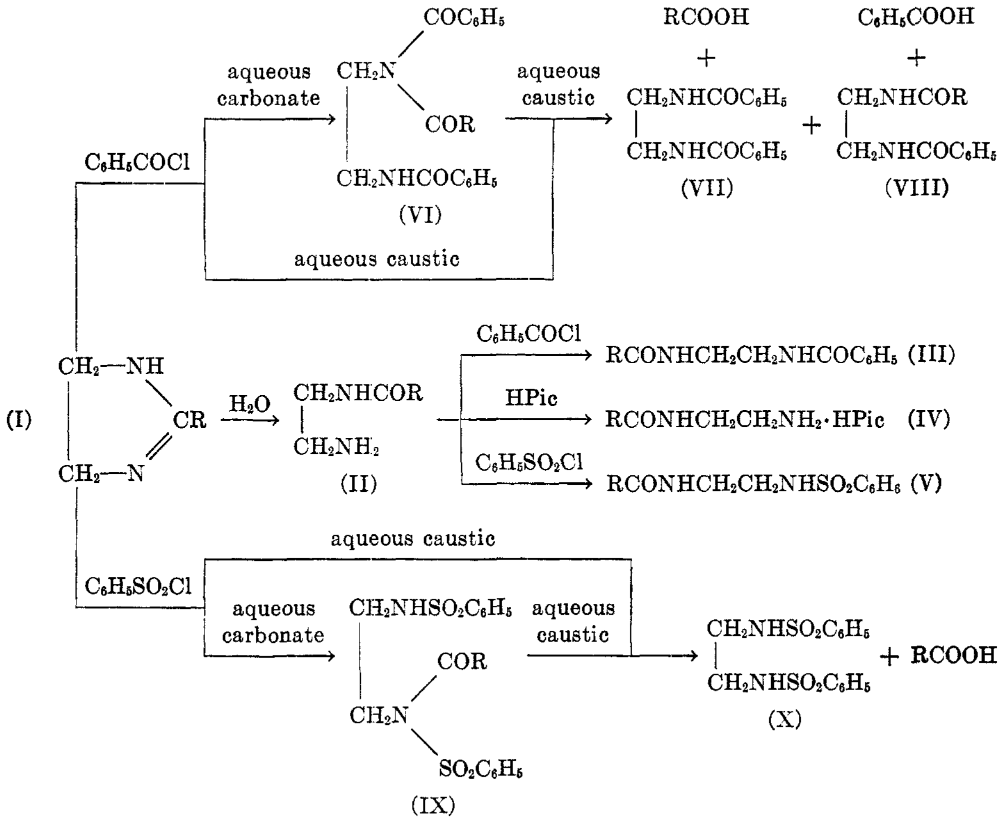
[c] Literature: 175°; U. S. Patent 1,926,014.

[d] Identified by mixed melting point with an authentic sample.

[e] Literature: 114°; *Ber.*, **28**: 3068 (1895).

In contrast to the situation with imidazoles, there is but one reference to the interaction of a 4,5-dihydroimidazole and an acid chloride (3), which states that 2-methyl-4,5-dihydroimidazole in carbonate solution reacts with benzoyl chloride to yield N-benzoyl-N′-acetylbenzoylethylenediamine which decomposes into dibenzoylethylenediamine and acetic acid when treated with caustic. This reaction, which is strictly analogous to that of an imidazole under the same conditions is quite interesting in view of the many dissimilarities between the two types of compounds.

FLOW-SHEET



Unprimed Roman numerals in the text mean R = CH_3; when primed, R = C_6H_5.

The present investigation consists of a more careful study of the action of benzoyl chloride on 2-substituted 4,5-dihydroimidazoles in aqueous solutions of carbonate and caustic, and the extension of the reaction to include benzenesulfonyl chloride. Contrary to former evidence, when a triacyl diamine is treated with cold caustic the diacylated nitrogen atom expels some of each one of its two substituents rather than exclusively eliminating the acid characteristic of the 2-substituent. This fact has no practical effect if the 2-substituent is the same as the radical of the acid chloride, but otherwise results in a mixture of products. When a monoacyldisulfonyl diamine is treated with caustic, it quantitatively eliminates the group derived from the 2-substituent. This is due to the much greater stability towards alkali of the N-SO_2R group over the N-COR group.

Although it cannot be stated with certainty that the reactions of 4,5-dihydroimidazoles with benzoyl and benzenesulfonyl chloride in alkaline solution proceed like those of imidazoles, the strict parallel in the two cases in products and reaction conditions heavily favor that belief. It is certain that the diacylated diamine cannot arise from hydrolysis of the dihydroimidazole followed by acylation, because the cyclic compound, although readily hydrolyzed by hot water, is quite stable under the conditions of benzoylation. Furthermore the triacyl diamines, which are shown to be intermediates in the formation of diacyl diamines, could not arise by a simple Schotten-Baumann reaction with monoacylethylenediamine, but must arise from some more complex reaction of benzoyl chloride with the original cyclic compound.

The flow-sheet outlines the work carried out in this investigation.

EXPERIMENTAL

Hydrolysis of a 4,5-dihydroimidazole. A solution of 1.02 g. (0.01 mole) of 2-methyl-4,5-dihydroimidazole (I) in 10 cc. of distilled water is boiled for 10 minutes. One equivalent (2.29 g.) of picric acid in 50% ethanol is added to the resulting solution, and after thorough chilling the quantitative amount (3.9 g.) of pure monoacetylethylenediamine picrate (IV) removed by filtration. That the boiled solution of 2-methyl-4,5-dihydroimidazole contains only monoacetylethylenediamine (II) is further shown by converting it into the theoretical amount of pure N-acetyl-N′-benzoylethylenediamine (III) and N-acetyl-N′-benzenesulfonylethylenediamine (V), using one equivalent of benzoyl chloride and benzene sulfonyl chloride, respectively.

The hydrolysis of an equivalent amount (1.46 g.) of 2-phenyl-4,5-dihydroimidazole (I′) is much slower, being complete only after boiling for one hour in 50% ethanol. The monobenzoylethylenediamine (II′) in solution is identified by converting it quantitatively into its picrate (IV′). (Shorter periods of hydrolysis lead to the formation of a mixture of picrates of monobenzoylethylenediamine and 2-phenyl-4,5-dihydroimidazole). The solution of monobenzoylethylenediamine was also identified by converting it into the quantitative amount of dibenzoylethylenediamine (III′) with one equivalent of benzoyl chloride.

Treatment of a 4,5-dihydroimidazole with benzoyl chloride in carbonate solution. A flask containing 5.1 g. (0.05 mole) of 2-methyl-4,5-dihydroimidazole (I) dissolved in a few cc. of water is immersed in an ice-bath and 0.1 mole of saturated aqueous sodium carbonate solution (10.6 g. Na_2CO_3) and 0.1 mole (14 g.) of benzoyl chloride alternately added with vigorous shaking during 15 minutes. The N-acetylbenzoyl-N′-benzoylethylenediamine (VI) is filtered, washed with water, and recrystallized from dilute ethanol; yield, 12.4 g. (80%). The results are identical when twice as much dihydroimidazole is used, indicating the impossibility of isolating the N-benzoyldihydroimidazole by this technique.

When carrying out this reaction with the water-insoluble 2-phenyl-4,5-dihydroimidazole, 7.3 g. (0.05 mole) is dissolved at 0° in 25 cc. of ethanol and treated with alternate portions of 21 g. (0.15 mole) of benzoyl chloride and 21 g. (0.15 mole) of potassium carbonate in concentrated aqueous solution. (The excess benzoyl chloride and carbonate are used because of the side reaction with the ethanol; with acetone as a solvent the calculated quantity of benzoyl chloride suffices, but the product is not so easily isolated.) The product is precipitated with excess water and becomes solid after standing in an ice-bath. The crude tribenzoylethylenediamine (VI′) is washed with water and ether (to remove ethyl benzoate) and recrystallized from dilute ethanol. The product thus obtained, (about 17 g., m.p. range about 100–115°) is fractionally recrystallized from dilute ethanol. The first crop melts at 122° and is of unknown constitution, the second melts at 104° and is pure tribenzoylethylenediamine (VI′). Several fractionations may be necessary to obtain the two pure products, which are produced in about equal amounts. Considerable work was done on the 122° compound, but no conclusive evidence for its constitution obtained.

Treatment of a triacyl diamine with aqueous caustic. One-hundredth mole (3.72 g.) of tribenzoylethylenediamine (VI′) is dissolved in a small amount of ethanol and treated at room temperature with 1 g. of potassium hydroxide in 50% ethanol. A precipitate begins to form in a few seconds and after 15 minutes the theoretical amount (2.68 g.) of pure dibenzoylethylenediamine (VIII′) is removed by filtration. The alcohol is evaporated from the filtrate, the aqueous residue acidified, and 1.2 g. (0.01 mole) of pure benzoic acid filtered off. Both products are identified by mixed melting point.

One-hundredth mole (3.1 g.) of N-acetylbenzoyl-N′-benzoylethylenediamine (VI) is dissolved at room temperature in 25 cc. of 60% ethanol and 1 g. of potassium hydroxide in 60% ethanol added. Precipitation begins immediately and is complete in 15 minutes. The solid product weighs 1.55 g. and is identified by mixed melting point as dibenzoylethylenediamine (VII). After evaporation to a small volume, the filtrate yields 0.84 g. of white solid, identified by mixed melting point as N-acetyl-N′-benzoylethylenediamine (VIII). The clear filtrate is acidified with sulfuric acid and 0.5 g. of benzoic acid filtered off. Finally the acidified filtrate is boiled and acetic acid detected in the vapor by its odor and action on litmus. These figures indicate that about 55% of this triacyl diamine becomes dibenzoylethylenediamine and 45% acetylbenzoylethylenediamine. The addition of the ethanol in these experiments is to dissolve the reactants, since the same results are obtained in pure aqueous solutions provided they are boiled or allowed to stand several hours.

Treatment of a 4,5-dihydroimidazole with benzenesulfonyl chloride in aqueous carbonate. An aqueous solution of 5.1 g. (0.05 mole) of 2-methyl-4,5-dihydroimidazole is treated at 0° with alternate portions of 17.7 g. (0.1 mole) of benzenesulfonyl chloride and 106 g. (0.1 mole) of 10% aqueous sodium carbonate. The reaction mixture is allowed to stand for 30 minutes after the addition is complete, and the N-acetylbenzenesulfonyl-N′-benzenesulfonylethylenediamine (IX) filtered, washed with water, and recrystallized from dilute ethanol; yield, 13 g. (70%). It is essential that the reaction does not get too warm or a mixture of IX and X will be formed.

A solution of 7.3 g. (0.05 mole) of 2-phenyl-4,5-dihydroimidazole in 40 cc. of ethanol is treated at room temperature with alternate portions of 26.5 g. (0.15 mole) of benzenesulfonyl chloride and 15.9 g. (0.15 mole) of sodium carbonate in saturated aqueous solution. Excess water is added, the N-benzoylbenzenesulfonyl-N′-benzenesulfonylethylenediamine (IX′) filtered, washed with water, and recrystallized from ethanol; yield, 15 g. (70%).

Treatment of a monoacyldisulfonyl diamine with aqueous caustic. One-hundredth mole (3.82 g.) of N-acetylbenzenesulfonyl-N′-benzenesulfonylethylenediamine (IX) is dissolved at room temperature in 25 cc. of 10% sodium hydroxide. After 15 minutes the clear solution is acidified with sulfuric acid and the theoretical amount of dibenzenesulfonylethylenediamine (X) is removed by filtration, washed with water, recrystallized from ethanol, and identified by mixed melting point. The filtrate is then made alkaline, evaporated to a small volume, re-acidified with sulfuric acid, and the acetic acid distilled out and identified as the isobenzylthiourea salt.

Similar results are obtained if N-benzoylbenzenesulfonyl-N′-benzenesulfonylethylenediamine (IX′) is substituted in the previous experiment, except that the quantitative amount of benzoic acid rather than acetic acid is liberated.

The action of carboxylic and sulfonic acid chlorides on 4,5-dihydroimidazoles in aqueous caustic. 4,5-Dihydroimidazoles react with acid chlorides in caustic media to yield the same products in the same yields as result from the stepwise treatment of the dihydroimidazoles in carbonate followed by caustic.

SUMMARY

2-Substituted 4,5-dihydroimidazoles readily undergo hydrolytic fission in hot water to yield monoacylethylenediamines.

Aromatic carboxylic and sulfonic acid chlorides react with 2-substituted 4,5-dihydroimidazoles in carbonate solution to yield triacyl diamines and monoacyldisulfonyl diamines respectively.

The triacid derivatives, which are new amides of ethylenediamine have been characterized by quantitative degradation to diamides of ethylenediamine.

Aromatic carboxylic and sulfonic acid chlorides react with 2-substituted 4,5-dihydroimidazoles in caustic solution to yield diamides of ethylenediamine.

SWARTHMORE, PA.

REFERENCES

(1) GERNGROSS, *Ber.*, **46**, 1913 (1913).
(2) WINDAUS, DÖRRIES, AND JENSEN, *Ber.*, **54**, 2745 (1921).
(3) LANDENBURG, *Ber.*, **28**, 3068, (1895).