tained after removal of the benzene from the filtrate under reduced pressure.

Anal. Calcd. for $C_{10}H_5O_{12}N_7Cl_2$: C, 24.7; H, 1.03; N, 20.2. Found: C, 24.7; H, 1.06; N, 20.2.

Several esters were prepared by adding the acid chloride at 25° to the minimum amount of anhydrous alcohol necessary for solution. The esters crystallized from the solution upon cooling.

TABLE I

ESTERS OF N,N'-DINITROSTYPHNYLBISGLYCINE

R	M.p. of product, °C. (dec.)	Crystallizing medium	Formula	Analyses, % Calcd.	Found
Methyl	161	EtOH	$C_{12}H_{11}O_{14}N_7$	C, 30.18	30.30
				H, 2.30	2.39
				N, 20.54	20.44
Ethyl[a]	130–131	EtOH	$C_{14}H_{15}O_{14}N_7$	C, 33.30	33.40
				H, 2.97	2.90
				N, 19.40	19.60
n-Propyl	145	MeOH	$C_{16}H_{19}O_{14}N_7$	C, 36.02	36.22
				H, 3.56	3.50
				N, 18.38	18.32

[a] A mixed melting point with an authentic specimen prepared by nitration of ester Va gave no depression.

Styphnylbis-β-alanine (IIb).—Styphnyl chloride, 2.82 g. (0.01 mole), 2.51 g. (0.02 mole) of β-alanine hydrochloride, 33.3 ml. of 95% ethanol and 20 ml. of water were placed in a 300-ml. three-neck flask equipped with stirrer, thermometer and dropping funnel. The mixture was heated to 50° and 3.18 g. (0.03 mole) of sodium carbonate dissolved in 13 ml. of water was added dropwise over a period of 40 minutes. Heating was continued for ten minutes at 60°; then the flask was cooled to 1° and the salt which precipitated was filtered. An orange colored salt (3.35 g.) was obtained. It was dissolved in 200 ml. of water and 3.12 ml. of 5 *N* hydrochloric acid was added. A total of 2.14 g. (55%) of product was obtained, m.p. 198° dec. The acid was soluble in acetone, dioxane, methanol and ethanol, but insoluble in benzene, chloroform, carbon tetrachloride and ether.

Anal. Calcd. for $C_{12}H_{13}O_{10}N_5$: C, 37.2; H, 3.36; N, 18.1. Found: C, 36.9; H, 3.18; N, 18.1.

Styphnylbis-β-alanine Methyl Ester (Vb).—Styphnyl chloride, 2.82 g. (0.01 mole), 2.79 g. (0.02 mole) of β-alanine methyl ester hydrochloride and 2.12 g. (0.02 mole) of sodium carbonate were added to 15 ml. of toluene and 20 ml. of water. The mixture was heated to 50° for four hours and after cooling, the precipitate was filtered. There was obtained 1.33 g. (31%) of product which melted at 149–153°, and at 151–155° after repeated recrystallization from acetone. The ester was soluble in acetone, dioxane, benzene and ethanol, but was insoluble in water.

Anal. Calcd. for $C_{14}H_{17}O_{10}N_5$: C, 40.5; H, 4.10; N, 16.8. Found: C, 40.9; H, 4.36; N, 16.6.

N,N'-Dinitrostyphnylbis-β-alanine (IIIb).—A 7.05-g. (0.018 mole) sample of styphnylbis-β-alanine was dissolved in a mixture of 15 ml. of concd. sulfuric acid and 15 ml. of fuming nitric acid. The solution was heated with stirring to 40–45° for 30 minutes and after cooling to 25° was poured onto 300 g. of ice. The white solid, which precipitated was filtered off and recrystallized from hot water. An 80% yield of IIIb was obtained, m.p. 170° dec. It was soluble in acetone, dioxane and methanol, but insoluble in benzene, chloroform, carbon tetrachloride and petroleum ether.

Anal. Calcd. for $C_{12}H_{11}O_{14}N_7$: C, 30.2; H, 2.31; N, 20.5. Found: C, 30.2; H, 2.38; N, 20.3.

N,N'-Dinitrostyphnylbis-β-alanine Methyl Ester (VIb).—Ester (Vb), 0.2 g. (0.48 mmole) was added to a mixture of 2 ml. of concd. sulfuric acid and 2 ml. of fuming nitric acid. The solution was heated to 40° for 30 minutes and after cooling to 25° was poured onto ice. A sticky, white solid settled out, which, after recrystallization from absolute ethanol was obtained in the form of white needles, m.p. 119–120° dec. (yield 70%).

Anal. Calcd. for $C_{14}H_{15}O_{14}N_7$: C, 33.3; H, 2.97; N, 19.4. Found: C, 33.6; H, 3.29; N, 19.3.

N,N'-Dinitrostyphnylbis-β-alanyl Dichloride (IVb).—N,N'-Dinitrostyphnylbis-β-alanine, 0.5 g. (0.001 mole), was added to 5 ml. of thionyl chloride, in a 50-ml. flask. A condenser topped with a drying tube was affixed to the flask and the mixture was heated to reflux. Dissolution of the acid had occurred after two hours, but heating was continued for four hours. The excess thionyl chloride was removed under reduced pressure, and 10 ml. of petroleum ether (60–70°) was added to the residue. The mixture was filtered and a total of 0.45 g. (90%) of product was obtained, m.p. 106° dec. It was soluble in benzene, acetone, dioxane, ethyl acetate, nitromethane and ethylene chloride, but was insoluble in carbon tetrachloride, chloroform and petroleum ether.

Anal. Calcd. for $C_{12}H_9O_{12}N_7Cl_2$: C, 28.0; H, 1.75; N, 19.1. Found: C, 28.18; H, 1.83; N, 19.1.

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[CONTRIBUTION FROM THE WHITMORE LABORATORIES OF THE PENNSYLVANIA STATE COLLEGE]

Methyl β-(*m*-Chloroanilino)-acrylate

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m-Chloroaniline readily adds in good yield to methyl propiolate to give the known methyl β-(*m*-chloroanilino)-acrylate which can be readily cyclized directly to 4-hydroxy-7-chloroquinoline. This constitutes another approach to this important quinoline intermediate for the synthesis of antimalarials of the chloroquin type.

A direct synthesis of 4-hydroxy-7-chloroquinoline has been achieved by Price, Leonard and Reitsema,[5] and Northey and Dreisbach[6] by the cyclization of methyl β-(*m*-chloroanilino)-acrylate (I, R, R' = H).

This intermediate, however, was obtained from *m*-chloroaniline and methyl formylacetate in only 31% yield.

We have undertaken a reinvestigation of this approach with the purpose of preparing the β-(*m*-chloroanilino)-acrylate by an alternate method. Efforts to prepare β-(*m*-chloroanilino)-acrylates (I, R, R' = H) by the condensation of *m*-chloroaniline with methyl or ethyl β-alkoxyacrylates failed to give any crystalline products; the products were oils which gave *sym*-bis-*m*-chlorophenylurea upon attempted cyclization. Methyl β,β-dimethoxypropionate reacted with *m*-chloroaniline hydrochloride to give a crystalline compound, m.p. 125–126°, which gave the correct analysis for methyl β-(*m*-chloroanilino)-acrylate (I, R, R' = H). However, this product gave only a poor yield of *sym*-bis-*m*-chlorophenylurea[5] on attempted cyclization.

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[1] Taken in part from the Ph.D. thesis of F. W. Gray, August, 1949. Colgate-Palmolive-Peet Co., Jersey City, N. J.

[2] Parke, Davis and Co. Fellow 1947–1948.

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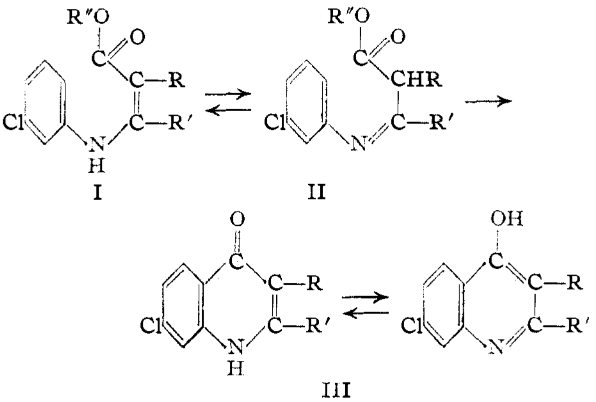
[4] Deceased.

[5] Price, Leonard and Reitsema, THIS JOURNAL, **68**, 1256 (1946).

[6] Northey and Dreisbach, U. S. Patent 2,478,125, Aug. 2 (1949).



I II III

On the other hand, methyl propiolate readily reacts with *m*-chloroaniline at room temperature without added catalyst or solvent to give the intermediate methyl β-(*m*-chloroanilino)-acrylate, m.p. 148–150°,[7] (I, R, R′ = H, R″ = Me) in good yield. This material, in contrast to that obtained from β,β-dimethoxypropionate, cyclized by heating in diphenyl ether to give 4-hydroxy-7-chloroquinoline.

Both the higher melting compound from *m*-chloroaniline and methyl propiolate and the lower melting compound from methyl β,β-dimethoxypropionate analyzed for the expected methyl β-(*m*-chloroanilino)-acrylate (I), and gave ultraviolet absorption spectra with maxima at 290 and 317 mμ. The differences exhibited by these two compounds on heating in diphenyl ether can be explained by assuming that the former is the *cis*-isomer in which the phenyl and carbethoxy groups are on the same side, while the latter is the *trans*-isomer. The possibility that these are the *syn* and *anti* form of the anil (II) cannot be excluded.

Methyl propiolate is readily available in laboratory quantities[8,9] and potentially available on a commercial scale by the reaction of acetylene with carbon dioxide.[10]

Experimental

Methyl β-(*m*-Chloroanilino)-acrylate (I).—Methyl propiolate[8,9] (9.5 g., 0.11 mole) and *m*-chloroaniline (9.0 g., 0.07 mole) were placed in a small flask fitted with a stirrer and reflux condenser. After 70 hours stirring at 25–30° the reaction mixture was chilled, the light yellow solid filtered, washed with pentane, and dried; yield Crop 1, 7.9 g., Crop 2, 3.3 g. (73.5%). The characteristic odor of methyl propiolate was noted in the final filtrate. A sample recrystallized twice from methanol gave colorless needles, m.p. 148–150°.[5,7]

Anal. Calcd. for $C_{10}H_{10}ClNO_2$: C, 56.74; H, 4.76; Cl, 16.75. Found: C, 56.77; H, 4.99; Cl, 17.05.

4-Hydroxy-7-chloroquinoline (III).—The above compound was cyclized to 4-hydroxy-7-chloroquinoline by the method of Price.[5]

Anal. Calcd. for C_9H_6ONCl: C, 60.18; H, 3.37. Found: C, 60.37; H, 3.49.

***m*-Chloroaniline and Methyl β,β-Dimethoxypropionate.**—To a cooled stirred solution of 19.8 g. (0.12 mole) of *m*-chloroaniline hydrochloride in 150 ml. of water at 10° was added 17.7 g. (0.12 mole) of methyl β,β-dimethoxypropionate.[11,12,13] After 15 minutes the mixture was warmed to 25° and a yellow precipitate began to appear. After stirring overnight, the precipitate was filtered, washed and dried to constant weight. Stirring with pentane and filtering gave 24 g., m.p. 78–84°. This crude material had a Dumas nitrogen analysis of 6.29% (calcd. for $C_{10}H_{10}ClNO_2$: N, 6.62). Repeated crystallization from methanol raised the m.p. to 123–126°.

Anal. Calcd. for $C_{10}H_{10}ClNO_2$: C, 56.74; H, 4.76; Cl, 16.75. Found: C, 56.79; H, 4.72; Cl, 16.70.

A sample of this material (2.0 g.) was heated with diphenyl ether according to the procedure above. The only crystalline material obtained was 0.15 g. of *sym*-bis-*m*-chlorophenylurea, m.p. 248°.

***m*-Chloroaniline and β-Alkoxyacrylates.**—A flask containing methyl β-methoxyacrylate[11,13] (4.5 g.) and *m*-chloroaniline (5.1 g.) was heated at 100° (740 mm.) in an oil-bath for one hour and then for an additional hour at 50° (15 mm.). Various attempts to obtain crystals from the solution were unsuccessful. The solution was added dropwise to 150 ml. of boiling diphenyl ether contained in a 300-ml. flask fitted with air condenser and then allowed to reflux one hour. The reaction mixture was cooled, allowed to stand at room temperature for four hours, and filtered. The crude, yellowish product that separated was filtered and washed with ligroin; 2 g., m.p. 240–243°. Two recrystallizations from methanol gave white crystalline needles, m.p. 250°. The melting point of a mixture with 4-hydroxy-7-chloroquinoline was 210–215°, but that of a mixture of *sym*-bis-*m*-chlorophenylurea was undepressed.

Ethyl β-ethoxyacrylate (7.6 g.) and *m*-chloroaniline (6.8 g.) treated substantially as above gave 1.3 g. of the substituted urea, m.p. 250°.

Numerous experiments using the acrylates with *m*-chloroaniline under varying conditions, including the use of acetic acid as a solvent or catalyst, yielded similar results.

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[7] This melting point is greatly dependent upon the rate of heating. If the sample was heated at a rate of one degree per minute from 100°, the melting point was 148–150°; but if the sample was placed in a bath preheated to 130°, and thereafter heated very slowly, the material was entirely melted at 135°. A sample of methyl β-(*m*-chloroanilino)-acrylate prepared by the method of Price[5] had this same melting behavior; the melting point of a mixture of the two samples was indistinguishable.

[8] Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, page 10.

[9] Perkin, *J. Chem. Soc.*, **91**, 834 (1907).

[10] Macallum, U. S. Patent 2,194,363 (1938).

[11] Deno, THIS JOURNAL, **69**, 2233 (1947).

[12] Dyer and Johnson, *ibid.*, **56**, 222 (1934).

[13] Gray, Mosher, Whitmore and Oakwood, unpublished work.