Studies on the Synthesis of Heterocyclic Compounds. Part V. A Novel Synthesis of Some Pyridazin-4-(1*H*)one Derivatives and their Reaction with Hydrazine

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Some phenylazo derivatives of β-dicarbonyl compounds **1a,b,c,d** reacted with dimethylformamide dimethylacetal to yield new 1-phenyl-3-*R*-4-(1*H*)pyridazinones **3a,e** and **4**. When compounds **3a** and **3e** were treated with hydrazine hydrate, they gave rise to pyrazolo[4,3-*c*]pyridazines **5** and **7**, respectively. By the action of hydrazine hydrate on compound **4**, the 1-phenyl-3-(1*H*-pyrazol-3-yl)-4-(1*H*)pyridazinone **8** was obtained. The structures of all the new compounds were assigned on the basis of satisfactory analytical and spectroscopic data.

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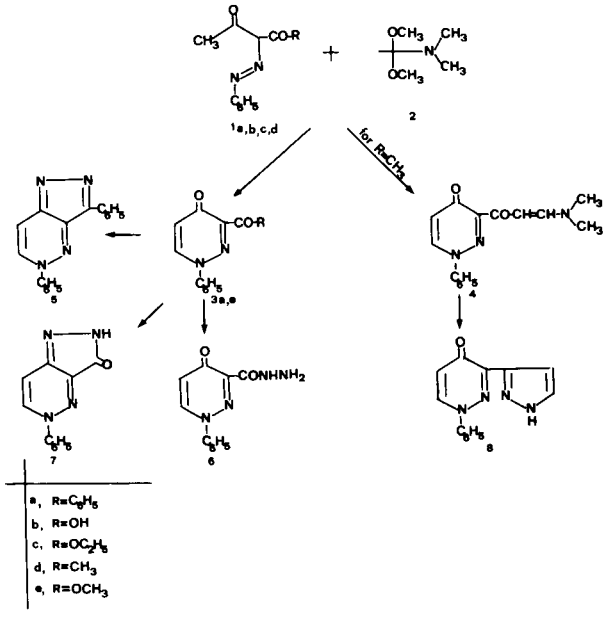
A previous synthetic route to pyrazolo[4,3-*c*]pyridazines was based on the patented work of Anderson, which afforded some antihypertensive arylpyrazolo[4,3-*c*]pyridazinones by treating a suitable chloropyridazinone with methylhydrazine and dimethylformamide dimethylacetal (1). Another work by El Khadem, *et al,* described the preparation of a pyrazolo[4,3-*c*]pyridazine derivative by reduction of dehydro-L-ascorbic acid phenylosazone with lithium aluminum hydride (2).

We report herein a new synthesis of pyrazolo[4,3-*c*]-pyridazines by an entirely different route, employing different starting materials than those previously described. The focal point for our preparation of this bicyclic ring system became the direct elaboration of an appropriately functionalized pyridazinone of type 3 (see Scheme). Thus, a facile novel synthesis of pyridazinones was developed starting from the readily available phenylazoderivatives **1a,b,c,d,** which were allowed to react with excess DFDA **2** (3) to give the desired pyridazin-4-(1*H*)ones bearing a carbonyl group at C-3 in very good yield.

We have found that both the phenylazo derivatives **1b,c** upon reaction with DFDA afforded the identical methylester **3e**. This fact indicated that the expected ethyl ester derived from **1c** transesterified in the presence of the methyl alcohol which separated by the condensation reaction. The expected acid derived from **1b** was methylated to give **3e**.

Moreover, treatment of **1d** with DFDA at reflux afforded the product **4**; in this case the DFDA attacked the two equivalent methyl groups of compound **1d**. Since we required a pyridazine substrate that was substituted in the 3 position with an acetyl group, this reaction proved to be a limiting factor in obtaining the pyrazolo[4,3-*c*]pyridazine system. In fact, **4** reacted smoothly with hydrazine hydrate at room temperature to afford 1-phenyl-3(5)-[1*H*-pyrazol-3(5)-yl]pyridazin-4-(1*H*)one **8**, the structure of which was supported by spectral data and elemental analysis. The presence of the pyrazole moiety in **8** was evident based on the infrared spectrum, which showed a broad absorption band at 3000-3300 cm^{-1} (NH), and the pmr spectrum, which exhibited the resonance of the pyrazole NH at δ 13.47 (1H) and the shift of the H-4 of pyrazole nucleus, seen as a doublet, at δ 7.22 (1H), with a coupling costant of 1.9 Hz, according to literature reported data (4). Moreover, the infrared absorption band at 1635 cm^{-1} was diagnostic for the presence of the carbonyl group of the pyridazinone moiety.

The structure of the new pyridazinones **3a,e** and **4** was established by analytical data and spectroscopic means, as well as by molecular weight determined by mass spectroscopy. Thus, the ir spectra showed the endocyclic carbonyl absorption band at 1625-1630 cm^{-1}, besides the ν CO due to the exocyclic carbonyl group. The structure of these compounds was further substantiated by pmr spectra, which exhibited two doublets with a coupling constant J_{5-6} = 8.0 Hz centered at δ 6.70 and 8.20, attributable to



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the H-5 and H-6 resonances, respectively.

Upon rection of **3e** with hydrazine hydrate at room temperature the corresponding hydrazide **6** was obtained. When the above compounds **3a** and **3e** were treated with hydrazine hydrate in refluxing ethanolic solution they gave rise to the desired pyrazolo[4,3-*c*]pyridazines **5** and **7**, respectively. Analytical, spectral data and molecular weight (ms) of these hitherto unknown compounds give support for the assigned structure as shown in the Experimental.

EXPERIMENTAL

Melting points were determined on Buchi-Tottoli apparatus and are uncorrected. Ir spectra were determined in nujol mulls with a Perkin-Elmer Infrared 299 spectrophotometer. A Jeol-JMS-O1-SG-2 mass spectrometer was employed for determination of low resolution 75 eV mass spectra. Nmr spectra were obtained with a Varian EM-390 90 MHz spectrometer (TMS as internal reference).

General Procedure for the Preparation of 1-Phenyl-3-*R*-4-(1*H*)pyridazinones.

A suspension of the phenylazo derivatives **1a** (5), **b** (6), **c** (7) **d** (5) (10 g.) in dimethylformamide dimethyl acetal (50 ml.) was refluxed for 30 minutes and then cooled at -10°. After standing at -10° overnight, the precipitate was filtered, washed with a little ethyl acetate and recrystallized. Starting from **1b** and **1c** the identical product **3e** was obtained.

Compound **3a**.

The product melted at 128-130° (ethanol), yield 70%; ms: m/e 276 (M^+); ir:cm^{-1} 1680 and 1625 (carbonyl bands); nmr (deuterochloroform): δ 6.69 (1H, d, H-5, J = 8.0 Hz), 7.33-8.00 (10H, m, 2 x C_6H_5), 8.33 (1H, d, H-6, J = 8.0 Hz).

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.95; H, 4.53; N, 10.20.

Compound **3e**.

The product melted at 122-124° (ethanol), yield 70%; ms: m/e 230 (M^+); ir: cm^{-1} 1730 (ester CO) and 1625 (endocyclic CO); nmr (deuterochloroform): δ 3.92 (3H, s, CH_3), 6.70 (1H, d, H-5, J = 8.0 Hz), 7.42-7.50 (5H, m, C_6H_5), 8.21 (1H, d, H-6, J = 8.0 Hz).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.78; H, 4.53; N, 12.21.

Compound **4**.

The product melted at 135-137° (ethyl acetate), yield 60%; ms: m/e 269 (M^+); ir: cm^{-1} 1630 and 1650 (carbonyl bands); nmr (deuterochloroform): δ 2.79-3.11 (6H, m, 2 x CH_3), 5.55 (1H, d, exocyclic proton, J = 12.6 Hz), 6.63 (1H, d, H-5, J = 8.0 Hz), 7.25-7.73 (6H, m, C_6H_5 and exocyclic proton), 8.20 (1H, d, H-6, J = 8.0 Hz).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.99; H, 5.66; N, 15.65.

1-Phenyl-3-(1*H*-pyrazol-3-yl)-4-(1*H*)pyridazinone (**8**).

A solution of **4** (1 g.) and 0.19 ml. of hydrazine hydrate in ethanol (5 ml.) was stirred at room temperature for 4 hours. The resulting gelatinous mixture was mixed with 5 ml. of ethanol and stirring was continued for 20 hours. The solid which separated was filtered and recrystallized from ethanol, yield 80%. The product melted at 186-188° (ethanol); ms: m/e 238 (M^+) ir: cm^{-1} 3000-3300 (broad, NH), 1635 (CO); nmr (DMSO-d_6): δ 6.67 (1H, d, H-5, J = 7.8 Hz), 7.22 (1H, d, pyrazole proton at C-4, J = 1.9 Hz), 7.50-8.02 (6H, m, C_6H_5 and pyrazole proton at C-5), 8.90 (1H, d, H-6, J = 7.8 Hz), 13.47 (1H, m, pyrazole NH, exchangeable).

Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.44; H, 4.07; N, 23.38.

1-Phenyl-3-carbohydrazide-4-(1*H*)-pyridazinone (**6**).

A suspension of **3e** (1 g.) and 0.22 ml. of hydrazine hydrate in ethanol (5 ml.) was stirred at room temperature for 4 hours. The crystalline material which separated was filtered and recrystallized from ethanol. The product melted at 179-181°, yield 80% ms: m/e 230 (M^+); ir: cm^{-1} 3100-3400 (NH_2-NH-), 1665-1710 (CO); nmr (DMSO-d_6): δ 4.75 (2H, s, NH_2), 6.81 (1H, d, H-5, J = 7.9 Hz), 7.46-7.83 (5H, m, C_6H_5), 8.90 (1H, d, H-6, J = 7.9 Hz), 10.60 (1H, broad, NH).

Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.30; H, 4.52; N, 24.43.

5-Phenylpyrazolo[4,3-*c*]pyridazin-3-(2*H*)one (**7**).

A suspension of 1-phenyl-3-carbomethoxy-4-(1*H*)pyridazinone (1 g.) in 5 ml. of ethanol and 0.33 ml. of hydrazine hydrate containing 0.03 ml. of 37% aqueous hydrochloric acid was refluxed for 40 hours. The warm mixture was filtered and the residue recrystallized. The product melted at 297-299° (*N,N*-dimethylformamide), yield 65%; ms: 212 (M^+); ir: cm^{-1} 2700-3500 (NH), 1670 (CO); nmr (DMSO-d_6): δ 7.27 (1H, d, H-7, J = 7.9 Hz), 7.45-7.84 (5H, m, C_6H_5), 8.45 (1H, d, H-6, J = 7.9 Hz), 12.05 (1H, s, exchangeable with deuterium oxide, NH).

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.22; H, 3.77; N, 26.45.

3,5-Diphenylpyrazolo[4,3-*c*]pyridazine (**5**).

A suspension of **3a** (1 g.) in 5 ml. of ethanol containing 0.27 ml. of hydrazine hydrate added to 0.03 ml. of 37% aqueous hydrochloric acid was refluxed for 4 hours. The warm mixture was filtered; the solid was collected and crystallized. The product melted at 271-273° (ethanol), yield 80% ms: m/e 272 (M^+) nmr (DMSO-d_6): δ 7.47-8.49 (11H, m, 2 x C_6H_5 and H-7), 9.20 (1H, d, H-6, J = 7.9 Hz).

Anal. Calcd. for $C_{17}H_{12}N_4$: C, 74.98; H, 4.44; N, 20.58. Found: C, 74.87; H, 4.53; N, 20.52.

REFERENCES AND NOTES

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