soluble than nicotinic acid, 1.77 g., under comparable conditions.

A saturated solution of the amides was made by the same procedure employed for the higher esters. Amide nitrogen determination was made on the aqueous solution by a Van Slyke procedure. One milliliter of saturated potassium hydroxide was added to 15 ml. of the aqueous sample, and the solution was refluxed for one hour. The hydrolyzed solution was washed into a 25-ml. volumetric flask and made to volume with water, and 1 ml. of this solution was analyzed for amino N by the Van Slyke manometric procedure. Since little or no amino nitrogen was detected prior to alkaline hydrolysis, it was concluded that hydrolysis of the amides by water was negligible.

It was expected that the water solubility of the amides and esters would vary inversely with the length of the *n*-alkyl group. The deviation from this anticipated result may have been due in part to the slight surface activity of the higher *n*-alkyl derivatives.

Acknowledgment.—The authors are indebted to C. A. Elvehjem, L. J. Teply and W. A. Krehl for the biological data herein reported.

Summary

The preparation of ten new esters and thirteen new amides of nicotinic acid is described. Preliminary biological and solubility data indicate these new compounds may be suitable water-insoluble anti-pellagra materials for the fortification of food products which are rinsed prior to cooking. However, the actual merit of these derivatives can be ascertained only by evaluation under conditions of intended use.

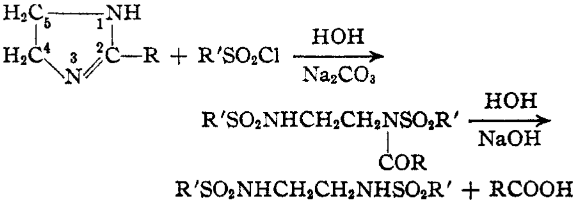
PHILADELPHIA, PA. RECEIVED MARCH 9, 1945

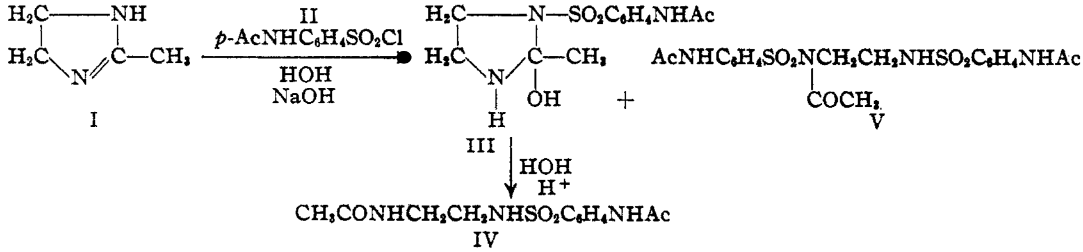
[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MONSANTO CHEMICAL CO., ST. LOUIS, MISSOURI]

The Acylation of 4,5-Dihydroimidazoles

BY F. B. ZIENTY

The action of aromatic sulfonyl chlorides and carboxylic acid chlorides on 4,5-dihydroimidazoles in the presence of aqueous alkali causes ring opening to form triacyl and diacyl derivatives of ethylenediamine.[1] While N-acyl derivatives of imidazoles[2] and benzimidazoles[3] have been prepared, no information is available in the literature on the formation or properties of the 1-acyl derivatives of 4,5-dihydroimidazoles. The preparation of acyl derivatives of 4,5-dihydroimidazoles without ring opening may now be described.





Reaction of 2-methyl-4,5-dihydroimidazole (I) with N-acetylsulfanilyl chloride (II) in water at 0–10° in the presence of an equivalent of alkali produced a 30% yield of 1-(N^4-acetylsulfanilyl)-2-hydroxy-2-methyl-tetrahydroimidazole (III), a considerable quantity of N-acetyl-N'-(N^4-acetylsulfanilyl)-ethylenediamine (IV), and a small amount of N-acetyl-N,N'-di-(N^4-acetylsulfanilyl)-ethylenediamine (V).

When the reaction was run at 60° a 98% yield of IV was obtained. It was found that III is very easily hydrolyzed to IV in the presence of mineral acids. The formation of hydroxy acylated imidazole derivatives is not new, since Gerngross[3] observed that the treatment of 1-benzoyl-benzimidazole with benzoyl chloride in anhydrous medium, followed by the addition of water, resulted in the formation of 1,3-dibenzoyl-benzimidazolol (VI).

Reaction of I and II in benzene, followed by quenching with water, resulted in the formation of a mixture consisting chiefly of III and V.

Compound IV was identified by mixed melting point with a sample prepared from N-acetylethylenediamine and II, and by alkali hydrolysis to the known N-sulfanilyl-ethylenediamine. The triacyl compound, V, was hydrolyzed by treatment with cold aqueous alkali to the known N,N'-di-(N^4-acetylsulfanilyl)-ethylenediamine which did not depress the melting point of a sample of this compound prepared from ethylenediamine and II, and which yielded on strong hydrolysis N,N'-disulfanilyl-ethylenediamine.

[1] Aspinall, *J. Org. Chem.*, **6**, 895 (1941); Ladenburg, *Ber.*, **28**, 3068 (1895).

[2] Lur'e, Starobogatov and Nikitskaya, *J. Gen. Chem.* (U. S. S. R.), **11**, 545 (1941); Gerngross, *Ber.*, **46**, 1909 (1913).

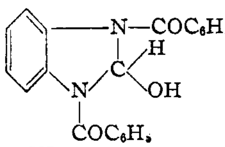
[3] Gerngross, *ibid.*, **46**, 1913 (1913); Bamberger and Berle, *Ann.*, **273**, 360 (1893).

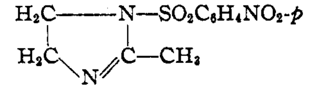
TABLE I

Ethylenediamine	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
N-Acetyl-N′-(N^4-acetylsulfanilyl)	177–178	$C_{12}H_{17}N_3O_4S$	14.0	14.0
N-Acetyl-N′-(*p*-nitrobenzenesulfonyl)	150–151	$C_{10}H_{13}N_3O_5S$	14.6	14.8
N-Acetyl-N′-sulfanilyl	149–150	$C_{10}H_{15}N_3O_3S$	16.3	16.0
N-(*p*-Nitrobenzenesulfonyl)[a]	165–166	$C_8H_{11}N_3O_4S$	17.1	17.2
N-Sulfanilyl. H_2SO_4	228–229	$C_8H_{15}N_3O_6S_2$	SO_4, 30.7	30.6
N-Sulfanilyl. 2HCl	219–220[b]	$C_8H_{15}Cl_2N_3O_2S$	Cl, 24.6	24.5
N,N′-Di-(N^4-acetylsulfanilyl)	310–312	$C_{18}H_{22}N_4O_6S_2$	12.3	12.4
N-Acetyl-N,N′-di-(N^4-acetylsulfanilyl)	218–219	$C_{20}H_{24}N_4O_7S_2$	11.3	11.3[c]
N,N′-Di-(*p*-nitrobenzenesulfonyl)	278–279	$C_{14}H_{14}N_4O_8S_2$	13.0	13.2
N,N′-Disulfanilyl	229–230[d]	$C_{14}H_{18}N_4O_4S_2$		

[a] Bright yellow. [b] Amundsen and Malentacchi, *Science*, **93**, 286 (1941), reported 217–220°. [c] Calcd.: C, 48.4; H, 4.8. Found: C, 48.6; H, 4.8. [d] Crossley, Northey and Hultquist, THIS JOURNAL, **62**, 533 (1940), reported 229.4–231.2°.

Reaction of I with *p*-nitrobenzenesulfonyl chloride in benzene, followed by quenching in water, produced 1-(*p*-nitrobenzenesulfonyl)-2-methyl-4,5-dihydroimidazole (VII), and not the hydroxy-tetrahydroimidazole as in the case of N-acetylsulfanilyl chloride. In the presence of aqueous acids VII hydrolyzed readily to N-acetyl-N′-(*p*-nitrobenzenesulfonyl)-ethylenediamine, which was identified by iron–dilute acetic acid reduction to N-acetyl-N′-sulfanilyl-ethylenediamine, followed by alkaline hydrolysis to the known N-sulfanilylethylenediamine. The iron reduction of N-acetyl-N′-*p*-nitrobenzenesulfonyl)-ethylenediamine did not hydrolyze the acetyl group on the ethylenediamine. Hydrolysis of N-acetyl-N′-(*p*-nitrobenzenesulfonyl)-ethylenediamine with 4% HCl gave a 98% yield of N-(*p*-nitrobenzenesulfonyl)-ethylenediamine.


VI


VII

In the preparation of 1-(*p*-nitrobenzenesulfonyl)-2-methyl-4,5-dihydroimidazole, N,N′-di-(*p*-nitrobenzenesulfonyl)-ethylenediamine also was isolated.

The hydrolysis of 1-arylsulfonyl-4,5-dihydroimidazoles and 1-arylsulfonyl-2-hydroxy-2-alkyltetrahydroimidazoles provides a general method for the preparation of mixed N-arylsulfonyl-N′-acyl-ethylenediamines.

Experimental

1 - (N^4 - Acetylsulfanilyl) - 2 - hydroxy - 2 - methyltetrahydroimidazole (III).—To a solution of 4.2 g. (0.05 mole) of 2-methyl-4,5-dihydroimidazole[4] in 200 cc. of water, stirred at 0–10°, there were added slowly and simultaneously 11.5 g. (0.05 mole) of anhydrous N-acetylsulfanilyl chloride and 4.0 g. (0.05 mole) of 50% NaOH solution. The reaction mixture then was stirred for two hours, the precipitate was filtered off, washed with water and dried *in vacuo* at 25–30°; yield for the crude substance was 4.6 g.; m. p. 196–197°,[5] after crystallization from a small volume of acetone.

Anal. Calcd. for $C_{12}H_{17}N_3O_4S$: C, 48.1; H, 5.7; N, 14.0; mol. wt., 299. Found: C, 47.8, 47.9; H, 5.6, 5.7; N, 14.0; mol. wt., 297.

When the reaction was performed as described above, but the final reaction mixture was heated at 60° for one hour, 10.7 g. (98%) of crude N-acetyl-N′-(N^4-acetylsulfanilyl)-ethylenediamine (IV) was obtained. The m. p. was 177–178° after recrystallization from dioxane-1,4.

In one experiment a 25% excess of N-acetylsulfanilyl chloride and a 25% excess of alkali were used. The reaction mixture was heated to 70°, cooled, the product was filtered off, washed with water, and dried at 70°. The product was heated with a small amount of alcohol and the insoluble material was filtered off. This proved to be N-acetyl-N,N′-di-(N^4-acetylsulfanilyl)-ethylenediamine (V). The m. p. was 218–219° after recrystallization from acetone.

A 1.00 g. sample of V triturated with 10 cc. of 0.5 *N* NaOH solution for five minutes consumed 4.0 cc. of the alkali (calcd. 4.0 cc.). The solid remaining after back-titration (phenolphthalein) was filtered off, washed with water and dried; it was shown to be N,N′-di-(N^4-acetylsulfanilyl)-ethylenediamine, m. p. 310–312°, giving no depression in melting point when mixed with an authentic sample prepared from ethylenediamine and N-acetylsulfanilyl chloride.

The best preparation of III was as follows: A mixture of 29.4 g. (0.35 mole) of 2-methyl-4,5-dihydroimidazole and 40.8 g. (0.175 mole) of N-acetylsulfanilyl chloride in 50 cc. of anhydrous benzene was stirred and refluxed for two hours. The mixture was cooled, the benzene was decanted, and the gum was treated with 200 cc. of water, whereupon it solidified. The product was disintegrated, washed thoroughly with 5% NaOH solution and then with water, and dried at 25° in a stream of air under reduced pressure; yield, 42 g. of crude product melting at 190–192° with previous softening. The solid was warmed with a small volume of acetone, the mixture was filtered and the filtrate was concentrated under slightly reduced pressure. Colorless crystals of III were obtained; yield, 20 g. (38%), m. p. 196–197°. The acetone-insoluble material (V, 14 g.) was purified by dissolving it in a large volume of hot alcohol followed by concentrating; m. p. 218–219°

Hydrolysis of 1 - (N^4 - Acetylsulfanilyl) - 2 - hydroxy - 2-methyl-tetrahydroimidazole (III).—The tetrahydroimidazole (1.0 g.) was dissolved in 7.7 cc. of 0.5 *N* HCl with shaking. Thirty cc. of water was added and the solution was kept at 30° for ten hours. The solution was neutralized to phenolphthalein indicator by means of 0.5 *N* NaOH, evaporated to a volume of 10 cc. on a steam-bath, and the slurry obtained was cooled to 30°. The crystalline product was filtered off, washed quickly with water, and dried at 80°; weight, 0.57 g.; m. p. 172–173°; mixed m. p. with an authentic sample of N-acetyl-N′-(N^4-acetylsulfanilyl)-ethylenediamine, 173–174°.

1-(*p*-Nitrobenzenesulfonyl)-2-methyl-4,5-dihydroimidazole (VII).—A mixture of 16.8 g. (0.2 mole) of 2-

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[4] Hill and Aspinall, THIS JOURNAL, **61**, 822 (1939).

[5] All melting points are corrected.

methyl-4,5-dihydroimidazole and 50 cc. of benzene was treated with 22.1 g. (0.1 mole) of *p*-nitrobenzenesulfonyl chloride,[6] fed in slowly at 25°, and the mixture then was refluxed for two hours and cooled. The benzene was decanted and the gummy residue was disintegrated with 150 cc. of water, filtered off and dried at 25° *in vacuo*. The yield was 13.4 g., for the crude substance; m. p. was 125-126°, recrystallized from methanol. This product was very soluble in acetone.

Anal. Calcd. for $C_{10}H_{11}N_3O_4S$: C, 44.6; H, 4.1; N, 15.6; mol. wt., 269. Found: C, 44.6; H, 4.1; N, 15.5; mol. wt., 263.

The material that was insoluble in methanol was purified by solution in dilute alkali, treatment with decolorizing charcoal, and precipitation with dilute acid. It proved to be N,N'-di-(*p*-nitrobenzenesulfonyl)-ethylenediamine; m. p. 278-279°. It did not depress the m. p. of an authentic sample prepared from ethylenediamine.

Hydrolysis of 1-(*p*-Nitrobenzenesulfonyl)-2-methyl-4,5-dihydroimidazole (VII).—The nitro compound (1.0 g.) was dissolved in 7.7 cc. of 0.5 *N* HCl with shaking. After one and one-half hours the crystalline precipitate that had formed was filtered off, washed with water, and dried at 80°. The product (0.45 g.) melted at 150-151° and did not depress the melting point of N-acetyl-N'-(*p*-nitrobenzenesulfonyl)-ethylenediamine.

Acknowledgments.—The author is indebted to Miss G. Pranger and Mrs. J. D. Nevins of the Monsanto Analytical Laboratory for several of the analyses reported.

Summary

The preparation of a 1-acyl-2-hydroxy-tetrahydroimidazole and a 1-acyl-4,5-dihydroimidazole by reaction of aromatic sulfonyl chloride with a 4,5-dihydroimidazole is described.

The 1-arylsulfonyl imidazole derivatives were shown to undergo hydrolysis in dilute acid solution to form N,N'-diacyl-ethylenediamines, the new acyl group being derived from the carbon atom and substituent in the 2-position of the 2-hydroxy-tetrahydroimidazole or dihydroimidazole.

ST. LOUIS 4, MISSOURI RECEIVED FEBRUARY 20, 1945

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[6] Bell, *J. Chem. Soc.*, 2776 (1928).

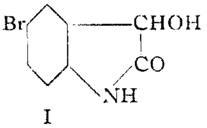
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WESTERN KENTUCKY STATE TEACHERS COLLEGE]

The Structures of the Bromodioxindoles of Baeyer and Knop

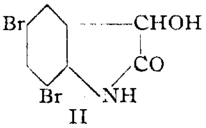
BY WARD C. SUMPTER

Monobromo and dibromo derivatives of dioxindole were prepared by Baeyer and Knop[1] through the action of bromine on aqueous solutions of dioxindole (3-hydroxyoxindole). The structures of these derivatives were not determined. The work described in this paper was undertaken in order to determine definitely the structures of these two derivatives.

It was found that both compounds could be prepared more readily through the bromination of aqueous solutions of dioxindole with aqueous bromine–potassium bromide solutions than by the procedure of Baeyer and Knop. It was also found that the same two compounds could be prepared by the reduction of 5-bromoisatin and 5,7-dibromoisatin, respectively. It follows that the two dioxindole derivatives are 5-bromodioxindole (I) and 5,7-dibromodioxindole (II). The identity of the sample of I prepared by the reduction of 5-bromoisatin with that prepared from dioxindole was established by melting point methods and by conversion of both samples to the same acetyl derivative through the agency of acetic anhydride. Similarly the two samples of dibromodioxindole prepared by reduction of 5,7-dibromoisatin and by the bromination of dioxindole were shown to be identical by melting point methods and by conversion to the acetyl derivative.



I



II

Further proof that the two derivatives were 5-bromodioxindole and 5,7-dibromodioxindole was obtained by their conversion to 5-bromoisatin-β-phenylhydrazone and 5,7-dibromoisatin-β-phenylhydrazone, respectively.

Experimental

5-Bromodioxindole (I) A.—By the procedure of Baeyer and Knop.[1] The substance crystallized from hot water as colorless prisms; m. p. 199–200°.[2]

B.—A solution of 8 g. of bromine (0.05 mole) in 25 cc. of water containing 12 g. of potassium bromide was added slowly at room temperature to a solution of 7.45 g. (0.05 mole) of dioxindole in 250 cc. of water. The nearly colorless product which separated almost immediately was collected and purified by crystallization from hot water; colorless prisms, m. p. 199–200°.

C. From 5-Bromoisatin.—5-Bromoisatin (0.01 mole) was suspended in 150 cc. of water and the mixture heated to boiling during the addition of 3 g. of sodium hydrosulfite. The mixture was then heated until all of the material was in solution. The product which separated on cooling was crystallized from hot water; colorless prisms, m. p. 199–200°. Mixtures of the 5-bromodioxindole prepared by procedures A, B and C also exhibited the same m. p.

Anal. Calcd. for $C_8H_6O_2NBr$: N, 6.15. Found: N, 5.90, 5.96.

3-Acetyl-5-bromodioxindole.[3]—A mixture of 3 g. of 5-bromodioxindole with 10 cc. of acetic anhydride was heated for thirty minutes at the reflux temperature. The product which separated on cooling was collected and

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[1] Baeyer and Knop, *Ann.*, **140**, 1 (1866).

[2] Baeyer and Knop, ref. 1, reported 165°.

[3] For evidence that dioxindole and acetic anhydride yield the 3-acetyl derivative see McKenzie and Stewart, *J. Chem. Soc.*, 104 (1935); and Heller and Lauth, *Ber.*, **62B**, 343 (1929).