0.05 mole of 4,5,6-triaminopyrimidine resulting from the reduction of 4,6-diamino-5-nitropyrimidine[26] was added 6.4 g. (0.05 mole) of selenous acid in 20 ml. of water. After standing 24 hr., 4.0 g. of product was collected. An analytical sample was recrystallized twice from water yielding red-brown platelets melting above 360°.

Anal. Calcd. for $C_4H_3N_5Se$: C, 24.0; H, 1.5; N, 35.0; Se, 39.5. Found: C, 23.7; H, 1.11; N, 35.3; Se, 38.3.

Spectra. The ultraviolet-visible absorption spectra of 6-hydroxy-8-selenapurine and 6-amino-8-selenapurine are listed in Table I.

6-Morpholyl-8-selenapurine. To the methanol solution of 4,5-diamino-6-morpholylpyrimidine resulting from the catalytic reduction of 0.004 mole of 4-amino-6-morpholyl-5-nitropyrimidine[29] was added 0.5 g. (0.004 mole) of selenous acid in 10 ml. of methanol. After standing 3 days, large yellow crystals of product were deposited, weighing 0.7 g. The compound melted at 205.5–206°.

Anal. Calcd. for $C_8H_9N_5OSe$: N, 25.9. Found: N, 25.5.

TABLE I

ULTRAVIOLET-VISIBLE ABSORPTION SPECTRA OF TWO 8-SELENAPURINE COMPOUNDS IN WATER

Compound	Values[a] Given as λ_{max} in mμ (Log ε)
6-Amino-8-selenapurine	233 (3.86)
	339 (3.93)
	302 (3.56)
	388 (3.19)
6-Hydroxy-8-selenapurine	236 (3.89)
	276 (3.32)
	337 (4.00)

[a] Underlined wavelengths denote shoulders.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE HEYDEN NEWPORT CHEMICAL CORP.]

Synthesis of Anhydro Analogs of Chloramphenicol

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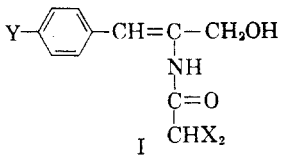
Four anhydro analogs of chloramphenicol have been prepared by the selective lithium aluminum hydride reduction of α-acylamidocinnamates derived from the alcoholysis of the corresponding azlactones. Bacteriostatic and fungistatic tests demonstrated that none of the four dehydro analogs possessed any significant degree of biological activity.

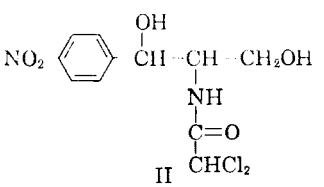
One phase of an antibiotics program conducted at these laboratories several years ago consisted of a search for analogs of chloramphenicol which would retain a high level of antibiotic activity and yet show a low order of toxicity. There resulted from this program four derivatives of cinnamyl alcohol with the general formula I.



I

X = H or Cl
Y = H or NO_2

The structural relationship of these compounds to chloramphenicol (II) is obvious.



II

C. F. Huebner and C. R. Scholz[2] describe the preparation of α-acetamido-*p*-nitrocinnamic acid, α-dichloroacetamido-*p*-nitrocinnamic acid, and ethyl α-dichloroacetamido-*p*-nitrocinnamate. The work described in this report is therefore a logical extension of their work, in view of the fact that the corresponding cinnamyl alcohols or the true anhydro analogs of chloramphenicol were prepared. In addition the cinnamyl alcohol structure was varied with respect to substitution in the ring and in the side chain.

α-Acetamidocinnamyl alcohol (III) was prepared by converting D,L-*threo*-phenylserine (IV) to 2-methyl-4-benzal-5-oxazalone (V) which was alcoholyzed to ethyl α-acetamidocinnamate (VI). The ester group was selectively reduced with lithium aluminum hydride to the desired alcohol.

α-Dichloroacetamidocinnamyl alcohol (VII) was prepared from D,L-*threo*-*N*-(dichloroacetyl)phenylserine (VIII), which was converted through the oxazalone (IX) and ester (X) as described in the conversion of (V) to (III).

α-Acetamido-*p*-nitrocinnamyl alcohol (XI) was synthesized by condensing *p*-nitrobenzaldehyde with aceturic acid in the presence of acetic anhydride to form 2-methyl-4-(*p*-nitrobenzal)-5-oxazalone (XII), which was converted as before to (XI) through the ester (XIII).

α-Dichloroacetamido-*p*-nitrocinnamyl alcohol, anhydrochloramphenicol (XIV), was synthesized by the nitration of α-dichloroacetamidocinnamyl alcohol (VII) with copper nitrate in an acetic anhydride–glacial acetic acid medium. Anhydrochloramphenicol was also synthesized by

(1) General Foods Corporation, Tarrytown, N. Y.

(2) C. F. Huebner and C. R. Scholz, *J. Am. Chem. Soc.*, **73**, 2089 (1951).

an alternate route. Ethyl α-dichloroacetamidocinnamate (X) was nitrated with cupric nitrate in an acetic acid–acetic anhydride solution to ethyl α-dichloroacetamido-*p*-nitrocinnamate (XV). The ester group was then selectively reduced with lithium aluminum hydride to yield anhydrochloramphenicol. Svoboda *et al.*[3] report the preparation of anhydrochloramphenicol by the Meerwein-Ponndorf reduction of α-dichloroacetamido-*p*-nitrocinnamaldehyde. These authors report a melting point of 148–149°C. which is in disagreement with the melting point reported here (96°).

Bacteriostatic and fungistatic tests were conducted *in vitro* with the following organisms: S. aureus, B. subtilis, E. coli, M. phlei, C. albicans, A. niger, C. globosum, A. oleraceae, and A. oryzae. The results of the screening test demonstrated that none of the four anhydro analogs of chloramphenicol possessed any significant degree of bacteriostatic and fungistatic activity.

EXPERIMENTAL

Melting points are uncorrected.

Ethyl α-acetamidocinnamate (VI). A mixture of 9 g. of 2-methyl-4-benzal-5-oxazalone (V)[4] prepared from DL-*threo*-phenylserine (IV),[4] 150 ml. of absolute ethanol, and 5 ml. of sodium ethylate solution (0.05 g. of Na/ml.) was stirred for 3 min. during which time complete solution occurred. The solution was distilled under reduced pressure (aspirator) until a volume of approximately 20 ml. remained. Crystallization occurred when the residue was poured into 250 ml. of water and cooled to 10°. The crude product was recrystallized from a 50–50 mixture of benzene and ligroin (6.1 g., 55.4%), m.p. 95.0–96.5°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: N, 6.02. Found: N, 6.02. This compound has been described by W. S. Fones.[5]

α-Acetamidocinnamyl alcohol (III). A mixture of 10 g. of ethyl α-acetamidocinnamate (VI) and 150 ml. of anhydrous ether dried by distillation over lithium aluminum hydride was cooled to 10°. A total of 68.8 ml. of a lithium aluminum hydride ether solution containing 0.02355 g. of lithium aluminum hydride per ml. was added during 30 min. at −10 to −15°. The mole ratio of ester to hydride was 1:1. The mixture was stirred at −10° for 1 hr. and then the temperature was allowed to rise to 15°. Any excess hydride was decomposed by the cautious addition of 25 ml. of water. The organometallic complex was decomposed with 50 ml. of 10% sulfuric acid. The yellow ether solution was separated from the aqueous phase, dehydrated with sodium sulfate, and evaporated to dryness under reduced pressure. The white crystalline residue was slurried with 10 ml. of benzene, filtered, and then recrystallized from 10 ml. of benzene to yield 2.57 g. (30.8%), m.p. 102–103.2°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.33; Hydroxyl, 8.91. Found: N, 7.28; Hydroxyl, 8.60.

The presence of the double bond was shown by bromine absorption and infrared analysis.

When this experiment was conducted using a mole ratio of ester to hydride of 1:0.75 the yield was halved. However, at −25° with a mole ratio of 1:0.75 a 30.2% yield was obtained. No product was isolated when the reaction was run at 25°.

α-Dichloromethyl-4-benzal-5-oxazalone (XIV). A mixture of 214.5 g. of *N*-dichloroacetylphenylserine (VIII) prepared according to a procedure described by Woolley,[6] and 429 g. of acetic anhydride was heated for 1 hr. on a water bath at 100°. Complete solution occurred at 68°. The reaction mixture was cooled to 15°, and the yellow crystalline product was filtered. The crude product was recrystallized from 425 ml. of glacial acetic acid and dried at 55–60° in a vacuum oven. The product weighed 118.5 g. (62.8%, m.p. 160–162°).

Anal. Calcd. for $C_{11}H_7Cl_2NO_2$: N, 5.48; Cl, 27.7. Found: N, 5.49; Cl, 27.6.

Ethyl α-dichloroacetamidocinnamate (X). A mixture of 75 g. of 2-dichloromethyl-4-benzal-5-oxazalone, 1875 ml. of ethanol, and 59 ml. of ethanolic hydrogen chloride (0.00152 g. HCl per ml.) was stirred at room temperature for 22 hr. Three additional 59 ml. portions of ethanolic hydrogen chloride were added, the first after 22 hr., the second after 24 hr. and the third after 30.5 hr. of stirring. The mixture was stirred for an additional 16 hrs. after the last addition. The clear yellow solution was diluted with 4 l. of water, and the resulting precipitate was filtered, and dried at 55° in a vacuum oven (68.5 g.). Recrystallization from 800 ml. of ligroin yielded 57.6 g. (67.9% of ethyl α-dichloroacetamidocinnamate, m.p. 105–108.5°).

Anal. Calcd. for $C_{13}H_{13}Cl_2NO_3$: N, 4.63; Cl, 23.5. Found: N, 4.64; Cl, 23.2.

α-Dichloroacetamidocinnamyl alcohol (VII). To a mixture of 15.8 g. of ethyl α-dichloroacetamidocinnamate (XV) and 500 ml. of anhydrous ether, cooled to −10°, there was added 63.2 ml. of an ether solution of lithium aluminum hydride (0.0236 g. of lithium aluminum hydride per ml.) during 30 min. The temperature was maintained at −10 to −20° throughout the addition and then for 30 min. after the addition. The reaction mixture was allowed to heat spontaneously to 15° during 1.5 hr. Excess hydride was decomposed with 35 ml. of water. The organometallic complex was decomposed by stirring with 75 ml. of 10% sulfuric acid for 10 min. The ether layer was separated, washed with two 50 ml. portions of water, dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The residue was slurried with 25 ml. of ether and filtered. The product was dissolved in 600 ml. of a 50/50 ether–ligroin mixture, and treated with carbon. The filtrate was evaporated to a volume of 150 ml. and allowed to crystallize. The product weighed 2.52 g. (29.3% yield), m.p. 114–115°.

Anal. Calcd. for $C_{11}H_{11}Cl_2NO_2$: N, 5.39; Cl, 27.3. Found: N, 5.42; Cl, 26.9.

Ethyl α-acetamido-p-nitrocinnamate (XIII). To a suspension consisting of 3 g. of 2-methyl-4-(*p*-nitrobenzal)-5-oxazalone (X) prepared according to Holland *et al.*[7] in 80 ml. of ethanol was added 3 ml. of sodium ethylate solution (1 g. of sodium per 50 ml. of ethanol). The solution turned orange-brown and thickened until it was almost solidified. The mixture was heated to reflux, all of the solid dissolving, and filtered hot. The cream-colored product (1.8 g., 48.2%) which separated on cooling was not further purified, m.p. 201.5–210°.

Anal. Calcd. for $C_{13}H_{15}N_2O_5$: N, 10.0. Found: N, 10.2.

α-Acetamido-p-nitrocinnamyl alcohol (XI). A solution of 6.0 g. of ethyl α-acetamido-*p*-nitrocinnamate in 400 ml. of anhydrous ether (dried and distilled over lithium aluminum hydride) was cooled to −10°. There was added, during 30 min. at −10° to −20°C., 26.2 ml. of an ether solution of lithium aluminum hydride (0.0236 g. of lithium aluminum hydride per ml.). The color of the solution changed from yellow to dark brown. The reaction mixture was held at −10 to −20° for 30 min. and then the temperature was allowed to rise spontaneously to 15°. Excess hydride was

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(4) G. Carrara and G. Weitnauer, *Gazz. chim. ital.*, **79**, 856 (1949).

(5) W. S. Fones, *J. Org. Chem.*, **17**, 1534 (1952).

(6) D. W. Woolley, *J. Biol. Chem.*, **185**, 293 (1950).

(7) D. O. Holland, P. A. Jenkins, and J. H. C. Nayler, *J. Chem. Soc.*, 273, (1953).

decomposed with 10 ml. of water, and then 10 ml. of 10% sulfuric acid was added to decompose the complex. The light yellow ether solution was separated, washed with two 50 ml. portions of water, dried over sodium sulfate, filtered, and evaporated to dryness. The crude product was recrystallized from a mixture of 15 ml. of ligroin (b.p. 65–110°) and 25 ml. of dioxane. The product weighed 0.25 g. (4.93% yield), m.p. 158.0–158.8°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: N, 11.87. Found: N, 11.71.

α-Dichloroacetamido-p-nitrocinnamyl alcohol (XIV). To a solution of 5 ml. of acetic anhydride and 2.5 ml. of glacial acetic acid was added, with stirring, 0.75 g. of pulverized cupric nitrate trihydrate. A temperature of 30–35° was maintained. After the exothermic reaction had ceased there was added 0.75 g. of α-dichloroacetamidocinnamyl alcohol portionwise during 20 min. at 10–20°. The temperature was allowed to rise to room temperature during 10 min. and then poured into 100 g. of ice and water. A yellow oil separated which crystallized. The nitro derivative was purified by recrystallization from petroleum ether. The colorless needles which separated were filtered and dried *in vacuo* at 25° over phosphorus pentoxide, m.p. 94–98°.

Anal. Calcd. for $C_{11}H_{10}Cl_2N_2O_4$: H, 3.28; Cl, 23.28; N, 9.18. Found: H, 3.61; Cl, 23.01; N, 9.05.

Infrared analysis demonstrated the presence of a *p*-nitrophenyl group. Qualitative tests for a double bond and a hydroxyl group were positive.

Ethyl α-dichloroacetamido-p-nitrocinnamate (XV). This compound was prepared by the nitration of ethyl α-dichloroacetamidocinnamate (X). The nitration reagent was prepared in the same manner as that described above. A mixture of 10 ml. of acetic anhydride, 5 ml. of glacial acetic acid, and 1.5 g. of cupric nitrate was used. To it was added 1.8 g. of (X) portionwise at 25–30°. The mixture was stirred for 0.5 hr. and then poured into 50 g. of ice and water. The oil which separated was dissolved in ether, dried over sodium sulfate, and the ether evaporated. The semi-crystalline residue of (XV) was used directly without purification in the lithium aluminum hydride reduction step described below. This compound has been described by Huebner and Scholz.[2]

α-Dichloroacetamido-p-nitrocinnamyl alcohol (XIV). To a solution of 1.2 g. of impure (XV) described above in 50 ml. of anhydrous ether there was added dropwise during 30 min., a lithium aluminum hydride solution consisting of 0.1040 g. lithium aluminum hydride ether. The mixture was stirred 10 min. and then stirred with 50 ml. of 10% sulfuric acid. The ether layer was washed with water, dried with sodium sulfate and then evaporated to dryness under reduced pressure. The residue was dissolved in carbon tetrachloride and precipitated by adding excess petroleum ether. The colorless crystalline product weighed 0.65 g., m.p. 96°.

Anal. Calcd. for $C_{11}H_{10}Cl_2N_2O_4$: N, 9.18. Found: N, 9.17.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Preparation of 5(6)-Fluorobenzimidazole and 4(7)-Fluorobenzimidazole

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5(6)-Fluorobenzimidazole and 4(7)-fluorobenzimidazole have been prepared by the Schiemann reaction from the corresponding amino compounds. The infrared and ultraviolet absorption spectra and *p*Ka values have been determined for both compounds.

Several fluorine-containing compounds have been reported to have useful physiological properties. *p*-Fluorobenzoic acid inhibits the growth of *E. coli* and the inhibition is reversed by tyrosine but not by *p*-aminobenzoic acid.[1] *m*-Fluoro-*p*-aminobenzoic acid also inhibits the growth of *E. coli* and the inhibition is reversed by *p*-aminobenzoic acid.[2] A number of fluorinated phenylalanines and tyrosines have been tested as growth inhibitors and were found to be competitive inhibitors of their parent amino acids. The preparation and resolution of the three DL-monofluorophenylalanines have been carried out since the observation was made that *m*-fluoro-DL-phenylalanine effectively inhibits the metabolism of phenylalanine by a competitive process.[3] Recently the biological activity of three fluoro derivatives of pyrimidines has been reported. 5-Fluorouracil and 5-fluoroörotic acid have shown appreciable activity against a number of mouse and rat tumors.[4] Very recently, also, several 2-fluoropurines have been prepared and it is reported that 2-fluoroadenosine inhibits the growth of Human Epidermoid Carcinoma (HE2).[5]

Since the benzimidazole nucleus is present in several physiologically active compounds it was believed that the preparation of fluorobenzimidazoles might lead to some interesting compounds. In the present study the 5(6)-fluoro- and 4(7)-

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