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Hofmann rearrangement of 5-carbamylpyridazine-4-carboxylic acid (**6**), obtained from pyridazine-4,5-dicarboxylic acid (**3**) through the corresponding anhydride (**5**), afforded 5-aminopyridazine-4-carboxylic acid (**1**) in good yield. Compound **1** cyclised with benzoyl chloride in pyridine to give 2-phenylpyridazino[4,5-*d*]-1,3-oxazin-4-one (**7**), a new heterocyclic ring system.

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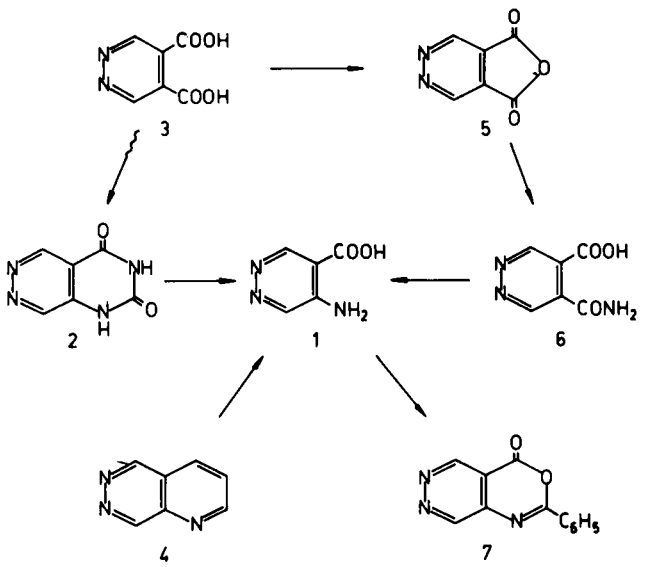
5-Aminopyridazine-4-carboxylic acid (**1**) has proven to be a useful intermediate for synthesising condensed pyridazine ring systems (1). It was first prepared (1) by hydrolytic ring opening of pyrimido[4,5-*d*]pyridazine-2,4-dione (**2**), obtained from pyridazine-4,5-dicarboxylic acid (**3**) by a three steps synthesis (2); more recently compound **1** was also prepared by permanganate oxidation of pyrido-[2,3-*d*]pyridazine (**4**) (3).

Scheme 1



We wish to describe a simple alternative procedure which enabled us to obtain the title compound from the same acid (**3**) in 65% yield.

Täuber reported unsuccessful attempts (4) to dehydrate compound **3** into the corresponding anhydride. Treatment of the former with acetic anhydride at different temperatures (100-140°), gave in our hands only a small amount of pyridazine-4,5-dicarboxylic acid anhydride (**5**) which, on the contrary, was obtained in excellent yield when the acid (**3**) was allowed to react with dicyclohexylcarbodiimide in anhydrous tetrahydrofuran at room temperature.

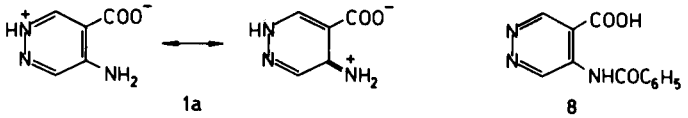
Compound **5**, a key intermediate for the synthesis of several 4,5-disubstituted pyridazines (5), was rapidly hydrolysed to **3** by exposure to the air moisture and it was converted quantitatively into 5-carbamylpyridazine-4-carboxylic acid (**6**) by reaction with dry ammonia gas.

In a series of experiments for converting compound **6** into **1**, the most satisfactory results were obtained when the former was refluxed in alkali hypobromite solution for about 15 minutes. As reported for *p*-nitrobromobenzamide (6), the Hofmann rearrangement largely predominated at high temperature on the competitive hydrolysis of **6** into **3**.

Compound **1** cyclised smoothly, by treatment with benzoyl chloride in pyridine, to give 2-phenylpyridazino-[4,5-*d*]-1,3-oxazin-4-one (**7**), a new heterocyclic ring system, whose structure followed from spectral evidence. The ir spectrum shows a strong band at 1780 cm^{-1} attributable to the stretching vibration of the lactone carbonyl group; the nmr spectrum in deuteriochloroform exhibits two multiplets at δ 7.6 (3H) and 8.37 (2H) for the phenyl group, and two doublets (1H, J 1.2 Hz) at δ 9.6 and 9.72, attributable to the ring protons at 8- and 5-position, respectively.

Attempts to diazotise compound **1** under a variety of

Scheme 2



conditions employed for anthranilic acid (7-9) and 3-aminopyridine-4-carboxylic acid (10) were unsuccessful; most of the starting material was recovered unchanged.

This lack of reactivity could be explained by a zwitterionic structure of the type **1a**, which largely reduced the nucleophilic character of the amino group at 5-position. Such a structure was strongly suggested by the ir spectrum showing two broad bands between 2900 and 1800 cm^{-1} (maxima at 2600, 2045, and 1960 cm^{-1}) and a strong band at 1625 cm^{-1} for the NH^+ and CO_2^- groups, respectively.

EXPERIMENTAL

All melting points were determined in capillaries and are uncorrected. Unless otherwise stated, the infrared spectra were

measured for potassium bromide discs with a Perkin-Elmer 457 Spectrometer, and the ultraviolet spectra were taken in chloroform with a Cary 14 Spectrophotometer. ^{1}H nmr spectra were recorded with a Perkin-Elmer R 32 instrument. Chemical shifts are reported in ppm downfield from internal tetramethylsilane.

Pyridazine-4,5-dicarboxylic Acid Anhydride (**5**).

Finely ground pyridazine-4,5-dicarboxylic acid (**3**) (0.5 g.) and dicyclohexylcarbodiimide (0.615 g.) were stirred overnight in anhydrous tetrahydrofuran (50 ml.) at room temperature. The reaction mixture was filtered and the white solid was washed with the same solvent (2-3 ml.). Evaporation to dryness of the filtrate under reduced pressure left a yellow-brown residue, which was kept in a vacuum dessiccator (phosphorus pentoxide) for about 30 minutes and sublimed at 80° and 0.02 mm to give the anhydride (**5**) (0.4 g., 89.7%) as a yellow solid. An analytical sample, prepared by crystallisation from anhydrous benzene and further sublimation, darkened above 170° and decomposed between 180° and 190°; ir (nujol): 3100, 1880, 1865, 1815, 1797, 1780, 1590, 1350, 1280, 1120, 978, 915, 725, 715, and 553 cm^{-1}; uv: 275 (log ϵ 3.42) nm; nmr (deuteriochloroform): δ 10.01 (s, 2,3- and 6-H).

Anal. Calcd. for $C_6H_2N_2O_3$: C, 48.0; H, 1.33; N, 18.66. Found: C, 48.23; H, 1.36; N, 18.67.

5-Carbamylpyridazine-4-carboxylic Acid (**6**).

Pyridazine-4,5-dicarboxylic acid (**3**) (0.5 g.) was converted into the corresponding anhydride by the method described above. After removal of dicyclohexylurea by filtration, the tetrahydrofuran solution was saturated with dry gaseous ammonia at room temperature. The solid, which separated, was filtered and dissolved in the minimum amount of water (*ca.* 10 ml.); acidification of the solution with concentrated hydrochloric acid (*p*H 1-2) precipitated the acid (**6**) (0.45 g., 90%). An analytical sample, obtained by crystallisation from water, gradually darkened above 180° and largely decomposed at 195°; ir: 3390, 3300, 3270, 3210, 3100, 3070, 2810, 2440, 1880, 1680, 1610, 1570, 1405, 1315, 1280, 1200, 1010, 965, 935, 820, 780, 730, 700, 650, 630, 590, and 535 cm^{-1}; nmr (DMSO-d_6): δ 7.87 and 8.22 (bd s, 2, NH_2), 8.4 (d, J 1 Hz, 1, 3- or 6-H), 8.5 (d, J 1 Hz, 1, 6- or 3-H) and 10.3 (vbd s, 1).

Anal. Calcd. for $C_6H_5N_3O_3$: C, 43.12; H, 3.02; N, 25.14. Found: C, 42.90; H, 3.0; N, 25.26.

5-Aminopyridazine-4-carboxylic Acid (**1**).

Compound **6** (1 g.) was added to a stirred alkali hypobromite solution, freshly prepared by dissolving bromine (1 g.) in aqueous potassium hydroxide (10%; 17 ml.) at 0°. Stirring was continued until the solid was completely dissolved and the resulting solution was gently refluxed for about 15 minutes. The reaction mixture was cooled, acidified with concentrated hydrochloric acid (*p*H 2), and set aside overnight. The pale yellow solid which separated was filtered to give the aminoacid (**1**) (0.43 g.); after addition of solid potassium bicarbonate (*p*H 5-6), the filtrate was concentrated under vacuum to yield a second crop (0.11 g.) of the same product which was isolated by filtration. An analytical sample, obtained by crystallisation from water (charcoal), gradually darkened above 300° and melted with decomposition at 310-312° (11) [lit. (1) 316° dec., (3) 319-320°].

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.33; H, 3.71; N, 30.11.

Addition of barium chloride dihydrate (0.75 g.) to the aqueous filtrate precipitated a solid which was treated with hydrochloric acid to give pyridazine-4,5-dicarboxylic acid (0.1 g.).

2-Phenylpyridazino[4,5-*d*]-1,3-oxazin-4-one (**7**).

5-Aminopyridazine-4-carboxylic acid (**1**) (0.3 g.) and benzoyl chloride (0.6 g.) were stirred in pyridine (6 ml.) at room temperature for 5 hours. The reaction mixture was treated with ice-cold water (30 ml.) and filtered immediately (12) to give compound **7** (0.33 g., 68%), m.p. 207-209° (after sublimation at 110-120° and 0.01 mm and crystallisation from ethyl acetate); ir: 3040, 1780, 1595, 1550, 1450, 1430, 1318, 1260, 1220, 1180, 1170, 1063, 1020, 1000, 958, 932, 920, 793, 770, 708, and 632 cm^{-1}; uv: 245 (log ϵ 4.04), 281 (log ϵ 4.14), 290 (log ϵ 4.17), and 324 (log ϵ 4.25) nm.

Anal. Calcd. for $C_{12}H_7N_3O_2$: C, 64.0; H, 3.13; N, 18.66. Found: C, 64.03; H, 3.09; N, 18.54.

5-(*N*-Benzoylamino)pyridazino-4-carboxylic Acid (**8**).

Compound **7** (0.1 g.) was stirred in aqueous sodium hydroxide (0.5%; 5 ml.) for 24 hours. Acidification of the solution with concentrated hydrochloric acid precipitated compound **8** (0.1 g.), m.p. 249-250° (from dimethylsulfoxide); ir: 3085, 2820, 2500, 2120, 1690, 1630, 1568, 1450, 1428, 1370, 1350, 1267, 1230, 1085, 922, 868, 830, 700, 682, 595, and 542 cm^{-1}.

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 58.96; H, 3.71; N, 17.22.

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(11) The melting point is sensitive to the rate of heating.

(12) Compound **7** was rapidly converted into the acid (**8**) under these conditions.