Bis-(amino Acid) Derivatives. II. Compounds of Glycine, Hydriodic Acid and Iodine[1]

By WALTER S. FROST AND ROBERT D. EDDY[2]

The search for a stable, non-hygroscopic preparation which would release elemental iodine when added to water has been carried out for several years. Partial success was achieved in 1942 when one of us (WSF) discovered that diglycine hydriodide[3] showed considerable affinity for iodine when dry, yet released this iodine when added to water. This resulted in the Bursoline[4,5] Canteen Water Sterilizing Tablet used to some extent by the U. S. Armed Services in World War II. The active ingredient was prepared by grinding together, dry, two moles of diglycine hydriodide with one of iodine. It was very evident that compound formation occurred between these two substances, because the vapor pressure of free iodine was reduced to the point where it became hardly noticeable. Later, Fair[6] reported "triglycine hydroperiodide, $(CH_2NH_2COOH)_3 \cdot HI \cdot I_2$," which was believed to be the formula of the compound prepared when glycine, hydriodic acid and iodine react in water.

After working with a variety of systems containing these four substances, it is our opinion that the compound $(CH_2NH_2COOH)_3 \cdot HI \cdot I_2$ cannot be prepared from aqueous solution, and probably does not exist,[7] although analyses approximating such a formula can be obtained from a mixture of diglycine hydriodide and the two compounds described below. If concentrated aqueous solutions containing glycine, hydriodic acid and iodine in the proportions indicated by this formula are cooled from 60°, two kinds of crystals are formed. The first to appear are flat needles (blades) with a brassy-bronze metallic luster. They remain as such on cooling to room temperature. The saturated solution in contact with them deposits (usually spontaneously, but always if seeded) a dark brown muddy paste which cements together the primary crystals. What has been a fluid mass of glittering crystals suspended in mother liquor becomes rigid and almost dry in appearance. If the mass is left in the open air to dry, fine hair-like crystals grow all over the surface, giving the resulting product the appearance of a purple plush.

By changing the proportions of glycine, hydriodic acid and iodine we have been able to isolate and

(1) For number I in this series see W. S. Frost, THIS JOURNAL, 64, 1286 (1942).

(2) A portion of the contribution of R. D. Eddy to this work was made as a consultant to Contract OEMcmr-251 between Harvard University and the Office of Scientific Research and Development.

(3) Refers to two glycine molecules, not glycylglycine.

(4) G. M. Fair, O.S.R.D., OEMcmr-251, Dec. 31, 1945.

(5) See also W. S. Frost, U. S. Patent 2,517,651, Aug. 8, 1950.

(6) G. M. Fair, ref. 4. See also G. H. Conant and J. C. Morris, U. S. Patent 2,464,198, Mar. 15, 1949, and J. C. Morris, U. S. Patent 2,498,174, Feb. 21, 1950.

(7) The material described by Fair and by Morris[6] as "triglycine hydroperiodide" has the appearance and approximate melting point (160–162°) of our compound, $(CH_2NH_2COOH)_4 \cdot HI \cdot 5/4I_2$. In addition later and more extensive analyses (by Morris) of recrystallized material prepared according to U. S. Patent 2,498,174 have given results essentially the same as those obtained by us for our compound. The material is now designated and being manufactured under the name *tetraglycine hydroperiodide* (private communication from J. C. Morris; see also Annual Summary Report, Contract W-44-109-qm-1159 between Harvard University and the Office of the Quartermaster General, U. S. Army).

identify the two substances formed in this mixture. The blade-like crystals, prepared in the presence of relatively large amounts of glycine are $(CH_2NH_2-COOH)_4 \cdot HI \cdot 5/4I_2$. The other compound, which occurs in three different forms, is $(CH_2NH_2COOH)_2 \cdot HI \cdot 5/4I_2$. Both compounds show remarkably low vapor pressures of iodine at room temperature.

Experimental

$(CH_2NH_2COOH)_2 \cdot HI \cdot 5/4I_2$.—This compound has been prepared in three different forms: compact purple crystals, dark brown finely-divided crystals and fine hair-like purple crystals.

At room temperature 139 g. of diglycine hydriodide was dissolved in 300 ml. of water; then 159 g. of iodine was added and the solution stirred vigorously. A finely-divided dark brown precipitate began to form within two or three minutes. After about 15 minutes, when the solid iodine had all dissolved, the mixture was filtered with suction and the precipitate allowed to dry in the open air. The filter cake became completely covered with a purple coating of fine hair-like crystals. The dried cake was broken open and warmed to remove any elemental iodine. This product was ground and air-dried. Because of decomposition, the melting point varied between 156° and 161°, depending on the rate of heating.

Anal. Calcd. for $C_8H_{22}I_7N_4O_8$: C, 8.07; H, 1.86; free I, 53.3; combined I, 21.3; total I, 74.6; N, 4.71. Found: C, 7.92; H, 1.84; free I, 51.7; combined I, 22.6; total I, 74.3; N, 4.68.

Separate samples of the hair-like purple crystals gave free I, 52.0; combined I, 23.9; total I, 75.9.

One hundred grams of diglycine hydriodide, 100 ml. of water and 100 g. of iodine were placed in a glass-stoppered bottle, heated to 70° in a water-bath and shaken well. After very slow cooling, filtering and drying at room temperature (or slightly above to sublime any elemental iodine present) compact purple-black crystals were obtained. These showed free I, 54.9; combined I, 20.5; total I, 75.4.

$(CH_2NH_2COOH)_4 \cdot HI \cdot 5/4I_2$.—This compound was prepared as flat needles (blades) having a brassy-bronze metallic luster in reflected light. In the powdered form they appear gray.

A solution of 139 g. of diglycine hydriodide in 1000 ml. of water was placed in a wide-mouth glass-stoppered bottle with 225 g. of glycine and 80 g. of iodine, heated to 70° and shaken well. After slow cooling, filtering and drying at room temperature (or slightly above), large blade-shaped crystals were obtained. The melting point, with decomposition, varied between 162° and 167°.

Anal. Calcd. for $C_{16}H_{42}I_7N_8O_{16}$: C, 12.89; H, 2.84;. free I, 42.6; combined I, 17.0; total I, 59.6; N, 7.52. Found: C, 12.97; H, 2.87; free I, 42.5; combined I, 16.9; total I, 59.4; N, 7.30 (micro); 7.49 (Kjeldahl).

The same compound was also prepared from solid starting materials. Dry glycine powder, 6.0 g., was ground with 11.1 g. of dry diglycine hydriodide, which had been passed through a 100-mesh sieve, and 15 g. of iodine. The intimate mixture was transferred to a closed container and stored for four days at about 35°, with occasional mixing. After exposure to the open air for two more days at the same temperature, the mass of tiny glistening crystals analyzed free I, 43.9; combined I, 17.3; total I, 61.2.

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Experiments on the Catalytic Hydrogenation of Oxazolidines

By E. GIL-AV

The catalytic hydrogenation of oxazolidines has been used by Cope and Hancock[1] and Senkus[2] for the preparation of N-substituted aminoalcohols.

(1) A. C. Cope and E. M. Hancock, THIS JOURNAL, 64, 1503 (1942).

(2) M. Senkus, *ibid.*, 67, 1515 (1945).

Cope and Hancock used as catalyst Raney nickel or copper chromite at about 150° and 1000–2000 p.s.i., since palladium–charcoal at room temperature reacted very slowly. Also, Senkus could achieve hydrogenation in presence of palladium only at 100° and 1000 p.s.i. Similar observations were made in this Laboratory in hydrogenating the product of the reaction between formaldehyde and ethanolamine.

It seemed interesting to ascertain whether palladium-activated hydrogen could be used to distinguish between oxazolidines (A) and their isomers, Schiff bases type (B), assuming that the former would be hydrogenated at a much slower rate than the latter.

The following three substances were chosen as models

I   II   III
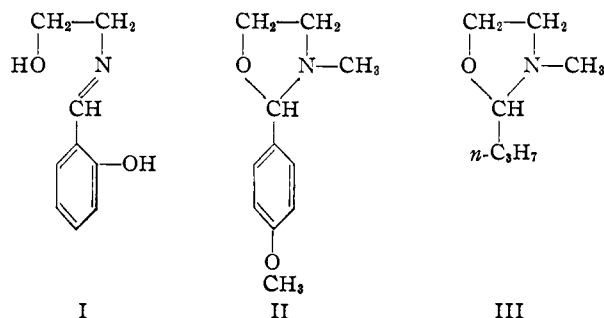
Substance (I) exists only in the form of the Schiff base[3] and does not show any tendency to isomerize to a cyclic structure,[4] whilst (II) and (III), due to the presence of the methyl group at the nitrogen atom, cannot exist in an open form. Hydrogenation of (II) and (III) would, therefore, necessarily be a ring splitting reaction. Contrary to expectation, however, (I), (II) and (III) did not show any outstanding difference in the rate of their hydrogenation at room temperature and a pressure of about four atmospheres.

Experimental

(1) N-(o-Hydroxybenzyl)-2-aminoethanol.—A solution of 9.2 g. of N-salicylideneaminoethanol (I)[3,4] in 100 cc. of 95% ethyl alcohol was hydrogenated in presence of 0.3 g. of 10% palladium–charcoal.[5] The reaction was carried out at 30° and under a pressure of 55–60 p.s.i. 70% of the theoretical amount of hydrogen was absorbed in seven hours. After completion of the hydrogenation, the product was recovered by filtration and evaporation of the solvent. The oily residue solidified upon standing at 0°; the solid was recrystallized from a benzene–light petroleum mixture (1:1); m.p. 66.5–67°.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.7; H, 7.8; N, 8.4; mol. wt., 167. Found: C, 64.9; H, 7.9; N, 8.6; mol. wt., 182.

The infrared spectrum (0.066 g. plus 1 cc. of chloroform) showed two bands, at 3300 and 3410 cm.$^{-1}$, characteristic for the OH and NH groups, respectively. No absorption was found in the C=N region.

(2) N-Methyl-N-(p-methoxybenzyl)-2-aminoethanol.—A solution of 9.0 g. of 2-(p-methoxyphenyl)-3-methyloxazoli-

dine (II)[4] in 120 cc. of 95% alcohol was hydrogenated in the presence of 0.4 g. of 10% palladium–charcoal catalyst. Carried out at 30° and under 53–56 p.s.i., the reaction was complete in six hours. The liquid product was recovered by evaporation of the solvent and subjected to fractional distillation in a Todd column; b.p. 154° (2 mm.); yield 2.6 g. (30%) of pure product; n^{29}D 1.531.

Anal. Calcd. for $C_{11}H_{17}NO_2$: N, 7.2; mol. wt., 195. Found: N, 7.2; mol. wt., 200.

The infrared spectrum of the hydrogenation product showed a band at 3450 cm.$^{-1}$, corresponding to the hydroxyl group. No absorption was found in the C=N region. The hydrogenation of (II) was also carried out in a mixture of cyclohexane and benzene (80:25) at atm. pressure (II) is only slightly soluble in cyclohexane; it then required about twice the time indicated above.

(3) N-Methyl-N-n-butyl-2-aminoethanol.—A solution of 16.4 g. of 2-n-propyl-3-methyloxazolidine (III)[4] in 110 cc. of 95% ethyl alcohol was hydrogenated at 30° and under 50–60 p.s.i., in the presence of 0.3 g. of the palladium catalyst. The reaction was complete in five and one-half hours. (In a mixture of cyclohexane and benzene (80:25) at atm. pressure, the hydrogenation is about one third as fast.) The oily product which remained after filtration and evaporation of the solvent, boiled (Todd column) at 122–123° (100 mm.); yield 9.5 g. (60%); n^{31}D 1.4389.

Anal. Calcd. for $C_7H_{17}NO$: N, 10.7; mol. wt., 131. Found: N, 10.7, 10.8; mol. wt., 143.

The infrared spectrum showed the OH band at 3450 cm.$^{-1}$ and no absorption in the C=N region.
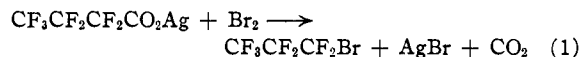
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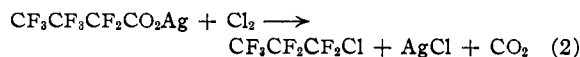

Perfluoroalkyl Halides Prepared from Silver Perfluoro-fatty Acid Salts. II. Perfluoroalkyl Bromides and Chlorides[1]

BY MURRAY HAUPTSCHEIN, EDWARD A. NODIFF AND ARISTID V. GROSSE

In our first paper of this series[2] we reported an excellent method for the preparation of perfluoroalkyl iodides by the degradation of the appropriate silver perfluoro-carboxylic acid salt by an excess of iodine. This method has been demonstrated to be equally well adapted to the preparation of perfluoroalkyl bromides and chlorides. The reaction of an excess of bromine and chlorine with silver trifluoroacetate, silver pentafluoropropionate and silver n-heptafluorobutyrate resulted in the formation of high yields of bromotrifluoromethane[3] and chlorotrifluoromethane,[3] bromopentafluoroethane and chloropentafluoroethane, as well as the new compounds, 1-bromoheptafluoropropane and 1-chloroheptafluoropropane. The latter two representative reactions are given by the equation

$$CF_3CF_2CF_2CO_2Ag + Br_2 \longrightarrow$$
$$CF_3CF_2CF_2Br + AgBr + CO_2 \quad (1)$$

and

$$CF_3CF_2CF_2CO_2Ag + Cl_2 \longrightarrow$$
$$CF_3CF_2CF_2Cl + AgCl + CO_2 \quad (2)$$

(1) Presented before the Twelfth International Congress of Pure and Applied Chemistry, New York City, September 10–13, 1951.

(2) M. Hauptschein and A. V. Grosse, THIS JOURNAL, 73, 2461 (1951).

(3) R. N. Haszeldine, J. Chem. Soc., 584 (1951), has independently prepared bromotrifluoromethane and chlorotrifluoromethane by this method. This reaction is an extension of the method of Hunsdiecker applied to normal "hydrocarbon" silver salts. See, for examples, Hunsdiecker, Hunsdiecker and Vogt, U. S. Patent 2,176,181 (1939), and the review of Kleinberg, Chem. Revs., 40, 381 (1947).

(3) L. W. Daasch and U. E. Hanninen, THIS JOURNAL, 72, 3673 (1950).

(4) E. Bergmann and co-workers, Rec. trav. chim., 51, in press (1952).

(5) Preparation according to Org. Syntheses, 26, 78 (1946).