

## CCLXXXIII.—1-Phenyl-4-amino-5-ketopyrazoline-3-carboxylic Acid.

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ALTHOUGH it is well established that under the influence of acids, diketosuccinic acid phenylosazone is converted into 1-phenyl-4:5-diketopyrazoline-3-carboxylic acid 4-phenylhydrazone (I), the reduction of this compound to 1-phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid (II) has never been satisfactorily effected (compare Bernthsen, *Chem.-Ztg.*, 1898, 457; Eibner and Laue, *Ber.*, 1906, 39, 2022). If, however, reduction is effected by using the theoretical amount of sodium amalgam, and the amino-acid is liberated in the presence of some excess of sulphur dioxide (to prevent oxidation), it can be isolated in a pure condition.

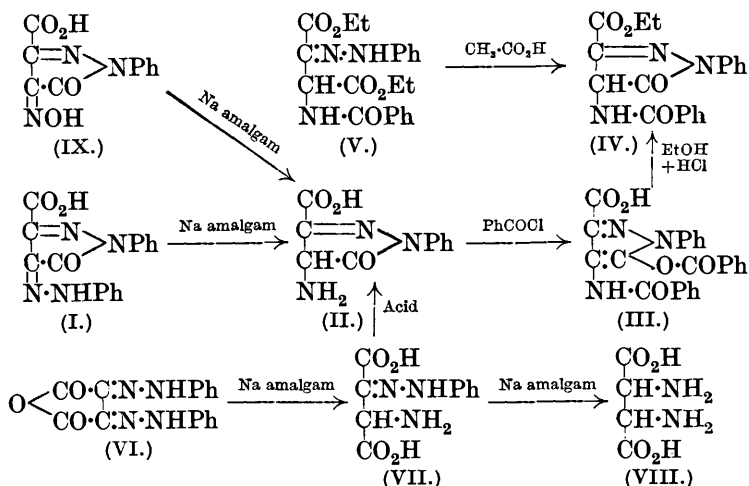
1-Phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid is a white, crystalline solid of neutral reaction. It is very sparingly soluble in all ordinary organic solvents, but dissolves readily both in aqueous acids and in alkalis, such solutions oxidising rapidly in presence of

air, especially when warm. Alkaline solutions are the more readily oxidised, giving a silver mirror with ammoniacal silver oxide, and precipitating cuprous oxide from warm Fehling's solution. Acid solutions reduce ferric chloride and potassium permanganate in the cold.

It combines with 1 mol. of hydrogen chloride yielding a comparatively stable *hydrochloride*, which, however, turns violet on exposure to air. With acetic anhydride it gives a soluble, well-crystallised *acetyl* derivative of marked acid character. With benzoyl chloride it yields a *dibenzoyl* derivative, and on boiling this for a short time with alcohol containing a little hydrogen chloride, it is converted into ethyl benzoate and the ester of a monobenzoyl derivative (IV), identical with the compound obtained by Wislicenus by boiling ethyl oxalylhippurate phenylhydrazone (V) with acetic acid (*Ber.*, 1891, 24, 1260).

1-Phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid may be obtained in several other ways. For example, it is formed when the alkaline solution of amino-oxalacetic acid phenylhydrazone (VII), obtained by partial reduction of anhydrodiketosuccinic acid phenylsazone (VI) by sodium amalgam, is acidified, ring closure occurring under the influence of acids, just as in the case of diketosuccinic acid phenylsazone.

The amino-ketopyrazoline has also been prepared by reduction of the corresponding oximino-compound (IX), obtained by the action of nitrous acid on 1-phenyl-5-ketopyrazoline-3-carboxylic acid.



The action of bromine upon 1-phenyl-4:5-diketopyrazoline-3-carboxylic acid 4-phenylhydrazone has been re-examined and

the product shown to be 1-phenyl-4 : 5-diketopyrazoline-3-carboxylic acid 4-*p*-bromophenylhydrazone, since on reduction it yields *p*-bromoaniline and 1-phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid. This constitution has been confirmed by its synthesis from 1-phenyl-5-ketopyrazoline-3-carboxylic acid and *p*-bromobenzenediazonium chloride.

Anhydrodiketosuccinic acid phenylosazone, like the corresponding halogenated derivatives (Chattaway and Humphrey, this vol., p. 1327), reacts with alcohols containing hydrogen chloride to give esters of the isomeric pyrazoline derivative. Several of these esters have been prepared, and it is noteworthy that the *n*-propyl and *n*-butyl esters have almost the same melting points.

#### EXPERIMENTAL.

*Reduction of 1-Phenyl-4 : 5-diketopyrazoline-3-carboxylic Acid 4-Phenylhydrazone (I) to 1-Phenyl-4-amino-5-ketopyrazoline-3-carboxylic Acid (II).*—17 G. of the phenylhydrazone were dissolved in 500 c.c. of a hot 1% solution of sodium hydroxide and placed in a wide-necked bottle closed by a cork, through which passed a wide glass tube reaching to the surface of the liquid and loosely stoppered at its upper end. The bottle was placed in a freezing mixture until about half of the liquid had frozen, and the air above the liquid was displaced by loosening the cork and passing a rapid stream of hydrogen down the tube. Successive small quantities of 2½% sodium amalgam were then introduced down the tube, and the mixture was vigorously shaken after each addition until the solution just became colourless and turbid due to the separation of aniline; about 250 g. of amalgam were required, and the reduction occupied 2—3 hours. The mixture was poured immediately into 800 c.c. of 2½% sulphuric acid (saturated with sulphur dioxide) and cooled to 0°. The 1-phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid at once separated as a white, crystalline precipitate. It was filtered off immediately, washed thoroughly with air-free water, alcohol, and ether, and dried in a vacuum desiccator over calcium chloride; yield, 10 g.; m. p. 225° (decomp.; with darkening from 215°) (Found: C, 54.6; H, 3.9; N, 18.8. C<sub>10</sub>H<sub>9</sub>O<sub>3</sub>N<sub>3</sub> requires C, 54.8; H, 4.1; N, 19.2%). This acid is comparatively stable when dry, but slowly oxidises and turns brownish-pink on keeping. It is very sparingly soluble in water or ether, and only sparingly soluble in boiling alcohol, benzene, chloroform, or acetone; such solutions rapidly oxidise and turn brown on exposure to air; it was therefore impossible to purify the compound by crystallisation.

The *hydrochloride* separates on cooling a hot saturated solution of the amino-ketopyrazoline in concentrated hydrochloric acid.

It forms long, colourless prisms which begin to darken and decompose at  $160^{\circ}$ ; it is fairly stable when dry, but its aqueous solution darkens on keeping and the crystals themselves slowly become pale violet (Found: C, 13.7.  $C_{10}H_{10}O_3N_3Cl$  requires Cl, 13.9%).

*Acetyl derivative.* 1-Phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid dissolves apparently unchanged in boiling acetic anhydride, the solution rapidly turning dark reddish-brown owing to oxidation. On adding a drop of concentrated sulphuric acid, a vigorous reaction occurs; on adding a few drops of water and cooling, the *acetyl* compound crystallises out. It is easily soluble in hot acetic acid, from which it separates in long, colourless prisms, m. p.  $216^{\circ}$  (Found: C, 55.0; H, 4.2; N, 16.0.  $C_{12}H_{11}O_4N_3$  requires C, 55.2; H, 4.2; N, 16.1%).

*Dibenzoyl derivative* (III). When an alkaline solution of 1-phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid is shaken with excess of benzoyl chloride, it is converted into a *dibenzoyl* derivative. The same compound is more readily prepared by heating the amine (2 g.) with benzoyl chloride (3 c.c.) until hydrochloric acid is no longer evolved, cooling, and adding ether. It was recrystallised from boiling acetic acid, in which it is easily soluble and from which it separates in long, colourless prisms, m. p.  $205^{\circ}$  (Found: C, 67.7; H, 3.9; N, 10.0.  $C_{24}H_{17}O_5N_3$  requires C, 67.5; H, 4.0; N, 9.8%).

*Ethyl ester of 1-phenyl-4-benzamido-5-ketopyrazoline-3-carboxylic acid* (IV). When the dibenzoyl derivative (III) is boiled for a short time with alcohol containing 1% of hydrogen chloride, an ethyl group is introduced and one benzoyl group removed. The bright yellow solution thus obtained smells strongly of ethyl benzoate, and on cooling, the *ethyl* ester separates in long, slender, canary-yellow prisms, m. p.  $195^{\circ}$  (Found: N, 12.1.  $C_{19}H_{17}O_4N_3$  requires N, 12.0%).

*Preparation of 1-Phenyl-4-amino-5-ketopyrazoline-3-carboxylic Acid by Reduction of Anhydrodiketosuccinic Acid Phenyllosazone.*—The reduction of anhydrodiketosuccinic acid phenyllosazone proceeds in two stages. The reduction by alkaline reducing agents of one phenylhydrazone group must first give amino-oxalacetic acid phenylhydrazone; this, however, cannot be isolated, for on acidification ring closure and pyrazoline formation occur and 1-phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid is produced. This change was to be expected, since the disodium salt of the osazone is itself converted quantitatively into a pyrazoline derivative on acidification.

The reduction of both phenylhydrazone groups by alkaline reducing agents yields the two stereoisomeric diaminosuccinic acids, which separate when the solution is acidified. These compounds

were prepared by Farchy and Tafel by reduction of the osazone (*Ber.*, 1893, **26**, 1980).

*Partial reduction.* A fine suspension of 17 g. of anhydrosuccinic acid phenylosazone in 500 c.c. of 1% sodium hydroxide solution was cooled in a freezing-mixture and treated with successive small quantities of 2½% sodium amalgam in the apparatus described above, until the yellow colour had just disappeared; about 250 g. of the amalgam were required. The colourless liquid was then decanted from the remaining mercury and slowly poured into 800 c.c. of ice-cold 2½% sulphuric acid saturated with sulphur dioxide; 1-phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid then separated as a white precipitate which was filtered off, washed, and dried as before; yield, 9 g. It was shown to be identical with the compound previously described, since it melted at 215–225° with complete decomposition, and yielded an identical acetyl derivative, m. p. 216°.

*Complete reduction.* A fine suspension of 19 g. of the anhydride in 500 c.c. of a 1% aqueous solution of sodium hydroxide was cooled and reduced with a considerable excess of 2½% sodium amalgam (650 g.) in the manner described by Farchy and Tafel for the corresponding osazone. From the alkaline solution thus obtained, the two stereoisomeric diaminosuccinic acids were isolated and purified in precisely the same manner as described by Farchy and Tafel. The two isomerides were identified by conversion to their dibenzoyl derivatives; the dibenzoyl derivative of the *meso*-modification melts with decomp. at 213°, and that of the *r*-acid at 183°.

*1-Phenyl-4-oximino-5-ketopyrazoline-3-carboxylic Acid (IX).*—10 G. of 1-phenyl-5-ketopyrazoline-3-carboxylic acid (prepared from ethyl oxalacetate phenylhydrazone, as described by Wislicenus, *Annalen*, 1888, **246**, 319) and 5 g. of sodium nitrite were dissolved in 150 c.c. of 30% aqueous potassium hydroxide; the solution was cooled to 0° and added slowly to 200 c.c. of 10% hydrochloric acid. The *oximino*-compound separated as a red precipitate, which after 12 hours was filtered off and crystallised from acetic acid, in which it is easily soluble, and from which it separates in glittering, red, slender prisms, m. p. 209° (decomp.); yield, 9 g. (Found: N, 17.8.  $C_{10}H_7O_4N_3$  requires N, 18.0%).

When reduced it yields 1-phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid. A solution of 2 g. of the *oximino*-compound in 100 c.c. of a 1% aqueous solution of sodium hydroxide was cooled in a freezing mixture and reduced with 40 g. of 2½% sodium amalgam. The colourless solution was then poured into 120 c.c. of 3% sulphuric acid, saturated with sulphur dioxide. The amino-keto-

pyrazoline separated as a white, crystalline powder, which was filtered off, washed, and dried as before. Yield 1.7 g. It was identified by its acetyl derivative, m. p. 216°.

*Bromination of 1-Phenyl-4 : 5-diketopyrazoline-3-carboxylic Acid 4-Phenylhydrazone.*—In view of recent work on the bromination of phenylhydrazones (J., 1925, 127, 975, 1687, 2407; this vol., p. 1323), it was of interest to determine to what extent bromine would enter the phenylhydrazone residue in 1-phenyl-4 : 5-diketopyrazoline-3-carboxylic acid 4-phenylhydrazone. 6 G. (1 mol.) of the hydrazone were suspended in 400 c.c. of glacial acetic acid containing 4 c.c. (4 mols.) of bromine, and boiled for 8 hours. Hydrogen bromide was evolved, and on cooling, the *bromination product* separated as a yellow solid. It was crystallised from boiling acetic acid, in which it is sparingly soluble, and from which it separates in short, yellow prisms, m. p. 258° (decomp.). Yield, 6 g. (Found : Br, 20.6.  $C_{16}H_{11}O_3N_4Br$  requires Br, 20.7%).

The bromine was shown to have entered the para-position by the production of *p*-bromoaniline on reduction : 5 G. of the bromination product were dissolved in 150 c.c. of 1% aqueous sodium hydroxide and reduced as before with 80 g. of 2½% sodium amalgam; when this was poured into 200 c.c. of 2½% sulphuric acid, saturated with sulphur dioxide, 1-phenyl-4-amino-5-ketopyrazoline-3-carboxylic acid separated as a white precipitate (yield, 2 g.; acetyl derivative, m. p. 216°). The acid filtrate was concentrated, made alkaline with caustic soda and steam-distilled. *p*-Bromoaniline (m. p. 63°) distilled over, and was identified by conversion to its acetyl derivative, m. p. 167°.

The constitution of the bromination product was further established by its synthesis from 1-phenyl-5-ketopyrazoline-3-carboxylic acid by the action of *p*-bromobenzenediazonium chloride. 2 G. of *p*-bromoaniline were suspended in 3.5 c.c. of concentrated hydrochloric acid and diazotised with 1 g. of sodium nitrite in 25 c.c. of water; the small excess of nitrous acid was removed by bubbling air through the solution, which was then added to a solution of 2 g. of 1-phenyl-5-ketopyrazoline-3-carboxylic acid in 100 c.c. of a 2% aqueous solution of potassium hydroxide. 1-Phenyl-4 : 5-diketopyrazoline-3-carboxylic acid 4-*p*-bromophenylhydrazone separated as a yellow precipitate, which, after the addition of excess of hydrochloric acid, was filtered off, washed with hot alcohol, and crystallised from acetic acid. It melted at 258° (decomp.) and was identical in all respects with the compound obtained by the direct bromination (above).

In the course of this investigation, several esters of 1-phenyl-4 : 5-diketopyrazoline-3-carboxylic acid 4-phenylhydrazone have

been prepared by the action of alcohols containing hydrogen chloride on anhydriketosuccinic acid phenylosazone. The *methyl* ester, obtained by boiling the phenylosazone (2 g.) for 24 hours with methyl alcohol (30 g.) saturated with dry hydrogen chloride, crystallises from alcohol, in which it is easily soluble, in fine, yellow needles, m. p.  $138^{\circ}$  (Found: N, 17.4.  $C_{17}H_{14}O_3N_4$  requires N, 17.4%). The ethyl ester (Wislicenus and Scheidt, *Ber.*, 1891, 24, 4210), m. p.  $153^{\circ}$ , is obtained in a similar manner. The *n-propyl* ester crystallises from acetic acid, in which it is easily soluble, in long, deep yellow prisms, m. p.  $116.5^{\circ}$  (Found: C, 65.0; H, 4.9; N, 16.1.  $C_{19}H_{18}O_3N_4$  requires C, 65.1; H, 5.1; N, 16.0%). The *n-butyl* ester crystallises from acetic acid in long prisms, not quite so deep in colour as those of the *n-propyl* ester but melting at practically the same temperature,  $117^{\circ}$  (a mixture of these two esters had m. p.  $112^{\circ}$ ) (Found: C, 66.2; H, 5.5; N, 15.5.  $C_{20}H_{20}O_3N_4$  requires C, 65.9; H, 5.5; N, 15.4%).

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