44. *A Synthesis of Histamine from But-2-yne-1 : 4-diol.*

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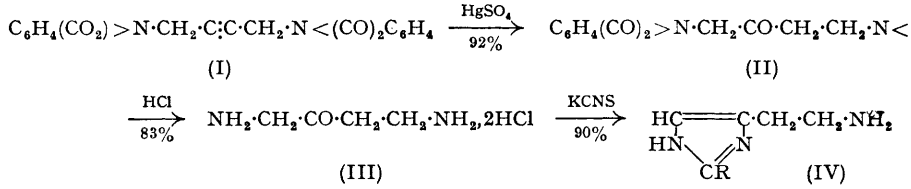
1 : 4-Diphthalimidobut-2-yne (I), prepared by the interaction of 1 : 4-dichlorobut-2-yne and potassium phthalimide, undergoes smooth hydration to 1 : 4-diphthalimidobutan-2-one (II) which is readily hydrolysed to the parent diamine dihydrochloride (III). Condensation of (III) with potassium thiocyanate and subsequent oxidation furnishes histamine (IV; R = H).

Although the synthesis of the allergenic agent histamine (4-2′-aminoethylglyoxaline) (IV; R = H) was first realised by Windaus and Vogt (*Ber.*, 1907, **40**, 3691) the first practicable preparation was devised by Pyman employing an eight-stage synthesis from citric acid (*J.*, 1911, **99**, 668; cf. Koessler and Hanke, *J. Amer. Chem. Soc.*, 1918, **40**, 1716). The recent availability of one of the intermediates (4-hydroxymethylglyoxaline) from fructose (Totter and Darby, *Org. Synth.*, 1944, **24**, 64) has shortened this reaction sequence but even with this improvement the synthesis is tedious and the overall yield is only moderate. The investigation of new synthetic methods has up to now revealed no more advantageous route (Akabori and Numano, *Bull. Chem. Soc., Japan*, 1936, **11**, 214; Dankova, Sidorova, and Preobrashenski, *J. Gen. Chem., U.S.S.R.*, 1945, **15**, 674).



The recent commercial availability of but-2-yne-1 : 4-diol suggested a new approach to the compound. This glycol was converted by thionyl chloride in high yield into 1 : 4-dichlorobut-2-yne (Johnson, *J.*, 1946, 1009). Reaction of the dichloride with a solution of potassium phthalimide in dimethylformamide (Sheehan and Bolhofer, *J. Amer. Chem. Soc.*, 1950, **72**, 2786) furnished an excellent yield (91%) of the corresponding diphthalimido-compound (I). Under the influence of mercuric sulphate catalyst in acetic acid the triple bond of (I) was smoothly hydrated, 1 : 4-diphthalimidobutan-2-one (II)

being obtained in nearly theoretical yield; hydrolysis with hydrochloric acid then produced 1 : 4-diaminobutan-2-one dihydrochloride (III). This compound has already been prepared by Pyman (*J.*, 1930, 98) by degradation of histamine and was reconverted by him into the parent compound. In an analogous but modified manner (III) was condensed with potassium thiocyanate to give, in almost quantitative yield, the hydrochloride of 2-mercaptohistamine (IV; R = SH), oxidation of which with ferric chloride, followed by treatment with picric acid, furnished the dipicrate of histamine (IV; R = H).

The facility with which the above reactions proceed is demonstrated by the high overall yield (41%) of histamine dipicrate from but-2-yne-1 : 4-diol. The sequence is obviously applicable to other similarly constituted acetylenic glycols to furnish analogues of histamine which may possibly possess anti-histaminic properties; this is now being investigated.

Experimental

1 : 4-*Dichlorobut-2-yne.*—This was prepared from the glycol by the action of 2·4 mols. of thionyl chloride in pyridine as described by Johnson (*loc. cit.*), yields similar to his being obtained. In some runs a small amount of 4-*chlorobut-2-yn-1-ol*, b. p. 87—88°/12 mm., 105—107°/25 mm., n_D^{19} 1·5007, was isolated (Found: C, 45·3; H, 4·9. C_4H_5OCl requires C, 45·95; H, 4·8%), the *phenylurethane* of which crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 77—78° (Found: N, 6·2. $C_{11}H_{10}O_2NCl$ requires N, 6·25%). This chloro-alcohol constitutes the main product when only 1 mol. of thionyl chloride is employed in the reaction (Dr. M. C. Whiting, personal communication).

1 : 4-*Diphthalimidobut-2-yne.*—To a stirred solution of potassium phthalimide (31 g.) in dimethylformamide (130 c.c.) was added slowly 1 : 4-dichlorobut-2-yne (10·2 g.), and the mixture heated by steam for 7 hours. After being cooled the reaction mixture was treated with water (200 c.c.), and the precipitated solid (26 g., 91%), m. p. 277—279°, filtered off, washed with water, and dried. The *diphthalimido*-compound crystallised from acetic acid in pale yellow prisms, m. p. 281—282° (Found: N, 8·3. $C_{20}H_{12}O_4N_2$ requires N, 8·15%).

1 : 4-*Diphthalimidobutan-2-one.*—To a solution of 1 : 4-diphthalimidobut-2-yne (3 g.) in 90% acetic acid (140 c.c.) was added mercuric acetate (750 mg.), followed by concentrated sulphuric acid (0·5 c.c.), and the mixture heated under reflux for 4 hours. Water (200 c.c.) was added to the resulting solution and, after an hour's standing, the precipitated solid was filtered off and washed with water. The *diphthalimido-ketone* (2·9 g., 92%) crystallised from acetic acid in white plates, m. p. 248—249° (Found: C, 66·3; H, 4·3; N, 7·5. $C_{20}H_{14}O_5N_2$ requires C, 66·3; H, 3·9; N, 7·7%). Treatment with hydroxylamine hydrochloride in pyridine gave the corresponding *oxime*, crystallising from alcohol in needles, m. p. 225—226° (Found: N, 10·65. $C_{20}H_{15}O_5N_3$ requires N, 11·1%).

1 : 4-*Diaminobutan-2-one Dihydrochloride.*—A mixture of the foregoing ketone (8·1 g.), acetic acid (150 c.c.), and concentrated hydrochloric acid (150 c.c.) was heated under reflux for 36 hours with further additions (each 40 c.c.) of the 1 : 1 acetic acid–hydrochloric acid after 4 and 24 hours. The resulting solution was treated with charcoal, filtered, and evaporated to small bulk (60 c.c.). On being cooled the solution deposited phthalic acid (6·1 g., 82%) which was filtered off and washed with a little water. The filtrate was evaporated under reduced pressure (20 c.c.), alcohol (100 c.c.) added, and the solution kept at 0°. The crystalline solid (3·15 g.) thus obtained was filtered off and the filtrate evaporated to obtain a further small quantity of the product. The combined yield was suspended in boiling alcohol, and hot water added slowly until dissolution was effected. On being cooled the solution deposited the diamino-ketone dihydrochloride (3·25 g., 83%) in elongated plates, m. p. 217° (decomp.) [Pyman, *loc. cit.*, gives m. p. 221° (decomp.; corr.)].

2-*Mercaptohistamine Hydrochloride.*—A solution of the diamino-ketone dihydrochloride (3·1 g.) and potassium thiocyanate (1·85 g.) in water (15 c.c.) was evaporated to a syrup which was then heated for 1 hour by steam. Just enough hot water was then added to dissolve the inorganic salts; when kept, the solution deposited pure 2-mercaptohistamine hydrochloride (0·94 g.) in long needles, m. p. 244—245° [Pyman, *loc. cit.* gives m. p. 248—249° (corr.)]. The mother-liquor was evaporated to dryness and extracted with three 25-c.c. portions of boiling methanol. Evaporation of the methanol in stages gave further quantities of the pure product (total yield, 2·84 g.; 90%).

Histamine Dipicrate.—A solution of 2-mercaptohistamine hydrochloride (155 mg.) and ferric chloride hexahydrate (1·39 g.) in water (10 c.c.) was heated under reflux for 1 hour. Enough solid sodium carbonate was then introduced to neutralise the mineral acid without

causing precipitation of iron carbonate, and a hot saturated aqueous solution of picric acid (395 mg.) added. After some time the crystalline precipitate of histamine dipicrate (384 mg., 80%) was filtered off and crystallised from aqueous ethanol whence it formed yellow prismatic plates, m. p. 234—235° (decomp.) [Pyman, *loc. cit.*, gives m. p. 238° (decomp.; corr.)].

Treatment of a portion of the dipicrate with concentrated hydrochloric acid and benzene, followed by removal of the benzene extract and evaporation of the aqueous layer, yielded histamine dihydrochloride as needles, m. p. 238—239° after crystallisation from methanol–ether [Koessler and Hanke, *loc. cit.*, give m. p. 244—246° (corr.)].

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