Gly.OH, from a partial hydrolysate of gelatin. In an alkaline partial hydrolysate of gelatin, Heyns, Anders and Becker[14] found H.Glu-Gly.OH, H.Ala-Gly.OH, H.Gly-Asp.OH, H.Ala-Ala-Gly.OH, H.-Ala-(Gly,Glu). Of the twenty or more dipeptides and tripeptides reported present in partial hydrolysates of collagen and gelatin, only five fit the collagen sequence -P-G-R-P-G-R- suggested by Astbury[15] and Pauling and Corey[16] where P represents either proline or hydroxyproline, G is glycine and R stands for one or other of the remaining residues. The five which fit are H.Lys-Pro-Gly.OH (Grassman and Riederle), H.Gly-Asp.OH (Heyns, *et al.*), H.Gly-Glu.OH and H.Hypro-Gly.OH (Schroeder, *et al.*), and H.Gly-Ala.OH (this paper). All of the peptides, except H.Gly-Gly.OH, conform to the -G-R-P-G-R-R- sequence suggested by Bergmann and Niemann[17] for the structure of gelatin. However, this formula was based on Bergmann's value of 19.7% proline[18] in gelatin which is much higher than the currently accepted values for proline of 14.8–15.1%.[19,20] Schroeder, *et al.*,[12] have pointed out that in view of these more reliable values for proline only three-fourths of the collagen structure could have the sequence suggested by Astbury.[15] A similar consideration would apply to the Bergmann–Niemann[17] sequence. The isolation of H.-Gly-Gly.OH (present work) would indicate that other sequences in addition to those suggested must be present. At present, sufficient data have not been accumulated to justify any conclusion as to the reliability of any proposed structure of collagen.

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Pyridazinemonocarboxylic Acids and Derivatives

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In connection with recent studies of nitrogen heterocyclic amides[1] and hydrazides, new syntheses of pyridazine-3-carboxylic acid and pyridazine-4-carboxylic acid were developed. Gabriel and Colman[2] first made pyridazine-3-carboxylic acid by the permanganate oxidation of 3-*p*-hydroxyphenylpyridazine.

In the present work two alternate routes to the 3-acid were explored. Permanganate oxidation of 3-hydroxymethylpyridazine and reductive dehalogenation of 6-chloropyridazine-3-carboxylic acid were found to give identical yields of the desired acid. The choice of the route depends, therefore, upon the availability of intermediates. 3-Hydroxymethylpyridazine can be prepared in two steps and 33% over-all yield from furfuryl acetate according to Clauson–Kass,[3] and we have confirmed this. Our yield of 6-chloropyridazine-3-carboxylic acid from levulinic acid in five steps was 40%. Pyridazine-3-carboxamide and pyridazine-3-carbohydrazide were prepared from the acid *via* the ethyl ester.

Partial decarboxylation of pyridazine-4,5-dicarboxylic acid[4] gave 4-carboxypyridazine. This new acid was converted to the ethyl ester, amide and hydrazide.

The pK_a values of the isomeric 3- and 4-carboxypyridazines are 3.0 and 2.8, respectively. Data on the basicities and reduction potentials of the corresponding amides have been previously reported.[1]

The hydrazides were tested for antituberculous activity in a standardized mouse assay by Dr. M. Solotorovsky of the Merck Institute for Therapeutic Research and found to be inactive.

Experimental

6-Chloropyridazine-3-carboxylic Acid.—The route to this acid involves the following steps, all previously described: preparation of 6-hydroxy-3-methyldihydropyridazine,[5] dehydrogenation to 6-hydroxy-3-methylpyridazine,[6] conversion to 6-chloro-3-methylpyridazine[7,8] and oxidation to 6-chloropyridazine-3-carboxylic acid.[9] The yields obtained for the reactions were 94, 76, 80 and 60%, respectively.

Two details deserve special mention. In synthesis of 6-chloro-3-methylpyridazine, the temperature of the reaction mixture containing phosphorus oxychloride is critical and should not exceed 100°. In workup of the 6-chloropyridazine-3-carboxylic acid preparation, the product must be extracted immediately after pouring the reaction mixture onto ice. Failure to observe these precautions results in very poor yields.

Pyridazine-3-carboxylic Acid. A. By Dehalogenation of 6-Chloropyridazine-3-carboxylic Acid.—Thirty grams of 6-chloropyridazine-3-carboxylic acid and 25 g. of Raney nickel were added to a cooled solution of 15.9 g. of sodium hydroxide in 330 ml. of water. The mixture was shaken at once with hydrogen at 40 p.s.i. Reduction was completed in two hours. The catalyst was removed by filtration and washed with water, then the combined filtrate and washings were concentrated to 80 ml. The concentrate was cooled to 35° and acidified to *p*H 2.5 with hydrochloric acid. After two hours standing at 0°, the product was removed by filtration and washed with a little water. When recrystallized from 525 ml. of boiling water, 19.0 g. (81%) of off-white acid, m.p. 195° (dec.), was obtained. A second recrystallization gave 13.4 g. of colorless product, m.p. 201° (dec.), and a second crop, 5.0 g., m.p. 194° (dec.). The reported melting point of pyridazine-3-carboxylic acid is 200–201°. The lower melting material obtained was satisfactory for ester preparation.

Anal. Calcd. for $C_5H_4N_2O_2$: N, 22.57. Found: N, 22.36.

B. By Oxidation of 3-Hydroxymethylpyridazine.—A solution of 22.4 g. of 3-hydroxymethylpyridazine (m.p. 60°) in 1 l. of water was added with stirring to a solution of 48 g. of potassium permanganate in 2 l. of water at 75° over a period of 10 minutes. After an additional 5 minutes all of the purple color of permanganate had disappeared. The manganese dioxide was filtered off and the filtrate evaporated to 500 ml., acidified to *p*H 2.5 and cooled. The precipitate

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of pyridazine-3-carboxylic acid was collected and air-dried, m.p. 201° (dec.), yield 22 g. (81%).

Pyridazine-4-carboxylic Acid.—A solution of 3.35 g. of pyridazine-4,5-dicarboxylic acid in 300 ml. of water was heated in a bomb at 200° for two hours. The resulting tan solution was boiled with Darco and filtered. The filtrate was evaporated to 70 ml., acidified to *p*H 2.5 and chilled, yielding a precipitate of pyridazine-4-carboxylic acid as white crystals, m.p. 230–235° (dec.); yield 1.4 g. (56%). An analytical sample recrystallized twice from water decomposed at 239–240° (slow heating).

Anal. Calcd. for $C_5H_4N_2O_2$: C, 48.39; H, 3.25; N, 22.57. Found: C, 48.78; H, 3.42; N, 22.40.

3-Carbethoxypyridazine.—Pyridazine-3-carboxylic acid (17.7 g.) was esterified by refluxing for six hours with 177 ml. of absolute alcohol and 18 ml. of concentrated sulfuric acid. The reaction mixture was concentrated *in vacuo* to 75 ml. and poured into a cold saturated solution of sodium carbonate. The ester was extracted from the aqueous solution with benzene and crystallized from benzene–petroleum ether. Recrystallization from absolute alcohol gave 11.1 g. of product, m.p. 68.0–68.5°, and a second crop of 2.8 g., slightly yellow, m.p. 65–67° (64% yield).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.52; H, 5.01.

4-Carbethoxypyridazine.—Pyridazine-4-carboxylic acid (6.5 g.) was esterified in a similar manner. The ester was obtained as a straw-colored oil which was distilled under vacuum; b.p. 125° (13 mm.), yield 4 g. (60%).

Anal. Found: C, 55.78; H, 4.97; N, 18.33.

Pyridazine-3-carboxamide.—A suspension of 109 g. of 3-carbethoxypyridazine in 800 ml. of absolute alcohol was treated with anhydrous ammonia. The mixture became warm, the ester dissolved and amide began to deposit. Gas introduction was halted after three hours when the reaction mixture had cooled to room temperature. The filtered crystals were recrystallized from water with charcoaling, giving 83.6 g. (95%) of colorless amide, m.p. 182–182.5°.

Anal. Calcd. for $C_5H_5N_3O$: C, 48.78; H, 4.09; N, 34.13. Found: C, 49.17; H, 3.92; N, 34.03.

Pyridazine-4-carboxamide.—Treatment of an alcoholic solution of 4-carbethoxypyridazine with ammonia gave the corresponding amide which when recrystallized from water melted at 191–192°.

Anal. Found: C, 48.77; H, 3.83; N, 33.96.

Pyridazine-3-carbohydrazide.—A mixture of 6 g. of 3-carbethoxypyridazine, 4.6 g. of 85% hydrazide hydrate and 35 ml. of alcohol was refluxed for one hour, then cooled. The hydrazide deposited as pale yellow crystals, m.p. 151–152°, yield 5.2 g. (95%). After recrystallization from alcohol, the product was cream-colored; the melting point was unchanged.

Anal. Calcd. for $C_5H_6N_4O$: C, 43.47; H, 4.38; N, 40.56. Found: N, 39.73.

Pyridazine-4-carbohydrazide.—Reaction of 4-carbethoxypyridazine with hydrazine hydrate as above gave the hydrazide, m.p. 124–125° (recrystallized from alcohol).

Anal. Found: C, 43.99; H, 4.13; N, 40.52.

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Characterization of Some Alkylbenzenes through their Phthalic Anhydride Derivatives[1]

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The identification of aromatic hydrocarbons has generally been possible only by physical methods such as examination of absorption spectra and comparison of the physical properties of unknown with authentic compounds. Identification based on the melting points of solid derivatives offers several advantages, especially in those instances where sufficient quantities of the hydrocarbons or equipment necessary for physical examination are unavailable. Consequently, an investigation of solid derivatives of aromatic hydrocarbons was begun at this Laboratory in order to ascertain the usefulness of certain derivatives in identifying the hydrocarbons.

While several types of solid derivatives of aromatic hydrocarbons are known, most of them have proved to be unsuitable for identification purposes, for one reason or another. Picric acid derivatives are frequently unstable,[3] while styphnic acid[4] and 2,4,7-trinitrofluorenone[5] derivatives have been prepared only from fused ring aromatics. The mono- and diacetamino as well as the benzamino derivatives have been prepared only from monoalkylbenzenes.[6,7] Trinitrobenzene derivatives from fused ring aromatics are stable,[4] but those from single-ring aromatics are not.[8]

The *o*-aroylbenzoic and *o*-aroyltetrachlorobenzoic acids, prepared by the condensation of aromatic hydrocarbons with phthalic and tetrachlorophthalic anhydride, respectively, have been proposed by Underwood and Walsh[9] as suitable crystalline derivatives for the identification of aromatic hydrocarbons. In the present investigation phthalic anhydride derivatives of 25 mono-, di- and trialkylbenzenes have been prepared, and the melting points of the derivatives have been compared to determine the usefulness of these compounds in distinguishing the hydrocarbons. The keto acid of *i*-propylbenzene could not be obtained in sufficient purity. In addition the 1,4-substituted alkylbenzenes formed derivatives only with difficulty and none could be obtained in the cases of the *o*-aroylbenzoic acid derivatives of 1-methyl-4-ethylbenzene and 1,4-diethylbenzene.

The melting points, carbon–hydrogen analyses and neutralization equivalents of 25 *o*-aroylbenzoic acids are presented in Table I; fourteen of these keto acids are reported for the first time. All the derivatives were recrystallized until successive recrystallizations gave no significant change in melting point. The melting points available from the literature are indicated in the tables and are generally in good agreement with the values obtained in the present work. In those instances where the melting points of derivatives of isomeric hydrocarbons were similar, mixed melting points were determined. In this way it was found that a common derivative was obtained from the three isomeric methyl-*t*-butylbenzenes.

In two other cases the mixed melting points taken with the derivatives of two isomeric hydrocarbons showed slight depressions; however, the degree of depression was not sufficient to permit a definite conclusion as to whether rearrangement of the hy-

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