TABLE I

ANALYSES AND PHYSICAL PROPERTIES

Compound	Formula	Carbon, % Calcd.	Carbon, % Found[a]	Hydrogen, % Calcd.	Hydrogen, % Found[a]	Neut. equiv. Calcd.	Neut. equiv. Found[b]	M.p., °C.	Recrystn.,[c] solvents, ml./g.	Recov., %	G./100 ml. cold H_2O	pH satd. H_2O sol.[d]
III	$C_8H_8Br_2N_2O_4S$	25.82	25.89	2.17	2.16			252–253	50% EtOH[e]	70	0.031[f]	
IV	$C_8H_8Br_2N_2O_3S$	25.82	26.11	2.17	2.28	372	372	199–200[g]	50% EtOH[h] 30–50	68–87	.007[i]	4.49
V	$C_{10}H_{10}Br_2N_2O_4S$	29.00	29.17	2.43	2.43	414	413	225–226	70% EtOH[j,k] 9–12	61–79	.062[i]	3.55
									50% acetone 12–50	61–84		
VI	$C_{12}H_{12}Br_2N_2O_5S$	31.60	32.02	2.65	2.71	456	456[l]	198–199	50% acetone[m] 12–35	75–88	.035[i,n]	3.69

[a] Best of two or three checking results. [b] Determined by titration in 95% alcohol with phenolphthalein indicator; best of two or three checking results given. [c] All compounds became colorless, generally without the use of decolorizing carbon. [d] Determined by a Beckman pH meter using a glass electrode. [e] One recrystallization was generally done from glacial acetic acid, 75% recovery, as it purified low melting samples well; 1,4-dioxane purified III well but the recovery was about 50%. [f] Determined by evaporating a saturated solution to dryness. [g] See footnote 5. [h] Decolorizing carbon was necessary. [i] Determined by titrating a saturated solution. [j] 1,4-Dioxane or diluted dioxane was also used; water alone gave very low recoveries. [k] The first material which separated on recrystallization seemed to be impure although it was high melting; it probably contained traces of less soluble III. Second precipitates, melting lower than the crude materials, gave better analytical values. [l] Sapn. equiv., calcd., 228, found, 230.[b] For method see earlier work, footnote 4, p. 3347. [m] With 50% alcohol, 20–25 ml., 60–93% recoveries. [n] This value is the only one higher than those of the dichloro analogs. Such a discrepancy may be caused by slight hydrolysis of the second N^4-acetyl group.

similar to those of the corresponding derivatives of II.[4] The differences are: (1) except for VI, they are one-half to one-fourth as water-soluble; (2) the melting points of III and V are much higher; (3) V does not appear to form a stable hydrate. Whether IV and I form a complex was not investigated. Preliminary potentiometric titrations indicated that the ionization constants of the three acidic compounds, IV, V and VI were similar to that of benzoic acid.

This work offers a second example[4] of the differential acetylation of the amino and amido groups, by control of the amount of sulfuric acid used as a catalyst or by the use of basic media, which distinguishes the 3,5-dihalogenosulfanilamides from sulfanilamide and its non-diortho substituted derivatives.

Experimental[6]

N^4-Acetyl-3,5-dibromosulfanilamide (III).—A 0.7-g. sample of I[7] was monoacetylated in the N^4 position exactly as described earlier for II[4]; the reaction, however, was complete after ten minutes. A 71% yield (0.56 g.) of crude, pale pink III, m.p. 240–249°, and an 18% yield (0.16 g.) of light peach-colored V, m.p. 198–212°, were obtained. Before recrystallization III was extracted with a saturated sodium bicarbonate solution; this operation removed further traces of V and raised the melting point to 252–254°. If longer times were allowed for the reaction, the amount of diacetylation increased at the expense of monoacetylation.[8] Substitution of acetyl chloride for acetic anhydride produced no acetylation. III was insoluble in carbonate solution, non-titratable and non-diazotizable.[9]

N^1-Acetyl-3,5-dibromosulfanilamide (IV).—A 2.0-g. sample of I,[7] dissolved in 2.4 ml. of warm pyridine, was monoacetylated in the N^1 position exactly as described for II[4]; it was necessary, however, to heat the reaction mixture for 30 minutes on the steam-bath to complete the reaction. A 93% yield (2.08 g.) of cream-colored product, m.p. 206–218°, was obtained. The use of larger volumes of pyridine or shorter times of reaction lowered the yield. Purification of this material lowered its melting point at first[10] and then raised it slightly. IV was soluble in bicarbonate solution, titratable with 0.1 N alkali and diazotizable.[9]

N^1,N^4-Diacetyl-3,5-dibromosulfanilamide (V).—I[7] (0.5 g., 0.00151 mole) was diacetylated in a mixture of acetic acid and acetic anhydride containing sulfuric acid in a manner analogous to that described for II[4] except that the amount of anhydride was reduced to 1.24 times the theoretical amount (0.00375 mole, 0.35 ml.). Spontaneous monoacetylation required 8 to 15 minutes at room temperature. The mixture was then boiled for only three or four minutes, during which time the monoacetyl derivative dissolved, but unlike the chloro analog the diacetyl derivative generally did not precipitate until the reaction mixture was cooled. After the usual method of isolation, 0.58 g. (93% yield) of flesh-colored powder was obtained, m.p. 229–231°. Other runs gave lower melting crude products. The amount of acetic acid used was not critical, but low yields resulted if none was used. Longer boiling caused too much decomposition, but no boiling gave a mixture of III and V. Larger amounts required longer times for reaction. V is soluble in bicarbonate solution, titratable with 0.1 N alkali but non-diazotizable. If heated rapidly, some samples appeared to melt below 100° and then resolidify, but no quantitative data indicating a stable hydrated form analogous to that of N^1,N^4-diacetyldichlorosulfanilamide[4] was obtained.[9]

N^1,N^4,N^4-Triacetyl-3,5-dibromosulfanilamide (VI).—A 2.0-g. sample of I[7] was triacetylated with excess acetic anhydride containing 0.0001 ml. of concentrated sulfuric acid per 0.5 ml. of anhydride by the method previously described for II.[4] No visible evidence of monoacetylation occurred when the mixture was shaken at room temperature for 15 minutes. It was necessary to reflux the mixture for one-half hour in order to complete the reaction. The cream-colored product obtained by adding water to the light brown solution weighed 2.38 g. (86% yield) and melted at 195–197°. Halving the time of reaction decreased the yield to 60%. VI was soluble in bicarbonate, gave both neutralization and saponification equivalents[4] with 0.1 N alkali and was non-diazotizable.[9]

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(6) Melting points are uncorrected and were taken by the method described by S. P. Mulliken, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1904, Vol. I, p. 218, on a 360° thermometer immersed in Dow Corning Silicone, DC 550.

(7) M.p. 234–236°, recorded 239–240°.[4,5]

(8) With II this did not occur.

(9) For data on recrystallization, melting point, analyses, solubility in water and pH of aqueous solutions, see Table I.

(10) The N^1-acetyl derivative of II behaved similarly.

Some Substituted Crotonolactones and Oxazolones

BY WALTER T. SMITH, JR., AND CALVIN HANNA

Substituted oxazolones and crotonolactones have been prepared by the condensation of suitable compounds with hippuric acid and β-benzoylpropionic acid. Thus, Erlenmeyer and Arbenz[1] prepared 2-phenyl-4-phthalal-5-oxazolone from phthalic anhydride and hippuric acid, and Borsche[2] prepared α-phthalal-γ-phenylcrotonolactone from

(1) E. Erlenmeyer and E. Arbenz, *Ann.*, **337**, 302 (1904).

(2) W. Borsche, *Ber.*, **47**, 2718 (1914).

TABLE I

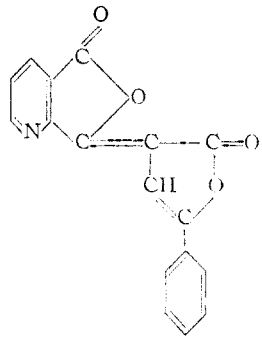
ANALYSES

Compound	M.p., °C.[a] Sealed tube	Yield, %	Formula	Nitrogen, % Calcd.	Found
α-(3- or 6-Nitrophthalal)-γ-phenylcrotonolactone	226–227	61–65	$C_{18}H_9O_6N$[b]	4.18	4.14
α-(4- or 5-Nitrophthalal)-γ-phenylcrotonolactone	245–246.3	59–64	$C_{18}H_9O_6N$[c]	4.18	4.25
α-(3- or 6-Quinolinal)-γ-phenylcrotonolactone	270–273	57–60	$C_{17}H_9O_4N$[d]	4.79	4.54
2-Phenyl-4-(3- or 6-nitrophthalal)-5-oxazolone	237–243.8	10–32	$C_{17}H_8O_6N_2$	8.32	8.03
2-Phenyl-4-(4- or 5-nitrophthalal)-5-oxazolone	258–259.5	61–65	$C_{17}H_8O_6N_2$	8.33	8.27

[a] Melting points are corrected. All compounds melted with decomposition. [b] Calcd.: C, 64.48; H, 2.70. Found: C, 64.88; H, 3.15. [c] Calcd.: C, 64.48; H, 2.70. Found: C, 64.99; H, 2.29. [d] Calcd.: C, 70.10; H, 3.11. Found: C, 70.71; H, 3.40.

phthalic anhydride and β-benzoylpropionic acid. It was of interest to us to use 3- and 4-nitrophthalic anhydride and quinolinic anhydride to prepare some new substituted crotonolactones and oxazolones.

α-(3- or 6-nitrophthalal)-γ-phenylcrotonolactone, α-(4- or 5-nitrophthalal)-γ-phenylcrotonolactone, α-(3- or 6-quinolinal)-γ-phenylcrotonolactone, 2-phenyl-4-(3- or 6-nitrophthalal)-5-oxazolone and 2-phenyl-4-(4- or 5-nitrophthalal)-5-oxazolone have been prepared and tested for cardiac (digitalis-like) action by the isolated frog heart perfusion method. Only α-(3- or 6-quinolinal)-γ-phenylcrotonolactone showed activity.



The lactones were prepared by heating β-benzoylpropionic acid and sodium acetate in acetic anhydride and then adding the proper phthalic or quinolinic anhydride. The oxazolone from 4-nitrophthalic anhydride was prepared in an analogous manner substituting hippuric acid for β-benzoylpropionic acid. The oxazolone from 3-nitrophthalic anhydride cannot be prepared in the same way since the reaction mixture decomposes with the evolution of heat and forms a black tar. If the color of the reaction mixture is watched carefully and water is added to stop the reaction when the color becomes light red, the desired oxazolone can be prepared in yields varying from 10 to 32%.

Experimental

α-(Substituted phthalal)-γ-phenylcrotonolactones.—A mixture of 0.01 mole of β-benzoylpropionic acid,[3] 0.01 mole of freshly fused sodium acetate and 15 ml. of acetic anhydride was heated until solution was complete. The beaker was then transferred to a steam-bath and 0.01 mole of the substituted phthalic anhydride (or quinolinic anhydride) was added in one portion with stirring. In a few seconds a precipitate started to form and the reaction mixture was removed from the steam-bath, cooled slightly and diluted with an equal volume of water. The product was removed by filtration, dried and recrystallized from the minimum amount of chlorobenzene.

(3) L. F. Somerville and C. F. H. Allen, "Org. Syntheses," Coll. Vol. 2, 81 (1943).

2-Phenyl-4-(substituted phthalal)-5-oxazolones.—By substituting an equivalent amount of hippuric acid for β-benzoylpropionic acid in the above procedure, 2-phenyl-4-(4- or 5-nitrophthalal)-5-oxazolone may be prepared.

A solution of 1.92 g. (0.01 mole) of 3-nitrophthalic anhydride and 0.8 g. (0.01 mole) of sodium acetate in 15 ml. of acetic anhydride was heated to 120° and allowed to cool slowly. When the temperature reached 100°, 1.79 g. (0.01 mole) of hippuric acid was added. The reaction mixture was stirred and when the temperature reached 82° a red color began to develop and the temperature started to rise. When the color is still a light red, water is added to stop the reaction. If the reaction is not stopped before the temperature reaches 86°, decomposition takes place and a brittle tar is formed. The product, 2-phenyl-4-(3- or 6-nitrophthalal)-5-oxazolone, is isolated and purified as described above.

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Neopyrithiamine: The Synthesis of 2-Methyl-3-(β-hydroxyethyl)-pyridine

BY ANDREW N. WILSON AND STANTON A. HARRIS

The synthesis of neopyrithiamine hydrobromide previously reported[1] has been confirmed by a separate investigator,[2] who has given details for improvements in the synthesis of the two components, 2-methyl-3-(β-hydroxyethyl)-pyridine (V) and 2-methyl-4-amino-5-bromomethylpyrimidine bromide hydrobromide. In this connection we should like to record some improvements and observations we have made in the synthesis of the pyridine molecule (V).

The first steps in the synthesis were carried out according to the directions of Tracy and Elderfield,[3] except that ammonium chloride was substituted for ammonium nitrate in the pressure reaction used for the preparation of the ethyl α-(β-ethoxyethyl)-β-aminocrotonate. The yields and physical properties were consistent with those described in the literature. The reaction of 2-methyl-3-(β-ethoxyethyl)-4,6-dihydroxypyridine (I) with phosphorus oxychloride, however, was carried out under pressure and yielded a trichloro compound, 2-methyl-3-(β-chloroethyl)-4,6-dichloropyridine (VI). On the other hand, when this reaction was carried out under high nitrogen pressure, the dichloro compound, 2-methyl-3-(β-ethoxyethyl)-4,6-dichloropyridine (II), previously described, was formed in excellent yield. The formation of the trichloro compound is due apparently to the hydrogen chloride liberated in the reaction,

(1) A. N. Wilson and S. A. Harris, THIS JOURNAL, **71**, 2231 (1949).
(2) R. F. Raffauf, *Helv. Chim. Acta*, **33**, 102 (1950).
(3) A. H. Tracy and R. C. Elderfield, *J. Org. Chem.*, **6**, 54 (1941).