Chloromethyl Bis-(*p*-chlorophenyl)-carbinols

BY J. M. PEPPER[1] AND MARSHALL KULKA

The heretofore unknown monochloromethyl (III) and dichloromethyl bis-(*p*-chlorophenyl)-carbinol (IV) have now been prepared from *p*-chlorophenylmagnesium bromide and the corresponding ω-chlorinated *p*-chloroacetophenones I and II.[2] Dehydration of the carbinols III and IV with concentrated sulfuric acid resulted in the ethenes V and VI.[3]

$$p\text{-ClC}_6\text{H}_4\text{MgBr} + p\text{-ClC}_6\text{H}_4\text{COCHR}_1\text{R}_2 \longrightarrow$$

(I, R_1 = H, R_2 = Cl)
(II, R_1 = R_2 = Cl)

$$(p\text{-ClC}_6\text{H}_4)_2\text{C(OH)CHR}_1\text{R}_2 \longrightarrow (p\text{-ClC}_6\text{H}_4)_2\text{C=CR}_1\text{R}_2$$

(III, R_1 = H, R_2 = Cl) (V, R_1 = H, R_2 = Cl)
(IV, R_1 = R_2 = Cl) (VI, R_1 = R_2 = Cl)

An attempt to prepare trichloromethyl bis-(*p*-chlorophenyl)-carbinol by the same method failed. The reaction product of *p*-chlorophenylmagnesium bromide and ω,ω,ω,*p*-tetrachloroacetophenone[2] was a low-boiling mixture of compounds (b. p. at 12 mm., 90–140°) one of which was identified as ω,ω,*p*-trichloroacetophenone (II). The formation of II must be attributed to the reducing action of the Grignard reagent.

Experimental

Chloromethyl Bis-(*p*-chlorophenyl)-carbinol (III).—A mixture of magnesium turnings (4 g.), *p*-chlorobromobenzene (28.8 g.), a crystal of iodine, and dry ether (150 cc.) was heated under reflux until no more magnesium dissolved (two hours). Then a solution of ω,*p*-dichloroacetophenone[2] (I) (23 g.) in dry ether (300 cc.) was added over a period of fifteen minutes with stirring and cooling on a water-bath. The resulting reaction mixture was heated under gentle reflux for ten minutes, poured into a mixture of cracked ice (200 g.) and concentrated hydrochloric acid (15 cc.), and shaken in a separatory funnel. The ether layer was separated, washed well with water and the solvent removed. The residue was distilled yielding a viscous liquid b. p. (0.06 mm.) 162–165°, yield, 31 g. or 85%.

Anal. Calcd. for $C_{14}H_{11}OCl_3$: C, 55.72; H, 3.65; Cl, 35.33. Found: C, 56.36, 56.28; H, 3.70, 3.88; Cl, 35.21, 35.37.

1-Chloro-2,2-bis-(*p*-chlorophenyl)-ethene (V).—The crude carbinol III (1.0 g.) was added to concentrated sulfuric acid (10 cc.) and the reaction mixture stirred for four and one-half hours. The dark solution was poured on ice, the white solid filtered, washed with water, dried and crystallized from methanol, m. p. 60–63°, yield, 0.80 g. Further crystallization from methanol or petroleum ether raised the melting point to 63–64°.

Anal. Calcd. for $C_{14}H_9Cl_3$: C, 59.25; H, 3.17; Cl, 37.56. Found: C, 59.75, 59.60; H, 3.40, 3.38; Cl, 37.73, 37.53.

Dichloromethyl Bis-(*p*-chlorophenyl)-carbinol (IV).—This was prepared from ω,ω,*p*-trichloroacetophenone[2] (II) and *p*-chlorobromobenzene by the same method as was III, b. p. (1 mm.) 200–210°, m. p. 108–109° from petroleum ether (60–80°), yield 52%.

Anal. Calcd. for $C_{14}H_{10}OCl_4$: C, 50.01; H, 2.98; Cl, 42.23. Found: C, 50.49, 50.25; H, 3.61, 3.25; Cl, 42.58, 42.64.

1,1-Dichloro-2,2-bis-(*p*-chlorophenyl)-ethene (VI).—This was prepared by dehydration of IV with sulfuric acid (see V above); yield, 90%; m. p. 86–87°, no depression when mixed with an authentic sample of 1,1-dichloro-2,2-bis-(*p*-chlorophenyl)-ethene.[3]

RESEARCH LABORATORIES
DOMINION RUBBER CO., LTD.
GUELPH, ONTARIO

RECEIVED SEPTEMBER 8, 1949

(1) Present address, Department of Chemistry, University of Saskatchewan, Saskatoon, Sask.

(2) Gautier, *Ann. chim.*, [6] **14**, 395, 402, 403 (1888).

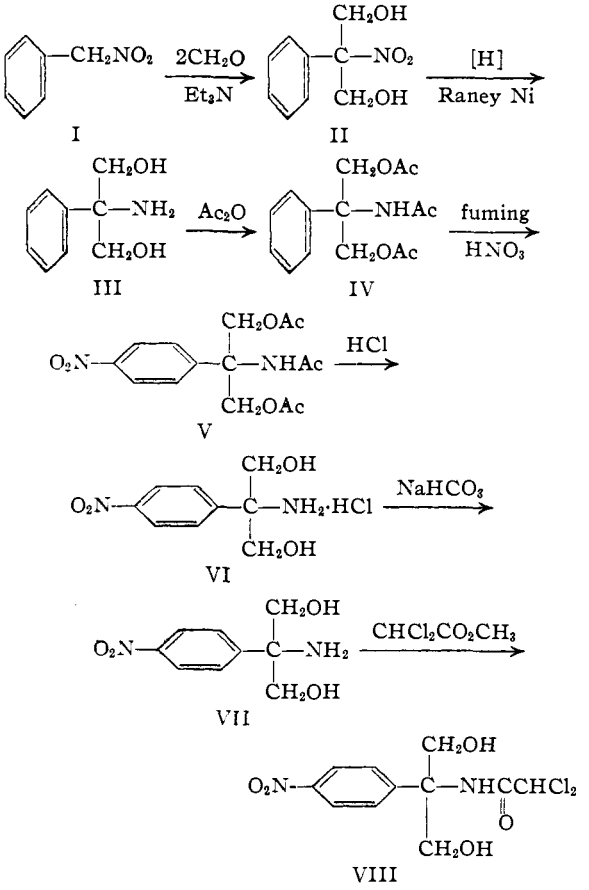
(3) Grummitt, Buck and Becker, THIS JOURNAL, **67**, 2265 (1945).

Synthesis of 2-Dichloroacetamido-2-*p*-nitrophenyl-1,3-propanediol, a Position Isomer of Chloramphenicol

BY P. M. RUOFF AND J. ROBERT MILLER[1]

In view of the marked activity against epidemic typhus, scrub typhus, typhoid fever and Rocky Mountain spotted fever reported for the antibiotic chloramphenicol,[2] D-*threo*-2-dichloroacetamido-1-*p*-nitrophenyl-1,3-propanediol, it appeared of interest to synthesize for biological screening a position isomer in which the *p*-nitrophenyl group was attached to the 2-position.

The synthesis of this isomer, 2-dichloroacetamido-2-nitrophenyl-1,3-propanediol, was carried out as illustrated in the following sequence of reactions



Phenylnitromethane (I) was prepared by the

(1) Bristol Laboratories, Inc., predoctoral fellow.

(2) See Controulis, Rebstock and Crooks, THIS JOURNAL, **71**, 2463 (1949), for the synthesis of and literature on chloramphenicol.

procedure of Black and Babers[3] and the 2-nitro-2-phenyl-1,3-propanediol (II) by the method of Fieser and Bates.[4]

Reduction of the 2-nitro-2-phenyl-1,3-propanediol (II) with platinum oxide at 35 p. s. i. failed, possibly due to a catalyst of low activity, but reduction with Raney nickel at 1140–1200 p. s. i. proceeded smoothly. Triacetylation of the amino compound (III) with acetic anhydride proceeded satisfactorily. The triacetyl derivative when nitrated with fuming nitric acid at −3 to 0° yielded an oil which could not be crystallized. However, when the oil was hydrolyzed with 10% hydrochloric acid, the crude 2-amino-2-*p*-nitrophenyl-1,3-propanediol hydrochloride (VI) was obtained as a solid which could be readily crystallized. The position of the nitro group was proved by alkaline permanganate oxidation[5] to *p*-nitrobenzoic acid which was identified by a mixed melt with an authentic sample of the acid and by a mixed melt of the *p*-bromophenacyl esters.[6]

Treatment of the hydrochloride with sodium bicarbonate in water precipitated the free base (VII), apparently sometimes as a hydrate and sometimes as a mixture of the hydrate and the anhydrous compound. Refluxing of the free base with one equivalent of methyl dichloroacetate in absolute ethanol for several hours yielded the 2-dichloroacetamido-2-*p*-nitrophenyl-1,3-propanediol (VIII).

Evidence for N-acetylation is based on the fact that the monoacylated base exhibited the same solubilities in water and in dilute hydrochloric acid while the unacylated free base was insoluble in water and readily soluble in dilute hydrochloric acid. Furthermore, when subjected to a Kunz hydrolysis[7] compound VIII gave no evidence of O-acylation.

Compounds III, IV, VI and VIII were submitted for antibacterial testing and were found to be devoid of activity against a variety of organisms.[8]

Acknowledgment is made to Dr. S. B. Binkley and Dr. L. C. Cheney of the Bristol Laboratories for their coöperation and encouragement.

Experimental[9]

Phenylnitromethane (I).—The procedure of Black and Babers[3] was followed. Attempted distillation of the crude product at 3 mm. using an air ebulliator resulted in pronounced decomposition as the boiling point was approached. Substitution of nitrogen for air in the ebulliator permitted smooth distillation at 2 mm.

2-Nitro-2-phenyl-1,3-propanediol (II).—This compound was prepared by the procedure of Fieser and Bates.[4]

2-Amino-2-phenyl-1,3-propanediol (III).—To a solution of 108 g. (0.55 mole) of 2-nitro-2-phenyl-1,3-propanediol in 1 liter of 95% alcohol was added approximately 300 g. (100 ml.) of commercial Raney nickel catalyst. The mixture was divided into two equal portions and each hydrogenated separately—one at an initial hydrogen pressure of 1200 p.s.i. and the other at 1140 p.s.i. In both cases the bulk of the hydrogen was taken up in ten minutes, when the maximum temperature of 60–75° was reached. No external heat was applied. Reduction was complete in forty minutes and no additional hydrogen was absorbed when the rocking was continued for another thirty minutes. The catalyst was filtered out and the filtrate concentrated at the aspirator. To the residual mixture of sirup and crystals 100 ml. of cold ether was added. The mixture was slurried until all the oil had disappeared, and the faintly colored crystals were washed with ether until entirely white. After thorough air drying the crystals weighed 45.7 g. (50%) m. p. 116–118.5°. The mother liquor yielded two additional crops totalling 6.3 g. and melting at 110–119° and 113–116°. A sample was recrystallized to a constant melting point from acetone and from ethyl acetate, m. p. 118–119°.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.64; H, 7.84. Found: C, 64.45; H, 7.75.

Triacetyl-2-amino-2-phenyl-1,3-propanediol (IV).—2-Amino-2-phenyl-1,3-propanediol (25.05 g., 0.15 mole) was acetylated in the usual fashion with 171 ml. of acetic anhydride. When the temperature had fallen to 35° the solution was refluxed for a few minutes and excess anhydride decomposed with cold water. Evaporation to a sirup *in vacuo* and addition of 600–700 ml. of ether yielded 27.7 g. of white crystals, m. p. 108.5–109°. Addition of petroleum ether to the mother liquor yielded another 9.5 g., m. p. 105–108°; total yield 37.2 g. (85%). The analytical sample was recrystallized from ether–petroleum ether and benzene, m. p. 108.5–109°.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.50; H, 6.70; N, 4.99.

2-Amino-2-*p*-nitrophenyl-1,3-propanediol Hydrochloride (VI).—In a beaker immersed in an ice-salt-bath 83 ml. of fuming nitric acid (sp. gr. 1.5) was cooled to −3° and to it 35.16 g. (0.12 mole) of triacetyl-2-amino-2-phenyl-1,3-propanediol was added portionwise with continuous shaking. The addition was carried out at such a rate as to maintain a temperature of −3 to 0°. Each portion dissolved immediately with the formation of a transient orange color. No gas was evolved. The yellow reaction solution was allowed to stand in the cold for an additional five minutes and then plunged into 420 ml. of ice and water. The resulting solution was extracted three times with chloroform (240, 120, 120 ml.) and the combined chloroform extracts washed with 60 ml. of saturated sodium bicarbonate solution with removal of most of the yellow color. The chloroform layer was taken to dryness at the aspirator following a water wash. The residual thick, slightly yellow sirup could not be crystallized. After refluxing the sirup for two hours in 540 ml. of 10% hydrochloric acid the solution was cooled and extracted three times with chloroform (100, 100, 50 ml.) to remove all the color. Evaporation of the chloroform extracts left an insignificant amount of yellow oil and solid. The water layer was evaporated to dryness *in vacuo* on a bath of 50–60° and finally at 100° at 20 mm. to remove the last traces of water. The white solid crystalline residue was dissolved in 400 ml. of absolute ethanol and the solution diluted with 500 ml. of anhydrous ether. On cooling overnight it deposited crystals which were washed with dry ether and dried *in vacuo*, yield 15.5 g. (52%), m. p. 208–210° (sealed tube). The mother liquor plus washings on standing a few days at 5° deposited another 2.6 g. melting at 206–210° (sealed tube). Manipulation of the mother liquor yielded no more of the para isomer; total yield 18.1

(3) Black and Babers, "Organic Syntheses," Coll. Vol. II, 512 (1943).

(4) Fieser and Bates, THIS JOURNAL, **68**, 2249 (1946).

(5) The oxidation procedure followed was that described by Shriner and Fuson, "Identification of Organic Compounds," 2d ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 164.

(6) The procedure for the preparation of the esters was that of Shriner and Fuson, *ibid.*, p. 132.

(7) Kunz and Hudson, THIS JOURNAL, **48**, 1978 (1936). The procedure described by Wolfrom, Konigsberg and Soltzberg, *ibid.*, **58**, 490 (1936), was used.

(8) We wish to thank Dr. George Valley of the Bristol Laboratories for the report on the antibacterial activity of these compounds.

(9) All melting points are uncorrected unless otherwise specified.

g. (61%). Recrystallization of the first crop from absolute ethanol–dry ether yielded two crops totalling 11.5 g. (39%) and both melting at 212–213° (sealed tube).

Anal. Calcd. for $C_9H_{13}ClN_2O_4$: C, 43.47; H, 5.27. Found: C, 43.57; H, 5.10.

Oxidation of 2-Amino-2-*p*-nitrophenyl-1,3-propanediol Hydrochloride (VI).—Oxidation of 0.52 g. (0.0021 mole) of the analytically pure hydrochloride with alkaline permanganate according to the procedure described by Shriner and Fuson[5] gave a 70% yield of the nitrobenzoic acid. Recrystallization from water and ether–petroleum ether and precipitation from an ammonia solution by addition of hydrochloric acid raised the melting point to 240.5° (cor.). The acid was identified as the para isomer by mixed melting point with an authentic sample (no depression) and by a mixed melt of the *p*-bromophenacyl esters (no depression). The esters were prepared by the procedure described in Shriner and Fuson.[6]

2-Amino-2-*p*-nitrophenyl-1,3-propanediol (VII).—To a solution of 2.48 g. (0.01 mole) of 2-amino-2-*p*-nitrophenyl-1,3-propanediol hydrochloride in 40 ml. of water was added 0.92 g. (0.01 mole plus 10%) of sodium bicarbonate. Shortly after evolution of carbon dioxide had subsided, crystals began to separate. The product was washed liberally with cold water and dried one and one-quarter hours at room temperature at <1 mm., yield 1.90 g. (*ca.* 90%), m. p. 114.5–115°. One recrystallization from ethyl acetate raised the melting point to 137.5–138°.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70. Found: C, 50.97; H, 5.63.

It seems probable that the original crystals (m. p. 114.5–115°) described above were a hydrate. Further drying of these crystals at room temperature at <1 mm. for one and one-half hours raised the melting point to 135–138°. An attempt to "rehydrate" a bit of the sample used for analysis by dissolving it in dilute hydrochloric acid and reprecipitating with sodium bicarbonate resulting in crystals which, when dried at room temperature at <1 mm. for one and one-half hours, melted at 135–136°. A second preparation of the free base was carried out in the same way as above except that a more concentrated water solution was employed. After being dried for five hours at room temperature at <1 mm. the product melted partially at 115° and partially at 130–132°. A very rapid determination of the melting point gave a value of *ca.* 120°. When this material was further dried in a drying pistol for five hours at 100° at <1 mm. it melted at 136–138°.

2-Dichloroacetamido-2-*p*-nitrophenyl-1,3-propanediol (VIII).—A mixture of 1.65 g. (*ca.* 0.008 mole) of 2-amino-2-*p*-nitrophenyl-1,3-propanediol (m. p. partially at 115° and partially at 132°), 1.14 g. (0.008 mole) of methyl dichloroacetate and 10 ml. of absolute ethanol was heated to solution and the solution refluxed for eight and one-half hours in a calcium chloride protected system. The solvent was evaporated on the steam-bath and the residual liquid dried at room temperature at < 1 mm. to remove unreacted ester. The last traces of unreacted ester were removed at 100° at <1 mm. No crystals could be obtained from the yellow sirup. A solution of the sirup in 75 ml. of ice-cold ethyl acetate was extracted with 10 ml. of ice-cold dilute hydrochloric acid and washed with 5 ml. of saturated sodium bicarbonate solution followed by two 5-ml. water washes. The ethyl acetate layer was evaporated to a gum on the steam-bath and the gum dried by dissolving it in absolute ethanol, treating with charcoal, filtering, and evaporating to dryness. The partially solid residue was taken up in acetone, diluted with benzene, concentrated to cloudiness typical of incipient crystallization, and the milky solution decanted from a fairly large quantity of precipitated gelatinous material. On being allowed to cool slowly overnight the decantate produced 1.2 g. (46%) of white needle rosettes, m. p. 123–128°. After being recrystallized from chloroform–ligroin and acetone–benzene it amounted to 0.9 g. (35%) and melted at 130.5–132.5°. A constant melting point of 132.5–133° was obtained by further recrystallizations from acetone–benzene and chloroform–ligroin.

Anal. Calcd. for $C_{11}H_{12}Cl_2N_2O_5$: C, 40.88; H, 3.74. Found: C, 41.23; H, 3.85.

DEPARTMENT OF CHEMISTRY
SYRACUSE UNIVERSITY
SYRACUSE 10, NEW YORK RECEIVED SEPTEMBER 6, 1949

A Safe Method for the Isolation of Acetyl Peroxide

BY E. S. SHANLEY

Acetyl peroxide is a versatile reagent useful in various connections where free radicals are desired. The preparation of acetyl peroxide is straightforward[1] but isolation of the product is very hazardous because the dry crystals detonate upon the slightest mechanical disturbance; serious accidents have been reported from this cause.[2]

This note reports upon a relatively safe way to isolate acetyl peroxide from the commercially available 25% solution in dimethyl phthalate.[3]

The rather high vapor pressure of acetyl peroxide suggested that it might be possible to volatilize the material from the DMP solution. This was successfully accomplished in a still consisting of an 18-mm. test-tube supported inside a 24-mm. side-arm test-tube by means of a tightly fitting rubber stopper. An outlet tube with stopcock was fused to the bottom of the outer test-tube.

With this stopcock closed, a 2-ml. charge of 25% acetyl peroxide in DMP was placed in the outer tube, after which the inner tube with stopper was inserted and adjusted to about a 5-mm. clearance above the liquid level. A mixture of hydrochloric acid and ice was then placed in the open inner tube, after which the still was evacuated through the side arm to a pressure of about 1 or 2 mm. The outer tube was not heated. After about an hour, the lower end of the inner "condenser" tube was covered with white crystalline material. The crystals were found to melt at about 30° and to detonate when struck but not when merely touched. The active oxygen content was found by iodometric titration to be almost 11%. It was concluded that the distillate contained about 80% acetyl peroxide with dimethyl phthalate as the most likely impurity.

It was found possible to estimate the amount of acetyl peroxide on the condenser by measuring the active oxygen loss from the DMP solution during distillation. The bottom drain was used to draw off the spent solution, and to admit any desired solvent or reaction mixture which could then be drawn up far enough to dissolve the acetyl peroxide from the condenser. This procedure constitutes a safe way to obtain a known small weight of fairly pure acetyl peroxide in any desired reaction mixture.

(1) S. Gambarjan, *Ber.*, **42**, 4010 (1909).

(2) L. P. Kuhn, *Chem. Eng. News*, **26**, 3197 (1948); E. S. Shanley, *ibid.*, **27**, 175 (1949).

(3) Product of Buffalo Electro-Chemical Company, Inc., Buffalo, N. Y.

RESEARCH DEPARTMENT
BUFFALO ELECTRO-CHEMICAL COMPANY, INC.
BUFFALO, N. Y. RECEIVED SEPTEMBER 6, 1949

m-Trifluoromethylphenyl Substituted Alcohols

BY H. HARRY SZMANT, JOSEPH F. ANZENBERGER AND ROBERT HARTLE[1]

By allowing *m*-trifluoromethylphenylmagnesium bromide to react with formaldehyde, ethyl-

(1) Present address: Battelle Memorial Institute, Columbus, Ohio.