Preparation of Pyrazinoyldiazomethane and ω-Chloromethylpyrazinoyl Ketone

BY MORTON D. GLANTZ[1] AND PAUL E. SPOERRI

Pyrazinoic acid was prepared according to the method of Hall and Spoerri.[2]

Pyrazinoyl Chloride.[3]—Five-tenths (0.5) gram of pyrazinoic acid was treated with 10 ml. of thionyl chloride and the mixture, protected by a calcium chloride tube, was refluxed for two hours to give a clear purple solution. Evaporation of excess reagent gave a purple residue which was sublimed to yield colorless needles. The pyrazinoyl chloride thus formed turns somewhat yellow on exposure to air; m. p. with decomposition, 55–56°.

Pyrazinoyldiazomethane.—A dried ethereal solution of diazomethane[4] was cooled to 0–5°. To this was added, with continuous cooling and efficient stirring in small portions, freshly prepared pyrazinoyl chloride. A brisk evolution occurred as the acid chloride was added. The solution was allowed to stand overnight at room temperature, after which it was filtered and the ether removed under reduced pressure. A golden residue is thus formed. This was recrystallized several times from low-boiling petroleum ether; m. p. 85.5–86°.

A sample of the material was tested with a few drops of concentrated hydrochloric acid. A vigorous evolution of nitrogen took place.

Anal. Calcd. for $C_6H_4ON_4$: C, 48.65; H, 2.72. Found: C, 48.14; H, 2.77. Side-chain nitrogen calcd., 18.92. Found: 18.63.

ω-Chloromethylpyrazinoyl Ketone.—A solution of pyrazinoyldiazomethane in anhydrous ether was treated with gaseous anhydrous hydrogen chloride until no further nitrogen was evolved. The white suspension was boiled gently to remove the excess hydrogen chloride and then extracted with hot low-boiling petroleum ether and allowed to crystallize; m. p. 89–89.5°.

Anal. Calcd. for $C_6H_5ON_2Cl$: C, 46.02; H, 3.22. Found: C, 45.85; H, 3.09.

The Wolff[5] rearrangement on the pyrazinoyldiazomethane did not prove successful.

---

(1) Department of Chemistry, Brooklyn College, Brooklyn, N. Y.

(2) Hall and Spoerri, THIS JOURNAL, **62**, 664 (1940).

(3) Meltzner, Thesis, Polytechnic Institute of Brooklyn, 1949.

(4) Arndt, *Org. Syntheses*, **15**, 4 (1935).

(5) Wolff, *Ann.*, **394**, 25 (1912).

DEPARTMENT OF CHEMISTRY
POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN NEW YORK

RECEIVED MARCH 29, 1950

Alanine, Glycine and Proline Contents of Casein and its Components[1]

BY WILLIAM G. GORDON, WILLIAM F. SEMMETT AND MAURICE BENDER

In a previous paper[2] on the amino acid composition of casein, α-casein and β-casein, alanine analyses were listed as provisional. We wish now to record results of more accurate alanine determinations as well as revised figures for glycine and proline. The present analyses were made by the radioisotope derivative technique of Keston, Udenfriend and Cannan,[3] a method both highly specific and accurate. γ-Casein, a third component of casein, recently isolated in this laboratory[4] has also been analyzed for these amino acids. Average results (corrected for moisture and true ash) of triplicate analyses, shown in the table are believed to be more accurate than our previously published figures. The values for whole casein are now in closer agreement with reliable figures in the literature (alanine, 3.5%[5]; glycine, 1.9%[6]; and proline, 10.5%[7]).

	Alanine	Glycine	Proline
	G./100 g. protein		
Whole casein	3.20	2.00	10.6
α-Casein	3.81	2.26	7.47
β-Casein	1.99	1.56	15.1
γ-Casein	2.29	1.48	17.0

The radioisotope derivative technique was used also for determination of hydroxyproline in protein hydrolyzates according to the method of Keston,[8] *et al.*, and showed that whole casein contains less than 0.1% of this amino acid.

---

(1) These analyses are included in a thesis submitted by M. Bender to the Graduate School of Georgetown University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Article not copyrighted.

(2) Gordon, Semmett, Cable and Morris, THIS JOURNAL, **71**, 3293 (1949).

(3) (a) Keston, Udenfriend and Cannan, *ibid.*, **71**, 249 (1949). (b) The I^{131} used in this investigation was supplied by Carbide and Carbon Chemicals Corp., Oak Ridge National Laboratory, on allocation from the Isotopes Division, U. S. Atomic Energy Commission.

(4) Hipp, Groves, Custer and McMeekin, Am. Chem. Soc., Philadelphia meeting, April, 1950.

(5) Tristram, *Biochem. J.*, **40**, 721 (1946).

(6) Shankman, Camien and Dunn, *J. Biol. Chem.*, **168**, 51 (1947).

(7) Dunn, McClure and Merrifield, *ibid.*, **179**, 11 (1949).

(8) Keston, Udenfriend, Levy and Cannan, personal communication.

EASTERN REGIONAL RESEARCH LABORATORY
UNITED STATES DEPARTMENT OF AGRICULTURE
AGRICULTURAL RESEARCH ADMINISTRATION
PHILADELPHIA 18, PENNSYLVANIA

RECEIVED APRIL 1, 1950

Dichlorodiphenyltrichloroethane. II. Analogs. *p,p'*-DFDT and its Degradation Products[1]

BY F. A. GUNTHER AND R. C. BLINN

Bradlow and VanderWerf[2] have reported the only available systematic study of the preparation and chemical composition of the insecticidal material 2,2-bis-(*p*-fluorophenyl)-1,1,1-trichloroethane (*p,p'*-DFDT). Despite its expensive synthesis when carried out in the usual manner, the fact that this compound has consistently been superior to 2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane (*p,p'*-DDT) when tested repeatedly against a number of species of insects in our own laboratories[3] has warranted the continuation of the investigation of this compound, begun in 1946. Because the mechanism(s) of action of the DDT-

---

(1) Paper No. 642, University of California Citrus Experiment Station, Riverside, California. Presented before the Division of Organic Chemistry of the American Chemical Society, San Francisco, March, 1949.

(2) Bradlow and VanderWerf, THIS JOURNAL, **69**, 662 (1947); *cf.* Iris and Mendizabal, *Rev. inst. salubridad y enfermedad. trop.*, **8**, 63 (1947); *Chem. Abstracts*, **42**, 1920i (1948).

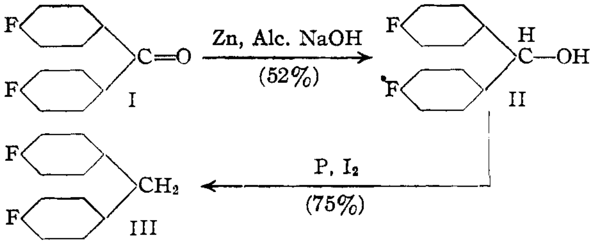
(3) Metcalf, *J. Econ. Entomol.*, **41**, 416 (1948).

type compounds is still obscure, it has also been of interest to prepare certain specific type-derivatives and degradation products for subsequent insecticidal evaluation when injected internally as well as applied topically to insects. It is hoped that such toxicological information will ultimately shed light upon the exact nature of the toxophoric group within the DDT-type molecule or else produced from such a molecule as it migrates from the epicuticle through the many layers of living tissue to the site of action.

Our transformation of present interest, however, is the stepwise reduction of 4,4′-difluorobenzophenone to the corresponding methane, a compound previously unrecorded in the available literature. Whereas the corresponding dichlorodiphenylmethane degraded from *p,p′*-DDT is easily obtained by the hydrolytic method of White and Sweeney,[4] Bradlow and VanderWerf[2] were unable to obtain the desired difluorodiphenylmethane by this method. We have confirmed these findings.

Unsuccessful efforts to produce the desired methane from the 4,4′-difluorobenzophenone included conversion to the thioacetal, followed by hydrogenolysis[5] with zinc and hydrochloric acid in 70% ethanol. The thioacetal of the dichlorodiphenyl ketone was successfully hydrogenolyzed to the methane derivative by this method, but the difluorodiphenyl ketone yielded anomalous products.

The desired 4,4′-difluorodiphenylmethane(III) was obtained in 39% over-all yield, however, by the following sequence of reactions



The carbinol (II) is a new compound. Its structure was confirmed by ultimate analysis and by the preparation of both its *p*-nitrobenzoate and a dinitro derivative. Our 4,4′-difluorobenzhydrol melted at 47.3–47.5°. The structure of the methane (III) was confirmed by ultimate analysis and by the preparation and ultimate analysis of a dinitro derivative; most significant, however, was the conversion of this methane, by oxidation, to the parent 4,4′-difluorobenzophenone in 83% yield. This 4,4′-difluorodiphenylmethane melted at 28.5–29.5°, a range somewhat lower than anticipated by analogy with the corresponding bromo and chloro compounds.

The insecticidal evaluations of all compounds recorded herein will be reported subsequently.

Experimental[6]

Pilot Thioacetal of 4,4′-Dichlorobenzophenone.—When 0.02 mole of this ketone was treated according to the procedure of Wolfrom and Karabinos,[5] there was recovered 0.01 mole of the starting material plus 2 g. of a dense, evil-smelling oil, which was carried to the next step without further purification.

Hydrogenolysis of the Thioacetal.—The above oil, in 70% ethanolic solution, was refluxed with zinc dust and hydrochloric acid for twenty-four hours. Upon being cooled, the reaction mixture yielded crystalline material, which after several recrystallizations from ethanol melted at 54-55°; total two-step yield 0.40 g. (10% of the theoretical). A mixed melting point with an authentic specimen of 4,4′-dichlorodiphenylmethane[4] did not exhibit depression.

Thioacetal of 4,4′-Difluorobenzophenone and its Hydrogenolysis.—From 3.0 g. (0.014 mole) of this ketone, when treated as above, there was recovered 0.36 g. (12%) of starting material. The oily reaction product, after the treatment with zinc and hydrochloric acid, afforded 1.4 g. of white needles, which after five recrystallizations from ethanol melted at 162-163°. The possibility that this product may be the result of fluoro-group hydrolysis is under investigation.

Pilot Reduction of 4,4′-Dichlorobenzophenone with Phosphorus and Hydrogen Iodide.—To 25 ml. of glacial acetic acid there were added 1.5 g. (0.048 mole) of red phosphorus and 0.5 g. (0.004 mole) of iodine. After thirty minutes, 0.5 ml. of water and 5.52 g. (0.015 mole) of the ketone were added, and the resulting mixture was refluxed for seven days, with the addition of another 0.5 g. of iodine on the fourth day. There were recovered three fractions from ethanolic solution: (1) 2.0 g., m. p. 90-120°; (2) 1.1 g., m. p. 50-52°; and (3) 1.5 g., m. p. 52-53°. Fractions (2) and (3) did not depress the melting point of an authentic specimen of the methane. The total yield of again recrystallized material was 2.5 g. (56% of the theoretical), m. p. 54-55°, as stubby white prisms from ethanol.

4,4′-Difluorobenzhydrol.—Eighteen grams (0.083 mole) of 4,4′-difluorobenzophenone, 18 g. (0.45 mole) of sodium hydroxide pellets, 18 g. (0.275 mole) of zinc dust, and 200 ml. of ethanol were stirred so as to keep the zinc dust well suspended. The temperature of the reaction mixture rose slowly to 45° when heat was applied to maintain the temperature at 70° for four hours. A residue of unreacted zinc was removed by hot filtration and washed well with boiling ethanol. The combined filtrates were poured into one liter of ice water containing 50 ml. of concd. hydrochloric acid. An oil separated, which was taken up in ether, washed with water, and dried over magnesium sulfate. Removal of the ether and distillation of the residue under reduced pressure afforded 9.65 g. of the desired product, b. p. 150-154° at 5 mm. One recrystallization from petroleum ether (b. p. 30-60°) afforded 9.2 g. (52% of the theoretical) of white needles, m. p. 46-48°. After several recrystallizations, this material exhibited a constant melting point of 47.3-47.5°. Other observed boiling ranges were 185-200° at 24.5 mm. and 143-150° at 4 mm.

Anal. Calcd. for $C_{13}H_{10}OF_2$: C, 70.90; H, 4.58; mol. wt., 220. Found: C, 70.58; H, 4.52; mol. wt. (Rast), 218.

***p*-Nitrobenzoate of 4,4′-Difluorobenzhydrol.**—Prepared according to the procedure of Shriner and Fuson; white needles from ethanol or ligroin, m. p. 112.8-113.2°.

Anal. Calcd. for $C_{20}H_{13}NO_4F_2$: C, 65.03; H, 3.55; mol. wt., 369. Found: C, 65.16; H, 4.00; mol. wt. (Rast), 368.

---

[4] White and Sweeney, *Public Health Reports*, **60**, 66 (1945).

[5] Wolfrom and Karabinos, THIS JOURNAL, **66**, 909 (1944); Bernstein and Dorfman, *ibid.*, **68**, 1152 (1946). We believe the use of zinc and acid, instead of Raney nickel, constitutes a novel modification of technique.

[6] In the following sections, pilot reactions with 4,4′-dichlorobenzophenone were used to test the potential applicability of the pertinent reduction procedures.

4,4′-Difluorodiphenylmethane.—A mixture of 1.22 g. (0.01 mole) of iodine, 3.5 g. (0.113 mole) of red phosphorus, and 100 ml. of glacial acetic acid was allowed to stand at room temperature for thirty minutes. Then 1.22 ml. of water and 7.0 g. (0.034 mole) of 4,4′-difluorobenzhydrol were added, and the resultant mixture was refluxed forty-four hours then filtered into 300 ml. of cold 2.5% sodium bisulfite solution to yield a tan oil which crystallized upon being seeded.[7] After one recrystallization from ethanol, the difluorodiphenylmethane occurred as 4.88 g. (75% of the theoretical) of white prisms, m. p. 27–29°. Several recrystallizations from petroleum ether (b. p. 30–60°) raised the melting point to 28.5–29.5°.

Anal. Calcd. for $C_{13}H_{10}F_2$: C, 76.46; H, 4.94; mol. wt., 204. Found: C, 76.90; H, 5.19; mol. wt. (Rast), 206.

4,4′-Difluoro-3,3′-dinitrodiphenylmethane.—One gram of the fluorophenylmethane was dissolved in 8 g. of concd. nitric acid (d. 1.50) with external cooling. This was poured into ice water and the resultant solid filtered and recrystallized; pale-yellow needles from glacial acetic acid, m. p. 177.5–178.5° (constant).

Anal. Calcd. for $C_{13}H_8N_2O_4F$: C, 53.07; H, 2.74. Found: C, 53.26; H, 2.94.

Oxidation of 4,4′-Difluorodiphenylmethane.—One gram of the above methane was mixed with 5 g. of chromic anhydride and 30 ml. of glacial acetic acid and refluxed five hours. Processing in the usual manner afforded 0.9 g. (83% of the theoretical) of colorless prisms of 4,4′-difluorobenzophenone from ligroin, m. p. 106–108°. Neither this compound nor its 2,4-dinitrophenylhydrazone, m. p. 196–198°, resulted in depression when melted with authentic samples.

---

(7) Crystallizes with extreme difficulty unless seeded.

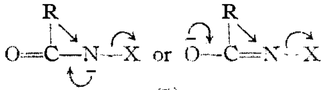
DIVISION OF ENTOMOLOGY
COLLEGE OF AGRICULTURE
UNIVERSITY OF CALIFORNIA
RIVERSIDE, CALIFORNIA

RECEIVED DECEMBER 9, 1949

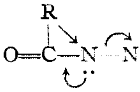
Some Observations on the Hofmann, Lossen and Curtius Rearrangements

BY CHARLES R. HAUSER AND SIMON W. KANTOR

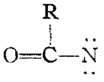
The univalent nitrogen radical (III) has often been represented as an intermediate in the Hofmann–Lossen and Curtius types of rearrangements of (I) and (II), respectively. If (III) had an appreciable life period it might be expected to add the elements of water to form a hydroxamic acid as well as undergo rearrangement. Radicals similar to (III) from the decompositions of hydrazoic acid[1] and phenyl azide[2] and the divalent carbon radical from diazoacetic ester[3] appear to add water readily. However, N-bromobenzamide (I, R = C_6H_5, X = Br) and benzazide (II, R = C_6H_5) undergo rearrangement in the presence of water without producing a detectable amount of benzhydroxamic acid (see experimental). Therefore the elimination of X^- from (I) and of N_2 from (II) is probably accompanied by the essentially simultaneous migration of R to form directly the isocyanate.



(I)



(II)



(III)

The relative rates of elimination of the anion X^- (substituted carboxylate anion) from anion (I) in the Lossen rearrangement have previously been shown to decrease as the eliminated anion X^- is made progressively a stronger base.[4] We have found that, at least under the usual conditions, the elimination and the rearrangement fail with the anion of benzhydroxamic acid ethyl ester, $(C_6H_5CONOC_2H_5)^-$, which would have to eliminate the more strongly basic ethoxide ion. Thus, the elimination of a weaker base than the anion (I) appears to be required for the rearrangement to be realized, the main driving force apparently being the formation of the weaker base. However, the rearrangement of the ethyl ester, $C_6H_5CONHOC_2H_5$, as well as of benzhydroxamic acid may be effected thermally especially in the presence of acids[5] which facilitate the removal of X with its bonding pair of electrons.

Experimental

Rearrangement of N-Bromobenzamide.—N-Bromobenzamide (1.0 g., 0.005 mole), m. p. 128–129°,[6] was dissolved in 110 ml. of approximately 1.0 *N* sodium hydroxide and the solution allowed to stand at room temperature for two hours. The reaction mixture, a drop of which gave a negative test for active bromine with a solution of potassium iodide, acetic acid and starch, was acidified with iced hydrochloric acid. To one ml. of this solution was added several drops of 2% ferric chloride solution, failing to produce the red-violet color characteristic of hydroxamic acids.[7] The remainder of the acidified solution was heated on a water-bath for one hour, made basic and aniline isolated; m. p. of the benzenesulfonamide, 111–112°.[8]

In a blank experiment, benzhydroxamic acid (0.001 g.), m. p. 129–131°,[9] was treated with alkali as described above. One ml. of the acidified solution gave a positive ferric chloride test for the hydroxamic acid, as did a ml. of the solution after it had been diluted with 3 ml. of water, showing that as little as 0.025% of benzhydroxamic acid is detectable.

Rearrangement of Benzazide.—Benzazide (1.0 g., 0.007 mole), m. p. 29–30°,[10] was heated with 110 ml. of water on a steam-bath for one-half hour. Decomposition accompanied by the evolution of nitrogen started at 40° and was very rapid at 70°. The evolution of nitrogen was over after fifteen minutes. The mixture was cooled and filtered. The filtrate after acidification gave a negative test for hydroxamic acid with ferric chloride. Diphenylurea, m. p. 237–239° after one recrystallization from alco-

---

(1) Schmidt, *Ber.*, **57**, 704 (1924).

(2) Bamberger, *Ann.*, **443**, 192 (1925); see also Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, London, England, 1942, p. 369.

(3) Bredig and Fränkel, *Z. Elektrochem.*, **11**, 525 (1905).

(4) Bright and Hauser, THIS JOURNAL, **61**, 618 (1939).

(5) Waldstein, *Ann.*, **181**, 384 (1876).

(6) Hauser and Renfrow, THIS JOURNAL, **59**, 121 (1937).

(7) Feigl, "Spot Tests," Elsevier Publishing Co., Inc., New York, N. Y., 1946, p. 355.

(8) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 193.

(9) Hauser and Renfrow, "Organic Syntheses," John Wiley and Sons, New York, N. Y., 1943, Coll. Vol. II, p. 67.

(10) Barrett and Porter, THIS JOURNAL, **63**, 3434 (1941).