Derivatives of Diphenylacetic and Diphenylpropionic Acids

BENJAMIN BLANK, FRANCIS R. PFEIFFER, and JAMES F. KERWIN
Research Division, Smith Kline & French Laboratories, Philadelphia, Pa. 19101

The preparation of basic derivatives of diphenylacetic and diphenylpropionic acids and intermediates required in their synthesis is described (I through XXI). Compounds VI, IX, X, and XIX were screened for natriuretic activity and found to have marginal activity. Evidence is presented to show that nitration of bis(*p*-tolyl)acetic acid and 2,2-bis(*p*-tolyl)propionic acid gave bis(3-nitro-4-tolyl)acetic acid and 2,2-bis(3-nitro-4-tolyl)propionic acid.

IN a previous communication (*16*), the preparation of a number of esters and ketones related to diphenylacetic acid was described. Subsequent biological screening of these compounds showed one, β-diethylaminoethyl 2,2-bis(3-amino-4-tolyl)propionate, to have natriuretic activity, as evidenced by its ability to elevate sodium excretion in rats, which were on a sodium-deficient diet and which had been given an excess of water and salt prior to drug administration (*11*). Consequently, several similar amines were prepared and tested. The compounds prepared together with appropriate analytical and physical data are listed in Table I.

Di(*p*-tolyl)acetic acid (*5*) prepared in 80% yield by the hydrolysis and decarboxylation of ethyl di(*p*-tolyl)malonate (*6*) was nitrated below 5° C. with a mixture of 70% and red fuming nitric acids. The resulting bis(3-nitro-4-tolyl)-acetic acid (I) was converted to the acid chloride and then to the amide III and ester V (*16*). Hydrogenation of the nitro ester V yielded β-diethylaminoethyl bis(3-amino-4-tolyl)acetate (VI) isolated as the trihydrochloride. Dehydration of III with refluxing acetic anhydride gave bis(3-nitro-4-tolyl)acetonitrile (IV) while hydrogenation of III gave bis(3-amino-4-tolyl)acetamide (VII). Acetic anhydride dehydration of VII produced the tetraacetyl nitrile VIII which was alkylated with β-diethylaminoethyl chloride to yield, eventually, 2,2-bis(3-acetamido-4-tolyl)-4-diethylaminobutyronitrile (IX).

Similar reactions converted 2,2-bis(3-nitro-4-tolyl)propionic acid (*7*, *8*) to X, XI, and XII. Lithium aluminum hydride reduction of 2,2-bis(*p*-tolyl)propionic acid (*8*) led to the corresponding propanol (*1*), which was acetylated and nitrated to give 1-acetoxy-2,2-bis(3-nitro-4-tolyl)propane (XIII). Basic hydrolysis of XIII gave the alcohol XIV. Catalytic hydrogenation of XIII gave the diamine XV which was hydrolyzed to the diamino alcohol XVI. The phthalimide XVII (resulting from the reaction of XV with phthalic anhydride) when heated with aqueous methanolic carbonate gave the phthalamido alcohol XVIII.

Ester XIX was obtained from 4-diethylamino-2,2-diphenylbutanoic acid (*3*) and β-diethylaminoethyl chloride using the method of Horenstein and Pählicke (*9*). Bromo-3,3′-dinitrodiphenylmethane resulted from the bromination of 3,3′-dinitrobenzhydrol (*4*) with phosphorus tribromide (*13*). 3,3′-Diphthalimidodiphenylmethane was obtained by phthaloylation of 3,3′-diaminodiphenylmethane (*12*).

Since I and 2,2-bis(3-nitro-4-tolyl)propionic acid were prepared by nitration of bis(*p*-tolyl)acetic acid and 2,2-bis-(*p*-tolyl)propionic acid, the position of the nitro groups in the nitrated compounds was determined by oxidizing these compounds with chromic acid to the known 4,4′-

Table I. Derivatives of Diphenyl

(4-*Y*-3-*Z*-

Compd.	R	*X*	*Y*	*Z*	M.P., ° C.[a]	Yield, %
I	H	CO_2H	CH_3	NO_2	148–149	81
II	H	CO_2CH_3	CH_3	NO_2	102–104	70
III	H	$CONH_2$	CH_3	NO_2	184–186	78
IV	H	CN	CH_3	NO_2	152–154	78
V	H	$CO_2(CH_2)_2N(C_2H_5)_2$	CH_3	NO_2	146[c]	66
VI	H	$CO_2(CH_2)_2N(C_2H_5)_2$	CH_3	NH_2	164–167[c]	56
VII	H	$CONH_2$	CH_3	NH_2	165–168	100
VIII	H	CN	CH_3	$N(COCH_3)_2$	158–159	45
IX	$(C_2H_5)_2N(CH_2)_2$	CN	CH_3	$NHCOCH_3$	155–156[c]	30
X	CH_3	$CONH(CH_2)_2N(C_2H_5)_2$	CH_3	NH_2	245[c]	
XI	CH_3	CO_2CH_3	CH_3	NO_2	93–95	67
XII	CH_3	CO_2CH_3	CH_3	NH_2	247–249	72
XIII	CH_3	CH_2OCOCH_3	CH_3	NO_2	99–101	
XIV	CH_3	CH_2OH	CH_3	NO_2	95–97	88
XV	CH_3	CH_2OCOCH_3	CH_3	NH_2	291–293[c]	
XVI	CH_3	CH_2OH	CH_3	NH_2	265–267[c]	
XVII	CH_3	CH_2OCOCH_3	CH_3	$N\genfrac{<}{>}{0pt}{}{CO}{CO}C_6H_4$	258–261	
XVIII	CH_3	CH_2OH	CH_3	$\cdot NHCOC_6H_4$—*o*—COOH	143[c]	
XIX	$(C_2H_5)_2N(CH_2)_2$	$CO_2(CH_2)_2N(C_2H_5)_2$	H		160–162	77
XX	H	Br	H	NO_2	154–156	92
XXI	H	H	H	$N\genfrac{<}{>}{0pt}{}{CO}{CO}C_6H_4$	245–247	66

[a] Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are corrected.
[b] 1. Toluene, 2. petroleum ether (b.p. 40° to 60° C.), 3. ethanol, 4. acetone, 5. 1-butanol, 6. ethyl acetate, 7. 1-propanol, 8. hexane, 9. methanol, 10. ether, 11. water, 12. chloroform, 13.

dimethyl-3,3′-dinitrobenzophenone (*10, 15*). These benzophenone samples were compared with a sample of the benzophenone prepared from bis(*p*-tolyl)methane according to the directions of Stephen, Short, and Gladding (*15*). The three samples of 4,4′-dimethyl-3,3′-dinitrobenzophenone had identical infrared spectra, melting points, mixture melting points, and R_f's on thin-layer chromatograms in three different solvent systems.

Compound XIII, obtained by nitration of 1-acetoxy-2,2-bis(*p*-tolyl)propane, when subjected to chromic acid oxidation, was recovered unchanged. Therefore, the ester XII was reduced with lithium aluminum hydride to 2,2-bis-(3-amino-4-tolyl)propan-1-ol (XVI). Compound XVI was compared with the amino alcohol prepared by hydrolysis of XV. The two were identical by the criteria used to establish the likeness of the 4,4′-dimethyl-3,3′-dinitrobenzophenone samples. Both alcohol samples contained a trace contaminant of unknown origin and structure which moved faster than the major component on thin-layer chromatograms. Compounds VI, IX, X, and XIX were examined in a natriuretic screen at a dose of 100 mg. per kg. (*11*). Compound X was toxic and the others had, at best, marginal activity.

EXPERIMENTAL

***N*-(β-Diethylaminoethyl)-2,2-bis(3-amino-4-tolyl)propionamide Trihydrochloride Sesquihydrate (X).** A mixture of 9.8 grams (0.03 mole) of 2,2-bis(3-nitro-4-tolyl)propionic acid (*7, 8*) and 15 ml. of thionyl chloride was refluxed for 2 hours. The excess thionyl chloride was removed and the residue was evaporated several times with toluene. A solution of the residue and 3.5 grams of *N,N*-diethylethylenediamine in 30 ml. of dry benzene was refluxed for 2 hours. The solution was cooled and washed with dilute hydrochloric acid. The acidic washes were combined, neutralized, and extracted with benzene. The benzene was dried and distilled. The residue (ca. 8.7 grams) was hydrogenated in ethanol (0.5 gram platinum oxide) under an initial pressure of 3 atm. of hydrogen. The reduction was completed in 2 hours. The catalyst was removed, the filtrate was concentrated, and the residue was dried by azeotropic distillations with ethanol. The resulting gum was dissolved in benzene and placed on a column of Fisher alumina. The column was washed successively with benzene, ether, chloroform, and ethyl acetate. The eluates were tested for the presence of diazotizable amine (2). The chloroform and ethyl acetate fractions gave positive reactions. These eluates were concentrated separately, dissolved in small volumes of ethyl acetate, and converted to identical hydrochlorides. The salts (total of 6 grams, m.p. 195° C. with decomposition) were combined and recrystallized from absolute ethanol-ethyl acetate and then from methanol-ethyl acetate to give material which decomposed at 245° C. after preliminary softening and sintering from 200° C.

4,4′-Dimethyl-3,3′-dinitrobenzophenone. A solution of 1.65 grams (5 mmoles) of I in 100 ml. of acetic acid was stirred at room temperature while 5 grams of chromic oxide was added. The solution was stirred for an additional 2 hours, and the reaction was quenched by pouring the solution into several volumes of cold water. The resulting solid was filtered, washed with water, and recrystallized from ethanol-water. Yield: 0.45 gram, m.p. 145–147° C.

A mixture of 1.72 grams (5 mmoles) of 2,2-bis(3-nitro-4-tolyl)propionic acid (*7, 8*), 5 grams of chromic oxide, and 100 ml. of acetic acid was stirred under reflux for 40 minutes. The reaction was quenched with several volumes of ice water. The product was isolated and purified as above. Yield 0.1 gram, m.p. 145–146° C. These yields of benzophenone are comparable with that reported by Shirley and Goreau (*14*) in a similar reaction.

4,4′-Dimethyl-3,3′-dinitrobenzophenone prepared from bis(*p*-tolyl)methane melted at 144–145° C.; literature (*15*) m.p. 144° C. The mixture melting points of this material with the products formed above were in each instance 144–146° C.

acetic and Diphenylpropionic Acids

$C_6H_3)_2$—CR-X

Recryst., Solvent[b]	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
		Calcd.	Obsd.	Calcd.	Obsd.	Calcd.	Obsd.
1, 2	$C_{16}H_{14}N_2O_6$	58.18	58.01	4.27	4.43	8.48	8.61
3	$C_{17}H_{16}N_2O_6$	59.30	59.30	4.68	4.93	8.14	8.11
3	$C_{16}H_{15}N_3O_5$	58.36	58.35	4.59	4.63	12.76	12.52
1	$C_{16}H_{13}N_3O_4$	61.73	62.14	4.21	4.39	13.50	13.29
4, 2	$C_{22}H_{27}N_3O_6 \cdot HCl$	56.71	56.70	6.06	6.11	9.02	9.16
5, 6	$C_{22}H_{31}N_3O_2 \cdot 3HCl$	55.18	54.99	7.16	7.36	...	...
7, 8	$C_{16}H_{19}N_3O$	71.35	71.27	7.11	7.19	...	...
9	$C_{24}H_{35}N_3O_4$	68.72	68.85	6.01	6.06	10.02	9.86
5, 10	$C_{26}H_{34}N_4O_2 \cdot HCl$[d]	62.70	62.65	7.69	7.78	11.25	11.26
9, 6	$C_{23}H_{34}N_4O \cdot 3HCl$[d]	53.23	53.17	7.77	7.69	10.80	10.49
9	$C_{18}H_{18}N_2O_6$	60.33	60.53	5.06	5.16	7.82	7.54
3, 10	$C_{18}H_{22}N_2O_2 \cdot 2HCl$[e]					7.20	7.31
9	$C_{19}H_{20}N_2O_6$	61.28	61.07	5.41	5.46	7.52	7.82
10, 2	$C_{17}H_{18}N_2O_5$	61.81	61.50	5.49	5.50	8.48	8.29
4, 11	$C_{19}H_{24}N_2O_2 \cdot H_2SO_4$[f]	55.59	55.67	6.38	6.41	6.82	6.70
9	$C_{17}H_{22}N_2O \cdot H_2SO_4$[g]	55.42	55.53	6.56	6.84	7.60	7.58
6, 2	$C_{35}H_{28}N_2O_6$	73.41	73.11	4.93	5.25	4.89	4.89
12, 2	$C_{33}H_{30}N_2O_7$	69.95	70.38	5.34	5.18	4.94	4.72
9, 6	$C_{26}H_{38}N_2O_2 \cdot 2HCl$[h]	60.10	59.82	8.54	8.72	5.39	5.60
12, 2	$C_{13}H_9BrN_2O_4$	46.31	46.54	2.69	3.03	8.31	8.42
13	$C_{29}H_{18}N_2O_4$	75.99	75.70	3.96	3.95	6.11	6.07

acetic acid. [c] Melted with decomposition. [d] Sesquihydrate. [e] Hydrate; Calcd.: Cl., 18.21; Obsd.: Cl., 18.03. [f] Calcd.: S, 7.81; Obsd.: S., 8.05. [g] Calcd.: S, 8.70; Obsd.: S., 8.65. [h] Dihydrate.

LITERATURE CITED

(1) Blank, B., Kerwin, J.F. (to Smith Kline & French Laboratories), U.S. Patent **3,203,991** (Aug. 31, 1965).
(2) Cheronis, N.D., Entrikin, J.B., "Identification of Organic Compounds," p. 132, Interscience, New York, 1963.
(3) Clarke, R.L., Mooradian, A., Lucas, P., Slauson, T.J., *J. Am. Chem. Soc.* 71, 2821 (1949).
(4) Deno, N.C., Schriesheim, A., *Ibid.*, **77**, 3051 (1955).
(5) Dox, A.W., Thomas, A., *Ibid.*, **45**, 1811 (1923).
(6) Fritsch, P., Feldman, F., *Ann.* **306**, 72 (1899).
(7) Haiss, A., *Ber.* **15**, 1474 (1882).
(8) Holmes, R.B., Hill, A.J. (to American Cyanamid Co.), U.S. Patent **2,432,025** (June 24, 1947).
(9) Horenstein, H., Pählicke, H., *Ber.* **71** 1644 (1938).
(10) Lange, K., Zufall, A., *Ann.* **271**, 1 (1892).
(11) Saunders, H.L., Steciw, B., Kostos, V., Tomaszewski, J., *Steroids*, **7**, 513 (1966).
(12) Schöpff, M., *Ber.* **27**, 2321 (1894).
(13) Shirley, D.A., "Preparation of Organic Intermediates," p. 136, Wiley, New York, 1951.
(14) Shirley, D.A., Goreau, T.D., *J. Am. Chem. Soc.* **72**, 3051 (1950).
(15) Stephen, H., Short, W.F., Gladding, G., *J. Chem. Soc.* **117**, 510 (1920).
(16) Wolff, M.E., Owings, F.F., *J. Org. Chem.* **25**, 1235 (1960).

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Enthalpy of Formation of Chlorine Pentafluoride

W. R. BISBEE[1], J. V. HAMILTON[2], J. M. GERHAUSER[3], and RONALD RUSHWORTH
Research Division, Rocketdyne, A Division of North American Rockwell Corp., Canoga Park, Calif. 91304

The enthalpy of formation of liquid chlorine pentafluoride was determined by two independent sets of experiments. In one, the compound reacted with hydrogen and in the other with ammonia. From the measured enthalpies of reaction and the known enthalpies of formation of products and reactants, corrected to their standard states, the standard enthalpy of formation of ClF_5 was derived. The enthalpy of formation calculated on the basis of the hydrogen reaction was $\Delta H_f^\circ(ClF_5) = -66.4 \pm 6.9$ kcal. per mole. Calculated on the basis of the ammonia reaction, $\Delta H_f^\circ(ClF_5) = -59.9 \pm 3.9$ kcal. per mole. Assuming that one questionable hydrogen run was invalid, the enthalpy of formation calculated with the data from both sets of experiments was $\Delta H_f^\circ(ClF_5) = -60.9 \pm 4.5$ kcal. per mole.

AS PART OF A PROGRAM to characterize the interhalogen, chlorine pentafluoride, its enthalpy of formation was determined by two independent sets of experiments. In one set, the compound reacted with hydrogen, and in the other set with ammonia.

EXPERIMENTAL

Materials. The chlorine pentafluoride used in both the hydrogen and ammonia reactions was prepared at Rocketdyne. Gas chromatographic analysis of the sample showed the following impurities (weight per cent): F_2, 0.1; Cl_2, 0.5; ClF, 0.2; and ClO_2, 0.1. The assay of ClF_5 was 99.1%; the F/Cl molar ratio was 4.89 to 1.

The hydrogen was a prepurified grade of 99.9% minimum purity (Matheson Co.).

The ammonia was a commercial grade which, by mass spectrometer analysis, contained considerable nitrogen. Therefore, the ammonia was vacuum-distilled over metallic sodium into a stainless steel container. After the transfer, the condensed ammonia was placed under vacuum to remove any volatile contaminants. This produced ammonia of a minimum purity of 99.9%.

The impurities (F_2, Cl_2, ClO_2, and ClF) in the starting materials, which are reactive under the conditions of these experiments, were accounted for in the calculations.

Chlorine pentafluoride is a very toxic chemical, and inhalation of even dilute concentrations should be avoided. Until more systematic and definitive studies have been conducted, the toxicity level now utilized for ClF_5 is that previously established for ClF_3 by the American Conference of Governmental Industrial Hygienists. This level is expressed as a threshold limit value (TLV) of 0.1 p.p.m., by volume, or 0.4 mg. per cu. meter. (The TLV represents the average concentration to which the average human can be safely exposed on a daily basis without adverse effects.) The odor of ClF_5 has been used as a warning of potential danger. ClF_5 vapors have been inhaled for short periods without any adverse effects. Any contact of this corrosive compound with living tissue will result in severe chemical burns that are difficult to heal.

Notwithstanding the toxicity of ClF_5, the greatest hazards associated with this strong oxidizer lie in its extreme reactivity with most inorganic and organic materials. These chemical reactions are often followed by fire and/or explosion, although ClF_5 itself is nonflammable in air and insensitive to mechanical shock.

Calibration. The energy equivalent of the calorimeter was determined in the standard manner by combustion of National Bureau of Standards Sample 39h benzoic acid. The combustions were carried out with the sample ampoule in place and pressurized with He to prevent collapse of the diaphragm.

The standard calorimeter system for these series of experiments was specified as the Bureau of Standards calorimeter containing the Parr fluorine combustion bomb plus sample ampoule. The standard bomb was defined as the Parr fluorine combustion bomb plus sample ampoule without

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[1] Present address: Cary Instruments, Monrovia, Calif. 91016
[2] Present address: Tarrant County Junior College, Fort Worth, Tex. 76101
[3] Present address: San Fernando Valley State College, Northridge, Calif. 91324