TABLE I

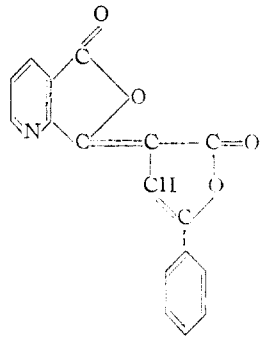
ANALYSES

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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RECEIVED DECEMBER 11, 1950

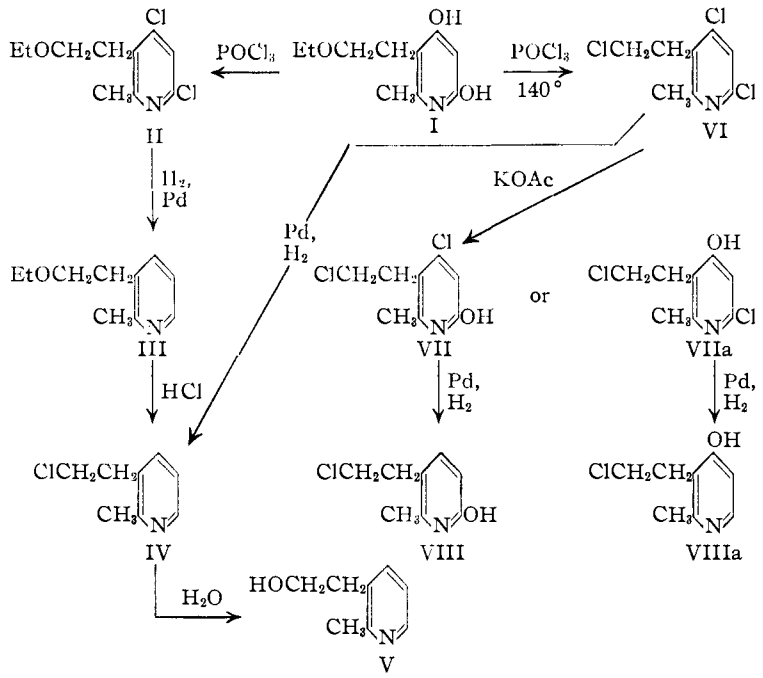
Neopyrithiamine: The Synthesis of 2-Methyl-3-(β-hydroxyethyl)-pyridine

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).



but is suppressed by the excess pressure of the nitrogen. Further heating of the dichloro compound with fresh phosphorus oxychloride under pressure did not yield any trichloro compound. The dichloro compound was converted to 2-methyl-3-(β-hydroxyethyl)-pyridine (V) by the series of reactions II to V, which are those described by Tracy and Elderfield.

The reduction of the trichloro compound to 2-methyl-3-(β-chloroethyl)-pyridine (IV) is somewhat surprising, as one would ordinarily expect the β-chloroethyl group to be most readily attacked.

Similarly, treatment of the trichloro compound with potassium acetate in glacial acetic acid solution did not result in the formation of an acetoxyethyl derivative, but of what appears to be a chloroethyl-hydroxypyridine VII or VIIa. Further reduction of this product resulted in a substance still containing one chlorine atom and the hydroxyl group, presumably VIII or VIIIa.

In agreement with the findings of Raffauf and of Dornow and Schacht,[4] the 2-methyl-3-(β-hydroxyethyl)-pyridine proved to be anhydrous, and does not contain one molecule of water as is described in the original literature.[3]

Experimental[5]

2-Methyl-3-(β-chloroethyl)-4,6-dichloropyridine (VI).—Forty-two grams of 2-methyl-3-(β-ethoxyethyl)-4,6-dihydroxypyridine (I) was dissolved in 200 ml. of freshly distilled phosphorus oxychloride. A small amount of heat was liberated, but there was no apparent evolution of hydrogen chloride. The solution was divided into four parts and heated in sealed combustion tubes at 140° for six hours. When the solutions had cooled, they were recombined, and the excess phosphorus oxychloride was removed under reduced pressure. The oily residue was chilled and a large amount of crushed ice was added rapidly so that no heating occurred. A crystalline material separated on short standing, which was filtered and washed, but not dried. The melting point of a dried sample was 55–56°.

The mother liquor and washes were combined, diluted to about 1500 ml., and partly neutralized with 30% sodium hydroxide solution until no further precipitation took place. This mixture was extracted twice with chloroform, which extract was washed with water, dried, and concentrated. The melting point of the residue was 51–53°.

Both solid fractions were combined and dissolved in an excess of petroleum ether. A small amount of brown insoluble amorphous material and some water were removed. The solution was washed with sodium bicarbonate, with water, was dried, and was concentrated to dryness under reduced pressure. The yield of 2-methyl-3-(β-chloroethyl)-4,6-dichloropyridine (VI) was 41 g. (86%); m.p. 55–56°.

Recrystallization of a sample for analysis from isopropyl alcohol showed no change in melting point.

Anal. Calcd. for $C_8H_8NCl_3$: C, 42.79; H, 3.59; N, 6.24. Found: C, 42.61; H, 3.63; N, 6.33.

2-Methyl-3-(β-chloroethyl)-4(or 6)-chloro-6(or 4)-hydroxypyridine (VII) or (VIIa).—One and one-tenth grams of 2-methyl-3-(β-chloroethyl)-4,6-dichloropyridine (VI) was dissolved in 30 ml. of glacial acetic acid and was placed in a combustion tube with 0.5 g. (one equivalent) of potassium acetate. The sealed tube was heated at 160° for six hours. On cooling a precipitate of potassium chloride separated. The acetic acid solution was filtered and concentrated to dryness under reduced pressure. The residue was recrystallized twice from a mixture of ethanol and water; m.p. 220°.

Anal. Calcd. for $C_8H_9NOCl_2$: C, 46.63; H, 4.40; N, 6.80. Found: C, 46.49; H, 3.84; N, 7.07.

2-Methyl-3-(β-chloroethyl)-6(or 4)-hydroxypyridine (VIII) or (VIIIa).—2-Methyl-3-(β-chloroethyl)-4(or 6)-chloro-6(or 4)-hydroxypyridine (VII) was dissolved in 125 ml. of methanol and reduced by hydrogen using 2 g. of palladium-on-barium sulfate as a catalyst. The reduction stopped spontaneously after two moles of hydrogen had been absorbed; the time required was about four hours. The catalyst was removed and the liquor was concentrated to dryness under reduced pressure. The solid residue was recrystallized twice from hot water; m.p. 218°.

Anal. Calcd. for $C_8H_{10}NOCl$: C, 55.98; H, 5.87; N, 8.16. Found: C, 56.14; H, 6.12; N, 8.26.

2-Methyl-3-(β-chloroethyl)-pyridine (IV).—Forty-one grams of 2-methyl-3-(β-chloroethyl)-4,6-dichloropyridine (VI) was dissolved in 2000 ml. of methanol and reduced by hydrogen using 30 g. of palladium-on-barium sulfate as a catalyst. The reduction stopped spontaneously when two moles of hydrogen had been absorbed; the time required was about thirty minutes.

After removal of the catalyst, the solution was concentrated to dryness under reduced pressure leaving a solid residue. The residue was identified by comparison with that described in the literature; the picrate was prepared, m.p. 135–136° (lit. 134–135°). The material was not purified but was used directly in the next step.

2-Methyl-3-(β-hydroxyethyl)-pyridine (V).—The crude 2-methyl-3-(β-chloroethyl)-pyridine (IV) described above was dissolved in 500 ml. of water and heated in a glass-lined autoclave at 160° for four hours. The solution was concentrated to 75–100 ml. in volume and made strongly alkaline with solid potassium hydroxide. This alkaline mixture was extracted with chloroform for three hours in a continuous extractor. The chloroform extract was dried and concentrated to a very small volume. An excess of petroleum ether was added to the residue and on scratching the product crystallized. It was filtered, washed and dried. The yield of 2-methyl-3-(β-hydroxyethyl)-pyridine (V) was 23 g. (90% over two steps); m.p. 62–64°.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.95; H, 8.30; N, 10.01.

The substance was further identified by preparation of several derivatives[3]: picrate, m.p. 119–120° (lit. 123–

(4) Dornow and Schacht, *Ber.*, **82**, 117 (1949).

(5) The microanalytical data reported in this paper were obtained by Mr. R. N. Boos and his associates of the Merck Laboratories.

124°); *p*-nitrobenzoate, m.p. 112–113° (lit. 114–115°); methiodide, m.p. 102–103° (lit. 103–104°). The benzyl bromide derivative was also prepared by reaction of the pyridine compound with an excess of benzyl bromide at room temperature. The crystalline derivative which separated was recrystallized twice from ethanol; m.p. 155–156°.

Anal. Calcd. for $C_{15}H_{18}NOBr$: C, 58.44; H, 5.89; N, 4.54. Found: C, 58.64; H, 5.95; N, 4.60.

2-Methyl-3-(β-ethoxyethyl)-4,6-dichloropyridine (II).—One-hundred and fifteen grams of 2-methyl-3-(β-ethoxyethyl)-4,6-dihydroxypyridine (I) was dissolved in 540 ml. of phosphorus oxychloride. The solution was heated in a glass-lined bomb nearly full for six hours at 140° under a nitrogen pressure of about 400 p.s.i. The excess phosphorus oxychloride was removed under reduced pressure and the residue was poured into an excess of crushed ice. No precipitate formed. The mixture was diluted, and partially neutralized with 30% sodium hydroxide solution to about *p*H 3. The solution was extracted several times with chloroform, which extract was washed, dried, and concentrated, leaving a brown, oily residue. It was distilled under reduced pressure; b.p. 96–97° (1 mm.). The yield of 2-methyl-3-(β-ethoxyethyl)-4,6-dichloropyridine (II) was 106 g. (90%).

RAHWAY, N. J. RECEIVED DECEMBER 8, 1950

Concerning *trans*-Acylation in Azlactone Synthesis

BY SERGE N. TIMASHEFF AND F. F. NORD

Although it is considered that in the synthesis of azlactones[1] no *trans*-acylation occurs,[2] Bennett and Niemann have reported that in the preparation of some azlactones of fluorinated benzene they were able to detect products of *trans*-acylation by means of ultraviolet absorption analysis[3] and in one instance by isolation. These authors reported that in the product obtained some benzamido groups from the expected phenyloxazolone had become replaced by acetamido groups from the acetic anhydride in which medium the reaction is carried out.

Realizing the significance of such a *trans*-acylation in the recently reported synthesis of thiophene azlactones,[4] a similar study was carried out using the first member of this series, namely, 2-phenyl-4-(2-thenal)-5-oxazolone. The ultraviolet absorption spectra of both the crude phenyloxazolone and the purified material along with that of the methyl compound are presented in Fig. 1. It can be seen that the curves of the absorption spectra of the phenyloxazolone preparations are very similar, both possessing peaks at 270 and 394 mμ. The crude preparation displayed neither a peak nor a plateau in the region of 362–364 mμ, which is characteristic for the methyloxazolone. Thus, it can be concluded that in the case of the phenyloxazolone derived from thiophene-2-aldehyde[5] *via* the Erlenmeyer–Plöchl synthesis using acetic anhydride as the medium, no *trans*-acylation occurs.

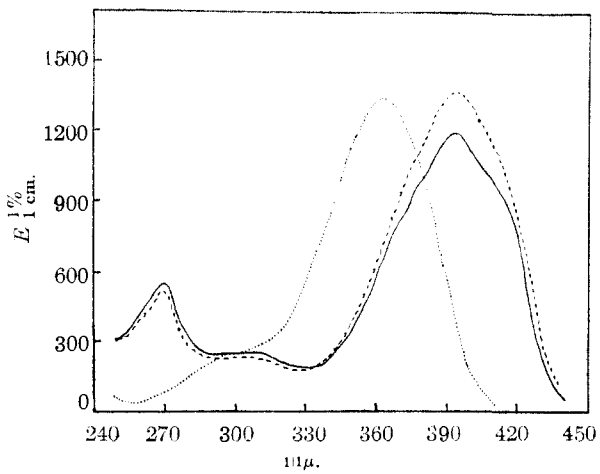


Fig. 1.—Ultraviolet spectra of thiophene azlactones: ....., methyloxazolone; - - - - - -, phenyloxazolone (purified); ——, phenyloxazolone (crude).

(1) J. Plöchl, *Ber.*, **16**, 2815 (1883); E. Erlenmeyer, *Ann.*, **275**, 1 (1893).

(2) J. W. Cornforth, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 733, 784.

(3) E. L. Bennett and C. Niemann, THIS JOURNAL, **72**, 1803 (1950).

(4) B. F. Crowe and F. F. Nord, *J. Org. Chem.*, **15**, 81 (1950).

(5) W. J. King and F. F. Nord, *ibid.*, **13**, 635 (1948).

DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY
FORDHAM UNIVERSITY
NEW YORK 58, N. Y. RECEIVED DECEMBER 11, 1950

The Synthesis of DL-Aspartic Acid-4-C^{14} [1]

BY S. C. WANG, T. WINNICK AND J. P. HUMMEL

Aspartic acid, labeled in the carboxyl adjacent to the substituted methylene group, has been synthesized in one step from ethyl formylaminomalonate and methyl bromoacetate-1-C^{14} (purchased from Tracerlab, Inc.). The procedure required no special equipment. The yield of the purified product was 63%. The specific radioactivity was about 16,000 counts per minute per mg., starting from 0.025 mole of methyl bromoacetate containing 1 mc. of C^{14}.

The position of the labeling, already established by the method of synthesis, was further confirmed by the Van Slyke ninhydrin–carbon dioxide method. Both carboxyls of aspartic acid are ninhydrin-labile.

Attempts were also made to prepare aspartic acid by the reduction of ethyl oxalacetate-4-C^{14} oxime with sodium amalgam. Only a 42% yield was obtained in this reduction. The potassium salt, from which the oxime was made, was prepared in 87% yield from sodium acetate-1-C^{14} by converting the latter to ethyl acetate with diethyl sulfate and condensing the ethyl acetate with ethyl oxalate in the presence of potassium.

(1) For detailed descriptions order Document 3125 from American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C., remitting $1.00 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or $1.05 for photocopies (6 × 8 inches) readable without optical aid.

RADIATION RESEARCH LABORATORY AND
DEPARTMENT OF BIOCHEMISTRY
STATE UNIVERSITY OF IOWA COLLEGE OF MEDICINE
IOWA CITY, IOWA RECEIVED JANUARY 12, 1951

The Structure of Ethylketene Dimer

BY R. L. WEAR

The structure of alkylketene dimers, prepared by the dehydrohalogenation of acyl halides, continues to be of interest.[1,2]

(1) C. D. Hurd and C. A. Blanchard, THIS JOURNAL, **72**, 1461 (1950).

(2) J. D. Roberts, R. Armstrong, R. F. Trimble, Jr., and M. Burg, *ibid.*, **71**, 843 (1949).