Hydrazinolysis of 4-Acyl and 4-Ethoxycarbonyl-3*H*-imidazo[1,5-*b*]-pyridazine-5,7-(6*H*)diones: 8-Oxo-1,4,7,8-tetrahydropyridazino-[4,5-*c*]pyridazine, 8-Oxo-7,8-dihydropyridazino[4,5-*c*]pyridazine and 5,8-Dioxo-1,4,5,6,7,8-Hexahydropyridazino[4,5-*c*]pyridazine Derivatives

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Reaction of 4-acyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7-(6*H*)diones with hydrazine hydrate gave 3*R*-5*R*'-8-oxo-1,4,7,8-tetrahydropyridazino[4,5-*c*]pyridazine together with 3*R*-5*R*'-8-oxo-7,8-dihydropyridazino[4,5-*c*]pyridazine derivatives. Their structures were assigned by means of elemental analyses and spectroscopic data (ir, uv, nmr and ms). The conclusive structural elucidation involved the fact that 2*R*-4-ethoxycarbonyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7-(6*H*)-diones treated with hydrazine hydrate afforded 3*R*-5,8-dioxo-1,4,5,6,7,8-hexahydropyridazino-[4,5-*c*]pyridazine which, upon dehydrogenation, gave products previously reported in the literature.

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The first reported pyridazino[4,5-*c*]pyridazines were obtained by Gault, *et a.*, (1). All other data about the synthesis and reactivity of this heterocyclic system are due to Singermann and Castle (2). The more recent papers describe the preparation of a number of derivatives of pyridazino[4,5-*c*]pyridazine (3,4).

A novel ring transformation of a 2,3-dihydrofuran to a pyridazino[4,5-*c*]pyridazine has been described recently (5). In this communication we wish to report the successful synthesis of this ring system by hydrazinolysis of the 4-acyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7-(6*H*)diones (**1a,b,c**) (6,7) with 95% hydrazine hydrate in ethanol at refluxing, which gave a mixture of two compounds, isolated in approximately equal amount by column chromatography or by fractional crystallization (Scheme I).

These substances which were obtained, were formulated as 3*R*-5*R*'-8-oxo-1,4,7,8-tetrahydropyridazino[4,5-*c*]pyridazines (**2a,b,c**) and 3*R*-5*R*'-8-oxo-tetrahydropyridazino-[4,5-*c*]pyridazines (**3a,b,c**), respectively.

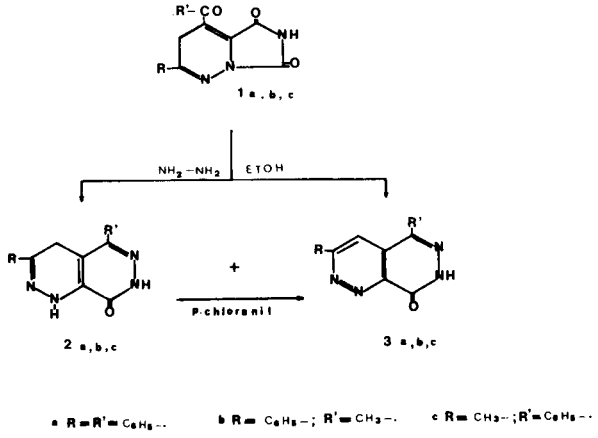
Clearly, the isolated compounds **3a,b,c** were formed through a spontaneous dehydrogenation reaction. Moreover, these dehydro derivatives could be also obtained by the action of *p*-chloranil on **2a,b,c**.

That transformation of imidazopyridazines **1a,b,c** into the bicyclic system pyridazinopyridazines has occured was established on the basis of analytical data together with ir, nmr and ms data. Thus, the nmr spectra of compounds **2a,b,c** showed, beside the signals for substituents, a singlet (2H) at δ 3.20-3.70 attributable to a cyclic -CH_2- and two signals exchangeable with deuterium oxide at δ 9.80-12.80 due to the two NH protons.

The carbonyl absorptions in the ir are more normal appearing at 1650-1680 cm^{-1}, indicating that these compounds were isolated in the lactam form.

The nmr spectra of compounds **3a,b,c** exhibited a singlet at δ 12.80-13.20, exchangeable with deuterium oxide due to a NH group; ir spectra showed absorption carbonyl bands at 1680-1700 cm^{-1} and were explained in terms of the lactam structures. In order to confirm that the assigned structures of pyridazino[4,5*c*]pyridazines **2** and **3** were correct, we allowed 2-phenyl-4-ethoxycarbonyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7-(6*H*)dione (**4a**) and 2-methyl-4-ethoxycarbonyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7-(6*H*)-dione (**4b**) to react with hydrazine in ethanol solution. Under these reaction conditions, a complex intractable mixture was obtained.

SCHEME I



Instead, direct action of 95% hydrazine hydrate upon **4a** and **4b** afforded the 3-phenyl-5,8-dioxo-1,4,5,6,7,8-hexahydropyridazino[4,5-*c*]pyridazine (**5a**) and 3-methyl-5,8-dioxo-1,4,5,6,7,8-hexahydropyridazino[4,5-*c*]pyridazine (**5b**), respectively in fairly good yields (Scheme II). For these compounds a lactam-lactim tautomerism is possible,

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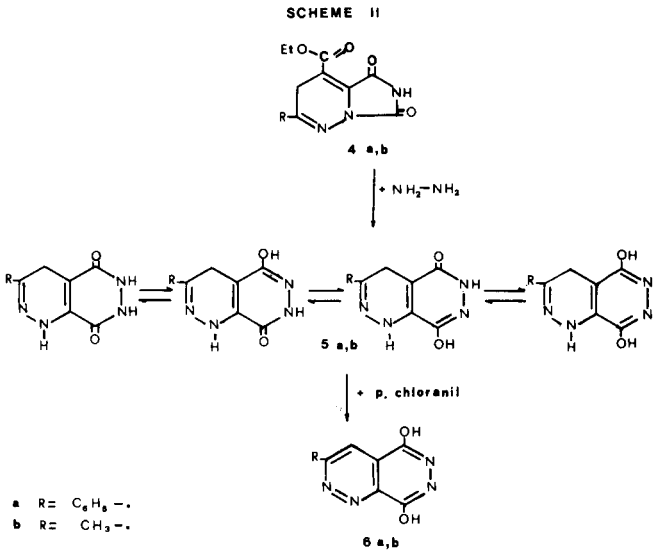
SCHEME II



so that the structures **5** outlined in the scheme must be considered.

However, we propose that the products **5a** and **5b** exist predominantly in DMSO solution as lactams. In fact, the nmr spectra exhibited a signal at δ 10.20-10.40 due to the NH proton (1H) and resonances at δ 11.20-12.50 attributable to NH groups (2H) exchangeable with deuterium oxide; moreover, the ir spectra showed absorption bands at 1670 and 1650 cm^{-1} attributable to carbonyl groups. Lastly, the dehydrogenation of **5b** yielded the 3-methyl-5,8-dihydroxypyridazino[4,5-*c*]pyridazine (**6b**) identical with an authentic sample (2).

The dehydrogenation of **5a** gave 3-phenyl-5,8-dyhydroxypyridazino[4,5-*c*]pyridazine (**6a**) which was mentioned in a Japanese patent, but neither physical nor spectroscopic data were reported for **6a** (3).

EXPERIMENTAL

All melting points were taken on Büchi-Tottoli capillary melting point apparatus and are uncorrected. Uv absorption spectra were determined in ethanol solution (unless otherwise specified) with Perkin-Elmer Itachi 200 spectrophotometer and ir absorption spectra with a Perkin-Elmer Infracord 299, using nujol mulls. Nmr spectra (DMSO-d_6) were measured using TMS as the internal standard, with a Jeol C-60 H spectrometer. The mass spectra were measured with a Jeol JMS-01SG-2 double focusing spectrometer at 75 eV (100μA). The samples were directly introduced and heated at about 200°. Exact masses were measured on Ilford Q-2 photoplates; per fluoro Kerosene was used as a reference at a resolving power better than 15,000. Silica gel for chromtography was Merck (0.05-0.2 mm) in the inactive form.

2-Methyl-4-benzoyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7(6*H*)dione (**1c**) and 2-Methyl-4-ethoxycarbonyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7 (6*H*)dione (**4b**).

Methyl 2,5-dioxo-3-benzoylhexanoate 5-semicarbazone (0.6 g.) (9) or ethyl 3-ethoxycarbonyl-2,5-dioxohexanoate 5-semicarbazone (0.6 g.) (9) were treated with 30 ml. of an ethanolic solution sodium ethylate (0.05%) and stirred at room temperature for 60 hours. Upon evaporation under reduced pressure, the residue was refluxed in ethanol saturated with hydrochloric acid (25 ml.) for one hour to complete the reaction. On cooling **1c** and **4b** were obtained.

Compound **1c** had m.p. 235° (1-butanol) (yield 42%); ir: cm^{-1} 3150 (broad, NH) 1780 (CO); nmr: δ 2.00 (3H, s, $-CH_3$), 3.30 (2H, s, $-CH_2-$), 7.30-8.20 (5H, m, C_6H_5-), 11.60 (1H, broad, NH, exchangeable with deuterium oxide); ms: 269 (M^+).

Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.53; H, 4.10; N, 15.73.

Compound **4b** had m.p. 195° (ethanol) (yield 51%); ir: cm^{-1} 3140 (broad, NH) 1780 (CO); nmr: δ 1.20 (3H, tr, $-COOCH_2-CH_3$, J ≅ 6.00 Hz), 2.00 (3H, s, $-CH_3$), 3.25 (2H, s, $-CH_2-$), 4.20 (2H, q, $-COOCH_2CH_3$, J ≅ 6.00 Hz), 11.55 (1H, broad, NH, exchangeable with deuterium oxide); ms: 237 (M^+).

Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.72. Found: C, 50.62; H, 4.60; N, 17.79.

General Procedure for Preparation of Pyridazino[4,5-*c*]pyridazine Derivatives.

The mixture of 2 mmoles of **1a,1b** or **1c** in 100 ml. of ethanol and 20 mmoles of hydrazine hydrate 95% was refluxed for 7 hours. The reaction solution was concentrated under reduced pressure. Compounds **2a,2b** and **3a,3b** were isolated by column chromatography on silica gel (100 g.). Compounds **2c** and **3c** were separated by fractional crystallization.

3,5-Diphenyl-8-oxo-1,4,7,8-tetrahydropyridazino[4,5-*c*]pyridazine (**2a**). 3,5-Diphenyl-8-oxo-7,8-dihydropyridazino[4,5-*c*]pyridazine (**3a**).

Elution with cyclohexane-ethyl acetate (8:2) gave 0.2 g. (yield 27%) of **2a**.

Further elution with cyclohexane-ethyl acetate (7:3) gave 0.3 g. (yield 40%) of **3a**.

Compound **2a** was obtained as yellow needles, m.p. 275° (1-butanol); uv: λ max nm log ε 240 (4.40) 270 (4.30) 360 (3.95); ir: cm^{-1} 3300 (broad, NH), 1680 (CO); nmr: δ 3.60 (2H, s, $-CH_2-$), 7.20-7.60 (10H, m, 2 × C_6H_5), 10.50 (1H, s, NH, exchangeable with deuterium oxide), 12.90 (1H, s, NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $C_{18}H_{14}N_4O$: 302.117. Found: 302.115 (± 0.002).

Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.68; H, 4.62; N, 18.45.

Compound **3a** was obtained as white needles m.p. 315° (1-butanol); uv: λ max nm log ε 228 sh (3.90) 275 (4.48) 340 (3.70); ir: cm^{-1} 3120 (broad, NH), 1680 (CO); nmr: δ 7.20-8.40 (11H, m, 2 × C_6H_5 and =CH-), 13.20 (1H, s, NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $C_{18}H_{12}N_4O$: 300.101. Found: 300.103 (± 0.002).

Anal. Calcd. for $C_{18}H_{12}N_4O$: C, 71.99; H, 4.03; N, 18.66. Found: C, 72.10; H, 4.19; N, 18.71.

5-Methyl-3-phenyl-8-oxo-1,4,7,8-tetrahydropyridazino[4,5-*c*]pyridazine (**2b**). 5-Methyl-3-phenyl-8-oxo-7,8-dihydropyridazino[4,5-*c*]pyridazine (**3b**).

Elution with cyclohexane-ethyl acetate (1:1) gave 0.2 g. (yield 39%) of **2b**.

Further elution with cyclohexane-ethyl acetate (2:3) gave 0.35 g. (45%) of **3b**.

Compound **2b** was obtained as orange needles, m.p. 285° (ethanol); uv: λ max nm log ε 225 (4.11) 267 (3.90) 365 (3.95); ir: cm^{-1} 3200 (broad, NH), 1650 (CO); nmr: δ 2.40 (3H, s, CH_3), 3.70 (2H, s, $-CH_2-$), 7.20-8.00 (5H, m, C_6H_5), 10.36 (1H, s, NH, exchangeable with D_2O), 12.48 (1H, s, NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $C_{13}H_{12}N_4O$: 240.101. Found: 240.103 (± 0.002).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 65.10; H, 4.98; N, 23.42.

Compound **3b** was obtained as white needles, m.p. 335° dec. (1-butanol); uv: λ max nm log ε 270 (4.34) 330 (3.60); ir: cm^{-1} 3180 (broad, NH), 1675 (CO); nmr: δ 2.56 (3H, s, CH_3), 7.60-8.40 (6H, m, C_6H_5 and =CH-), 12.80 (1H, s, NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $C_{13}H_{10}N_4O$: 238.085. Found: 238.082 (± 0.002).

Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.70; H, 4.23; N, 23.54.

3-Methyl-5-phenyl-8-oxo-1,4,7,8-tetrahydropyridazino[4,5-*c*]pyridazine (**2c**). 3-Methyl-5-phenyl-8-oxo-7,8-dihydropyridazino[4,5-*c*]pyridazine (**3c**).

The reaction solution was concentrated to a small volume when a crystalline product **3c** was separated (0.19 g., yield 40%).

The mother liquor gave, on standing, product **2c** (0.144 g., yield 30%).

Compound **2c** was obtained as red crystals m.p. 185° (ethanol); uv: λ max nm log ε 228 (4.36) 257 (4.14) 335 (4.01); ir: cm^{-1} 3300 (broad, NH), 1670 (CO); nmr: δ 1.90 (3H, s, CH_3), 3.20 (2H, s, $-CH_2-$), 7.40-8.00 (5H, m, C_6H_5) 9.80 (1H, s, NH, exchangeable with deuterium oxide), 12.80 (1H, s, NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $C_{13}H_{12}N_4O$: 240.178. Found: 240.173 (± 0.002).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.88; H, 5.13; N, 23.42.

Compound **3c** was obtained as orange needles, m.p. 325° (ethanol); uv: λ max nm log ε 228 (4.04) 260 (3.80) 355 (3.30); ir: cm^{-1} 3125 (broad, NH), 1700 (CO); nmr: δ 2.80 (3H, s, CH_3), 7.40-7.80 (6H, m, C_6H_5 and =CH-), 13.20 (1H, s, NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $C_{13}H_{10}N_4O$: C, 238.1616. Found: 238.1621 (± 0.0025).

Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.47; H, 4.35; N, 23.61.

General Procedure for Dehydrogenation of Tetrahydro Derivatives **2a,2b,2c** into Dihydro Derivatives **3a,3b,3c**.

A solution of 1.5 g. of **2a,2b** or **2c** and *p*-chloranil (1.5 g.) in acetic acid (150 ml.) was heated under reflux for 16 hours and then concentrated *in vacuo*. The resulting residue was chromatographed on a silica gel column (150 g.).

Compound **3a** was obtained by elution with cyclohexane-ethyl acetate (7:3) (400 ml.) (800 mg.), m.p. 302°.

Compound **3b** was obtained by elution with cyclohexane-ethyl acetate (1:1) (450 ml.) (700 mg.), m.p. 335°.

Compound **3c** was obtained by elution with cyclohexane-ethyl acetate (7:3) (300 ml.) (850 mg.), m.p. 325°.

These three products were identical in all respects with the compounds described above.

Reaction of Hydrazine Hydrate with **4a** and **4b**. 3-Phenyl-5,8-dioxo-1,4,5,6,7,8-hexahydropyridazino[4,5-*c*]pyridazine (**5a**) and 3-Methyl-5,8-dioxo-1,4,5,6,7,8-hexahydropyridazino[4,5-*c*]pyridazine (**5b**).

A mixture of **4a** (6) (0.5 g.) or **4b** (0.5 g.) and 20 ml. of 95% hydrazine hydrate was heated under reflux for 7 hours. Excess hydrazine hydrate was then removed by distillation under reduced pressure. The residue was washed with ice-water (20 ml.) and a few ml. of acetic acid, filtered and air dried.

Compound **5a** had m.p. 325° (acetic acid, yield 80%); uv: λ max nm log ε 240 sh (3.95) 270 (4.30) 345 (3.70); ir: cm^{-1} 3330 (broad, NH) 1670 (CO); nmr: δ 3.50 (2H, s, $-CH_2-$), 7.20-8.00 (5H, m, C_6H_5), 10.20 (1H, s, NH, exchangeable with deuterium oxide), 11.20 (2H, broad, 2 × NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $C_{12}H_{10}N_4O_2$: 242.080. Found: 242.082 (± 0.002).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.60; H, 4.05; N, 23.04.

Compound **5b** had m.p. 310° dec. (acetic acid, yield 70%); uv: λ max 230 sh 315 (8); ir: cm^{-1} 3330 (broad, NH) 1650 (CO); nmr: δ 1.90 (3H, s, CH_3), 3.05 (2H, s, $-CH_2-$), 10.40 (1H, s, NH, exchangeable with deuterium oxide), 12.50 (2H, s, 2 × NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $C_7H_6N_4O_2$: 180.122. Found: 180.121 (± 0.002).

Anal. Calcd. for $C_7H_6N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.63; H, 4.62; N, 31.02.

Dehydrogenation of **5a** and **5b**. 3-Phenyl-5,8-dihydroxypyridazino[4,5-*c*]-pyridazine (**6a**) and 3-Methyl-5,8-dihydroxypyridazino[4,5-*c*]pyridazine (**6b**).

A mixture of **5a** (0.8 g.) or of **5b** (1 g.) and *p*-chloranil (1.5 g.) in acetic acid (250 ml.) was refluxed for 8 hours. Upon removal of the solvent under reduced pressure a residue was obtained.

Compound **6a** was purified by sublimation under vacuum, m.p. 345° (0.4 g.) (3); uv: λ max 275 and 335 sh (8); ir: cm^{-1} 3200 (broad) 1640; nmr: δ 7.60-8.40 (5H, m, C_6H_5), 8.60 (1H, s, =CH-); exact mass measurement: Calcd. for $C_{12}H_8N_4O_2$: C, 240.065. Found: C, 240.064 (± 0.002).

Compound **6b** was purified b column chromatography over silica gel (100 g.). Elution with ethyl acetate-methanol (8:2) (400 ml.) gave 0.5 g. of **6b**, m.p. 270° dec. Spectral data were identical with those of described product (2); exact mass measurement: Calcd. for $C_7H_6N_4O_2$: C, 178.049. Found: 178.050 (± 0.002).

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(7) The synthesis of compounds 2-methyl-4-benzoyl-3*H*-imidazo-[1,5-*b*]pyridazine-5,7(6*H*)dione (**1c**) and 2-methyl-4-carboxyethyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7(6*H*)dione (**4b**) was accomplished by the previously reported method (6) slightly modified (see experimental). The analytical and spectral data are consistent with the structure previously described (6) for imidazo[1,5-*b*]pyridazine derivatives.

(8) Because of solubility limitations, it was not possible to calculate ε values.

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