moles) of potassium hydroxide in 150 cc. of water, and two liters of ethanol was heated to reflux with stirring, and 44 g. (0.36 mole) of methyl α-pyridyl ketone was added rapidly. After working up the reaction product by customary procedures there was obtained 100 g. (87%) of product melting at 328–330°. An analytical sample of this acid was prepared by dissolving a small portion in hot dilute potassium hydroxide solution and heating with Norite. The warm filtrate was neutralized with acetic acid, and the solid obtained in this manner was filtered and washed with hot ethanol. After drying in the oven at 130°, the compound melted at 336–337°.

Anal. Calcd. for $C_{15}H_8O_2N_2Cl_2$: Cl, 22.18; N, 8.78. Found: Cl, 21.99; N, 8.95.

Ethyl 6,8-Dichloro-2-(2′-pyridyl)-cinchoninate.—The acid was esterified by heating 45 g. (0.14 mole) with 250 cc. of absolute ethanol, and 100 cc. of sulfuric acid at the reflux temperature for eight hours. Recrystallization from ethanol (1800 cc.) gave 35 g. (72%) of product melting at 113–114°. The same melting point was observed after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{17}H_{12}O_2N_2Cl_2$: N, 8.05; Cl, 20.43. Found: N, 7.81; Cl, 20.19.

6,8-Dichloro-2-(2′-pyridyl)-cinchoninyl Chloride.—From twenty-five grams (0.078 mole) of 6,8-dichloro-2-(2′-pyridyl)-cinchoninic acid and 100 cc. of thionyl chloride there was obtained 28 g. (100%) of material melting at 255–263°. The melting point varied somewhat on different preparations. Another batch melted at 260–268°. The difference in melting points might be due to varying amounts of hydrogen chloride in the product.

6,8-Dichloro-4-(α-bromoacetyl)-2-(2′-pyridyl)-quinoline.—Twenty-five grams (0.074 mole) of 6,8-dichloro-2-(2′-pyridyl)-cinchoninyl chloride was added slowly to 0.3 mole of diazomethane in 900 cc. of dry methylene chloride[4] solution at 5°. Then, following standard procedures, 30 cc. of 48% hydrobromic acid was added. There was obtained 28 g. (95%) of material melting at 229–231°. Recrystallization of a small amount of this material from acetic acid and a few drops of 48% hydrobromic acid gave a product melting at 265–268°.

Anal. Calcd. for $C_{16}H_9ON_2BrCl_2 \cdot HBr$: N, 5.87; Cl, Br, 48.41. Found: N, 6.22 and 6.20; Cl, Br, 47.24.

A low combined-halogen analysis may be explained by the loss of some hydrogen bromide from the weakly basic product.

α-Bromomethyl-6,8-dichloro-2-(2′-pyridyl)-4-quinoline methanol.—A mixture of 20 g. (0.05 mole) of 6,8-dichloro-4-(α-bromoacetyl)-2-(2′-pyridyl)-quinoline, 11 g. of aluminum *i*-propoxide, and 200 cc. of anhydrous *i*-propanol was heated with a water-bath so that slow distillation occurred.[5] The residue was cooled and 100 cc. of 6 *N* hydrochloric acid was added slowly. The solid was filtered and washed with a little 6 *N* hydrochloric acid and about 200 cc. of water. After drying, the product weighed 16.5 g. (83%) and melted at 245–248°. From another preparation, the yield of carbinol melting over a wider range (245–250°) was 97%.

6,8-Dichloro-2-(2′-pyridyl)-α-di-*n*-butylaminomethyl-4-quinolinemethanol.—Five grams (0.012 mole) of α-bromomethyl-6,8-dichloro-2-(2′-pyridyl)-4-quinolinemethanol, 7.8 g. (0.06 mole) of di-*n*-butylamine and 20 cc. of toluene was heated in an oil-bath at 95–100° for fourteen hours.[5,6] The reaction mixture was poured into anhydrous ether and filtered. The filtrate was first distilled on a steam-bath at reduced pressure, and finally the residue was distilled at 0.5 mm. from a boiling water bath to remove the excess of di-*n*-butylamine. The viscous oil that remained was dissolved in a mixture of two parts anhydrous ether to one part acetone. The monohydrochloride was precipitated from this solution by the addition, with vigorous mechanical stirring, of 10-cc. portions of 0.26 *M* ethereal hydrogen chloride.[7] The first three portions of acid gave a total of 3.3 g. (57%) of material melting at 182–184°.[8] An analytical sample of this product melting at 188–190° was obtained by recrystallization from absolute ethanol–ethyl acetate solution.

Anal. Calcd. for $C_{24}H_{29}ON_3Cl_2 \cdot HCl$: N, 8.70; Cl, 22.05. Found: N, 8.71; Cl, 22.08 and 22.07.

Methyl α-Pyridyl Ketone.—Details are given for this preparation because of a 25% improvement in yield.[9] To 1.2 moles of sodium ethoxide in 1100 cc. of warm benzene, prepared from 27.6 g. (1.2 g. atoms) of sodium sand and 55.2 g. (1.2 mole) of absolute ethanol, was added with vigorous stirring a mixture of 120.2 g. (0.8 mole) of ethyl picolinate[10] and 140.8 g. (1.6 moles) of anhydrous ethyl acetate at a rate to maintain gentle refluxing. During the addition the sodium ethoxide disappeared; the mixture became clear, and then formed a thick yellow mush. The mixture was refluxed with stirring for twelve hours, cooled and poured into a cold solution of 40 g. of sodium hydroxide in 800 cc. of water. The light yellow solid was filtered off and 800 cc. of water was added to the filtrate. The benzene and aqueous layers were separated. The benzene layer was extracted with 400 cc. of water and the combined aqueous layers extracted with 100 cc. of benzene. The yellow precipitate was suspended in the aqueous solution and the mixture acidified with 350 cc. of concentrated hydrochloric acid. The solution was refluxed for two hours, cooled, made basic with solid sodium carbonate and extracted with 1500 cc. of ether in two portions. The ether was dried over anhydrous sodium sulfate. Removal of the ether and distillation of the residue at 79–80° (10 mm.) gave 72 g. (75%) of methyl α-pyridyl ketone.

(4) The authors are grateful to Dr. Robert E. Lutz for general directions on the use of methylene chloride in this reaction.

(5) This procedure followed a general method of Dr. Robert E. Lutz for the preparation of the corresponding 2-phenyl derivative.

(6) The temperature does not appear to be very critical in this condensation as good yields were obtained by heating at 70°. The period of heating was varied from six to fourteen hours without appreciable change in yield.

(7) It was found helpful in some cases where mixtures of amines were involved to effect separation by fractional precipitation of the hydrochlorides, using dilute ethereal hydrogen chloride.

(8) The melting points vary with the rate of heating. The melting points reported were taken by inserting the tube into the bath at 170° and heating the bath at 8° per minute. The pure compound also melted in twenty-eight seconds when inserted into a constant temperature bath of 198–199°.

(9) Kolloff and Hunter, THIS JOURNAL, **63**, 490 (1941).

(10) This ester was prepared in 73% yield by the esterification of picolinic acid with ethanol using hydrogen chloride.

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Antitubercular Studies. Bis-(*p*-aminophenyl) Derivatives of Ethyl Ether and Trichloroethane

BY EDITH GRAEF[1] AND ALFRED BURGER

On the basis of the observation[2] that the substitution of other "inhalation-anesthetic" groups for the trichloroethyl group in DDT led to compounds approaching, or rivaling, this insecticide in activity, it seemed advisable to substitute similar groups in 1,1,1-trichloro-2,2-bis-(*p*-aminophenyl)-ethane since one of its acyl derivatives had shown considerable antitubercular activity.[3]

As the first example in this series we have prepared α,α′-bis-(*p*-aminophenyl)-ethyl ether by condensation of 1-(*p*-acetamidophenyl)-ethyl bromide with sodium 1-(*p*-acetamidophenyl) eth-

(1) Du Pont Post-Graduate Fellow.

(2) Läuger, Martin and Müller, *Helv. Chim. Acta*, **27**, 892 (1944).

(3) Burger, Graef and Bailey, THIS JOURNAL, **68**, 1725 (1946).

oxide, and subsequent alkaline hydrolysis of the acetamido groups.

The relative insolubility of 1,1,1-trichloro-2,2-bis-(*p*-benzamidophenyl)-ethane[3] made it desirable to attempt the preparation of a soluble derivative of the parent amine of this compound. 1,1,1-Trichloro-2,2-bis-(*p*-phthalamidophenyl)-ethane[4] appeared suitable, but we did not succeed in purifying the product from the partial hydrolysis of the corresponding phthalimido compound.

Experimental

1-(*p*-Acetamidophenyl)-ethyl Bromide.—This halide, previously described by Rousset,[5] was obtained from 1-(*p*-acetamidophenyl)-ethanol[5] which, in turn, could be prepared by reduction of *p*-acetamidoacetophenone with aluminum isopropoxide in the customary manner. A solution of 30 g. of 1-(*p*-acetamidophenyl)-ethanol in 300 cc. of dry chloroform was cooled to −10° in an ice–salt-bath. Phosphorus tribromide (10 cc.) was dropped in with constant stirring, the temperature being kept below 0°, and the solution was then allowed to warm to room temperature. Stirring was discontinued, the mixture allowed to stand overnight, the chloroform and excess phosphorus tribromide removed under reduced pressure, and the residue poured into 100 cc. of ice and water. The oil formed was extracted into ether; drying and evaporation of the ether extract yielded 24 g. (58%) of platelets which were recrystallized from ethanol. The crystals melted at 93–95° and darkened on standing.

α,α′-bis-(*p*-Acetamidophenyl)-ethyl Ether.—To 0.5 g. of sodium finely dispersed under xylene, was added a solution of 3.7 g. of 1-(*p*-acetamidophenyl)-ethanol in 50 cc. of dry ether at room temperature with mechanical stirring. When the spontaneous refluxing had ceased, a solution of 5 g. of 1-(*p*-acetamidophenyl)-ethyl bromide in 50 cc. of ether was added, and the mixture stirred overnight. It was washed with 50 cc. of water, the ether solution was dried over sodium sulfate, and the solvents were evaporated in a vacuum. The residual oil solidified on cooling and was crystallized from ethanol-acetone. It weighed 3 g. (44%) and melted at 109–111°.

Anal. Calcd. for $C_{20}H_{24}N_2O_3$: N, 8.23. Found: N, 8.51.

α,α′-bis-(*p*-Aminophenyl)-ethyl Ether.—A solution of 14 g. of α,α′-bis-(*p*-acetamidophenyl)-ethyl ether in 150 cc. of 15% ethanolic potassium hydroxide was refluxed for ten hours. The ethanol was distilled under reduced pressure, the residue taken up in water, and the solution acidified. The oil formed was separated and the acid solution extracted with ether which removed 4 g. of unhydrolyzed starting material. The aqueous layer was then made alkaline, the oil extracted into ether, dried, and fractionated. Six grams (57%) of a pale yellow oil boiling at 110–114° (70 mm.) was collected.

The **monohydrochloride** formed readily on treatment of an acetone solution of the oil with ethereal hydrogen chloride. It was recrystallized from ethanol–ether and melted at 186–187°.

Anal. Calcd. for $C_{16}H_{20}N_2O \cdot HCl$: N, 9.57. Found: N, 9.73.

1,1,1-Trichloro-2,2-bis-(*p*-phthalimidophenyl)-ethane.—A suspension of 100 g. of phthalanil and 50 g. of chloral in 500 cc. of 100% sulfuric acid was allowed to stand at room temperature for three days with occasional shaking. The solid gradually disappeared leaving a clear yellow-brown solution. This was poured onto 2000 g. of crushed ice, and the colorless precipitate thus formed was filtered. It weighed 112 g. (87%). Recrystallization from ethanol yielded colorless crystals, m. p. 97–99°.

Anal. Calcd. for $C_{30}H_{17}Cl_3N_2O_4$: N, 4.87. Found: N, 4.76.

(4) Suggested by Dr. Randolph T. Major.

(5) Rousset, *Bull. soc. chim.*, [3] **11**, 321 (1892).

Hydrolysis of the phthalimido groups patterned upon the method of Kuhara and Fukui[6] using a barium hydroxide-barium chloride solution led to an alkali-soluble product which, however, resinified during its isolation.

Succinanil and chloral could not be condensed under the same conditions.

(6) Kuhara and Fukui, *Am. Chem. J.*, **26**, 454 (1901).

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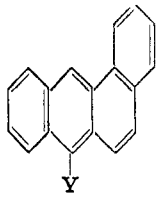
The Conjugation of Peptides with 1,2-Benzanthryl-10-isocyanate[1]

BY LARRY Q. GREEN AND HUGH J. CREECH

In connection with immunological studies[2] of hydrocarbon–protein conjugates,[3] it was found desirable to have as inhibitors some compounds with greater water solubilities than the amino acid conjugates[4] employed previously. It was thought that the use of di- and tripeptides or of dicarboxylic amino acids as components of the conjugates might solve this problem. Accordingly, 1,2-benzanthryl-10-isocyanate was coupled to glycylglycine, triglycine and glutamic acid in aqueous dioxane solution. As was the case with the glycine and ε-amino caproic acid conjugates prepared from this isocyanate, the new compounds were obtained only in an amorphous condition. Although the compounds were not isolated in an absolutely pure state because of their susceptibility to decomposition, they were suitable for the immunological tests.



I. Y = —NHCONHCH$_2$CONHCH$_2$COOH
II. Y = —NHCONHCH$_2$CONHCH$_2$CONHCH$_2$COOH
III. Y = —NHCONHCHCH$_2$CH$_2$COOH
COOH

Experimental[5]

Glycylglycine, charring point 225°, was prepared by the hydrolysis of 2,5-diketopiperazine.[6] A solution of 375 mg. of this compound in 5 cc. of water adjusted to *p*H 9 with sodium hydroxide was added slowly with stirring to a solution of 500 mg. of 1,2-benzanthryl-10-isocyanate in 50 cc. of purified dioxane. After ten minutes at room temperature, 150 cc. of water was added to the light yellow suspension and the mixture was heated to 40° whereupon most of the precipitate went into solution. Normal

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(2) Manuscripts in course of preparation; also, Creech and Franks, *Am. J. Cancer*, **30**, 555 (1937).

(3) Creech and Jones, THIS JOURNAL, **63**, 1661, 1670 (1941).

(4) Fieser and Creech, *ibid.*, **61**, 3502 (1939).

(5) Analyses by Miss E. Werble.

(6) Fischer, *Ber.*, **34**, 2868 (1901).