Synthesis of Pyridazino[4,5-*b*]indole Derivatives from 2-(3-Carboxy-1-methylindole)acetic Acid Anhydride

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2-(3-Carboxy-1-methylindole)acetic acid anhydride (**1**) reacts with aryldiazonium salts to give 85-95% of the corresponding α-hydrazono anhydrides **2**. Treating **2** with boiling hydrazine hydrate in xylene, the respective 2-aryl-4-carbohydrazido-5-methyl-1-oxo-1,2-dihydro-5*H*-pyridazino[4,5-*b*]indoles **3** were obtained (47-67%), and these compounds characterized as the respective benzylidene derivatives **4**. Compounds **2** react with amines (aniline, morpholine, piperidine) to give the respective 2-(3-carboxy-1-methylindole)acetamide **5** or the respective 2-aryl-4-carboxamido-5-methyl-5*H*-pyridazino[4,5-*b*]indole **6**, the product obtained depending on the structure of the aryl substituent. Boiling **2b** (aryl = 4-chlorophenyl) with 5% sodium hydroxide gave (80%) 2-(3-carboxy-1-methylindole)acetic acid (**7**). Hydrolysis of **2b** gave a mixture of **7** and 2-(3-carboxy-1-methylindolyl)-2-(4-chlorophenylhydrazono)acetic acid (**8**).

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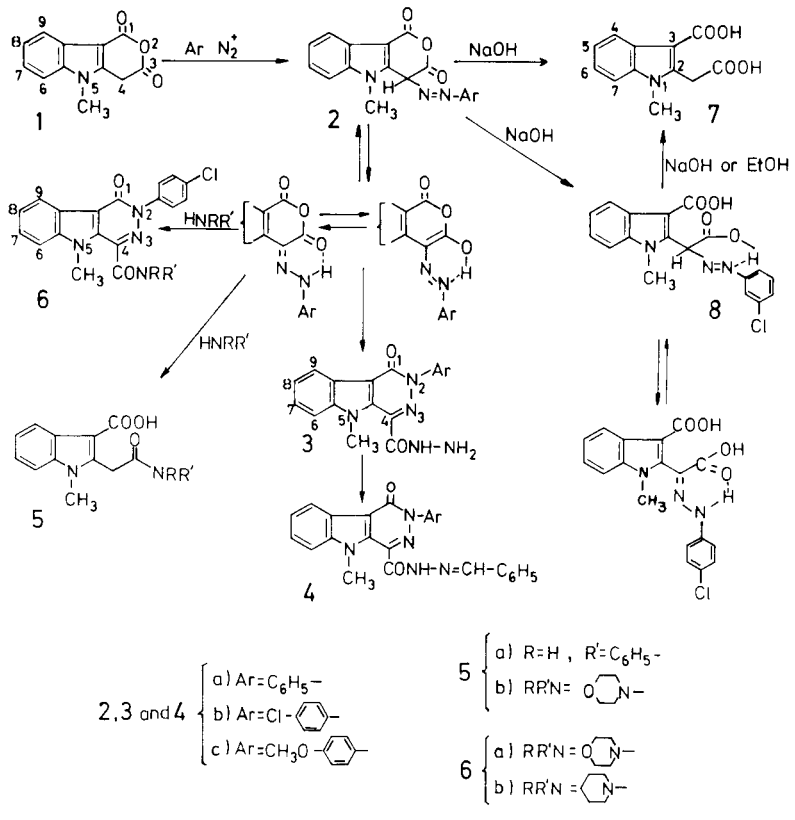
As a continuation of our previous work on the synthesis [1] and biologic and pharmacologic properties [2] of pyridazino[4,5-*b*]indole derivatives, we report in this paper a new synthesis of 1-oxo-1,2-dihydro-5*H*-pyridazino[4,5-*b*]indole derivatives, starting with 2-(3-carboxy-1-methylindole)acetic acid anhydride **1** (Scheme).

It is well known that certain cyclic anhydrides, as glutaconic anhydrides [3,4], homophthalic anhydride [5] and 1-alkylindole-2-carboxy-3-acetic acid anhydrides [6] react with diazonium salts to give the α-hydrazono cyclic anhy-

Scheme



drides, which isomerize by aqueous alkali, to lead to pyridazine derivatives, by incorporation to the ring of the hydrazo linkage. Similar reactions take place with other nucleophiles [5]: with secondary amines, the anhydride is opened to the respective amide and further recycling gives the respective 4-pyridazine carboxamide derivative; however, if a primary amine is used [5], the anhydride is opened to the respective amide, but recycling gives the hydrazonopyridine derivative. We have studied this type of reaction with 2-(3-carboxy-1-methylindole)acetic acid anhydride **1**. The Scheme illustrated the studied reactions and the structure of the products obtained.

Compound **1** reacts with aryldiazonium salts to give (85-95%) the respective α-hydrazono anhydrides **2**. These coloured (yellow to orange) compounds were insoluble in the usual solvent and no ^{1}H-nmr could be registered. The compounds were characterized by elemental analysis and ir spectra. Several tautomeric structures may be formulated for them (see Scheme) and the α-hydrazono form [5] seems the most probable.

Compounds **2** react with hydrazine hydrate in boiling xylene to give (47-67%) the respective pyridazino[4,5-*b*]indolecarbohydrazide derivatives, **3**. The reaction is explained by ring opening of the anhydride to give the carbohydrazide and further recycling to form the pyridazine derivative ring. Compounds **3** give the benzylidene derivatives **4** (78-80%). Compounds **3** and **4** were insoluble in the usual solvents for ^{1}H-nmr and they were characterized by elemental analysis and ir spectra.

The reactions of **2a,b** or **c**, with aniline in boiling xylene gave the amide **5a** (about 75%) in all the three cases; **5a** was characterized by elemental analysis and ^{1}H-nmr and ir spectra. This was an unexpected reaction, because in a similar reaction with α-hydrazono homophthalic anhydride [5] the obtention of the respective 4-hydrazonopyridine derivative was reported. Similarly, boiling **2a** or **c** with morpholine in xylene we obtained the amide **5b** (80%), but no the expected [5] 4-pyridazinecarboxamide derivative; **5b** was also characterized by analysis and ^{1}H-nmr and ir spectra.

On the other hand, the reactions of **2b** with morpholine and piperidine in boiling xylene gave 45-55% of the expected [5] 4-pyridazinocarboxamide derivatives **6**, which were characterized by analysis and ^{1}H-nmr and ir spectra.

We have not an explanation of the observed differences in the reaction products of **2a, 2b** and **2c** with the amines employed (aniline, morpholine and piperidine).

As above mentioned, it has been reported [3,4,6] that treating hydrazono cyclic anhydrides with hot aqueous alkali an isomerization takes place to give the respective 4-carboxypyridazino derivatives. We were not able to carry out this reaction with compounds **2b**. When **2b** was boiled for 1 hour with 5% sodium hydroxide, only the acid **7** was obtained. On the other hand, when **2b** was warmed with 5% sodium hydroxide just to total dissolution, a mixture with about 30% of **7** and 70% of **8** was obtained. The attempted recrystallization of this mixture from ethanol gave **7**. So that treating **2b** with hot sodium hydroxide, ring opening of the anhydride takes place to give **8**, which hydrolizes to **7** and not cyclization to the respective 4-carboxypyridazino[4,5-*b*]indole derivative could be observed.

EXPERIMENTAL

Melting points were determined in a Koffler apparatus and they are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorus pentoxide at 3-4 mm Hg, 2-3 hours, at about 60-70°). The ir spectra were recorded on a Perkin-Elmer 681 apparatus, using potassium bromide tablets for solid products; the frequencies were expressed in cm^{-1}. The ^{1}H-nmr spectra were obtained on a Perkin-Elmer R-32 (90 MHz) instrument, with TMS as the internal reference, at a concentration of about 0.1 g/ml and solvent as indicated; the chemical shifts are reported in ppm and are given in δ units.

Thin-layer chromatography (tlc) was carried out on silicagel (DSF-5, Cammaga 0.3 mm thickness) with benzene:dioxane:acetic acid (90:25:4) as solvent and the plates were scanned under ultraviolet light, λ = 254 and 366 nm.

Compounds **1** (mp 252-253°) and **7** (mp 261°) were obtained according to reported procedures [7,8].

4-Arylhydrazono-5-methyl-1,3-dioxo-1,3,4,5-tetrahydro-5*H*-pyrano[4,3-*b*]-indoles, **2**.

General Procedure.

To a solution of compound **1** (2.15 g, 10 mmoles) in acetone (180 ml), cooled in an ice-bath at about 0°, a cold solution of the corresponding aryldiazonium salt was added with constant stirring. [The solutions of the diazonium salts were prepared by diazotizing a solution of the respective arylamine (10 mmoles) in 6*N* hydrochloric acid (6 ml) with a solution of sodium nitrite (0.69 g, 10 mmoles) in water (10 ml)]. Within a short time a coloured precipitate of the respective compound starts to separate. After stirring for an additional 30 minutes, water (400 ml) was added to the reaction mixture and the precipitate collected by filtration, washed with water, dried at air and recrystallized. In this way the following compounds were obtained:

5-Phenylhydrazono-5-methyl-1,3-dioxo-1,3,4,5-tetrahydro-5*H*-pyrano-[4,3-*b*]indole, **2a**.

Compound **2a** was obtained from aniline, mp 257° (ethanol/*N,N*-DMF), cottony yellow coloured crystals, yield 85%; ir: 3140 (NH), 1740, 1760 (C=O), 1680 (C=N), 950 (C-O-C), 745, 770 (aromatic monosubstitution and 1,2-disubstitution).

Anal. Calcd. for $C_{18}H_{13}N_3O_3$: C, 67.71; H, 4.10; N, 13.16. Found: C, 67.40; H, 4.03; N, 13.00.

4-(4-Chlorophenyl)hydrazono-5-methyl-1,3-dioxo-1,3,4,5-tetrahydro-5*H*-pyrano[4,3-*b*]indole, **2b**.

Compound **2b** was obtained from *p*-chloroaniline, mp 175° (ethanol/*N,N*-DMF), cottony orange coloured crystals, yield 87%; ir: 3140 (NH), 1750 (C=O), 1680 (C=N), 950 (C-O-C), 830 (aromatic 1,4-disubstitution), 770 (aromatic 1,2-disubstitution).

Anal. Calcd. for $C_{18}H_{12}ClN_3O_3$: C, 61.10; H, 3.40; N, 11.88. Found: C, 60.88; H, 3.41; N, 11.59.

4-(4-Methoxyphenyl)hydrazono-5-methyl-1,3-dioxo-1,3,4,5-tetrahydro-5*H*-pyrano[4,3-*b*]indole, **2c**.

Compound **2c** was obtained from *p*-methoxyaniline, mp 246-248° (*N,N*-DMF), cottony orange coloured crystals, yield 95%; ir: 3120 (NH), 1740 (C=O), 1670 (C=N), 950 (C-O-C), 830 (aromatic 1,4-disubstitution),

770 (aromatic 1,2-disubstitution).

Anal. Calcd. for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 65.09; H, 4.19; N, 11.87.

2-Aryl-4-carbohydrazido-5-methyl-1-oxo-1,2-dihydro-5*H*-pyridazino-[4,5-*b*]indoles, **3**.

General Procedure.

A mixture of the corresponding compound **2** (2 mmoles), 100% hydrazine hydrate (0.20 g, 4 mmoles) and xylene (20 ml) was boiled for 1 hour. On cooling, the respective compound **3** crystallized. In this way the following compounds **3** were obtained:

2-Phenyl-4-carbohydrazido-5-methyl-1-oxo-1,2-dihydro-5*H*-pyridazino-[4,5-*b*]indole, **3a**.

Compound **3a** was obtained from **2a**, mp 260° (from xylene), yield 47%, orange needles; ir: 3310, 3320 (NH), 1665, 1635 (C=O), 685, 765 (aromatic monosubstitution), 750 (aromatic 1,2-disubstitution).

Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.89; H, 4.55; N, 20.89.

2-(4-Chlorophenyl)-4-carbohydrazido-5-methyl-1-oxo-1,2-dihydro-5*H*-pyridazino[4,5-*b*]indole, **3b**.

Compound **3b** was obtained from **2b**, mp 280° (from *N,N*-DMF), yield 67%, cottony orange coloured crystals; ir: 3300 (NH), 1685, 1645 (C=O), 830 (aromatic 1,4-disubstitution), 745 (aromatic 1,2-disubstitution).

Anal. Calcd. for $C_{18}H_{14}ClN_5O_2$: C, 58.77; H, 3.80; N, 19.04. Found: C, 58.81; H, 3.54; N, 18.90.

2-(4-Methoxyphenyl)-4-carbohydrazido-5-methyl-1-oxo-1,2-dihydro-5*H*-pyridazino[4,5-*b*]indole, **3c**.

Compound **3c** was obtained from **2c**, mp 240-242° (ethanol/*N,N*-DMF), cottony orange coloured crystals, yield 62%; ir: 3300 (NH), 1670, 1640 (C=O), 830 (aromatic 1,4-disubstitution), 750 (aromatic 1,2-disubstitution).

Anal. Calcd. for $C_{19}H_{17}N_5O_3$: C, 62.80; H, 4.72; N, 19.27. Found: C, 62.66; H, 4.73; N, 19.22.

2-Aryl-4-(N^2-benzylidenecarbohydrazido)-5-methyl-1-oxo-1,2-dihydro-5*H*-pyridazino[4,5-*b*]indoles, **4**.

General Procedure.

A mixture of the corresponding compound **3** (2 mmoles), benzaldehyde (0.40 g, 4 mmoles) and ethanol (30 ml) was boiled for 2 hours. On cooling the respective **4** crystallized. In this way the following compounds were prepared:

2-(4-Chlorophenyl)-4-(N^2-benzylidenecarbohydrazido)-5-methyl-1-oxo-1,2-dihydro-5*H*-pyridazino[4,5-*b*]indole, **4b**.

Compound **4b** was obtained from **3b**, mp 285-286° (ethanol/*N,N*-DMF), yield 78%, orange needles; ir: 1680, 1640 (C=O), 690, 750, 770, 820 (aromatic 1,4-, 1,2- and monosubstitutions).

Anal. Calcd. for $C_{25}H_{18}ClN_5O_2$: C, 65.86; H, 3.95; N, 15.37. Found: C, 65.65; H, 3.92; N, 15.22.

2-(4-Methoxyphenyl)-4-(N^2-benzylidenecarbohydrazido)-5-methyl-1-oxo-1,2-dihydro-5*H*-pyridazino[4,5-*b*]indole, **4c**.

Compound **4c** was obtained from **3c**, mp 264° (ethanol/*N,N*-DMF), yield 80%, cottony orange crystals; ir: 1680, 1630 (C=O), 700, 740, 770, 820 (aromatic 1,4-, 1,2-, and monosubstitutions).

Anal. Calcd. for $C_{26}H_{21}N_5O_3$: C, 69.17; H, 4.69; N, 15.51. Found: C, 68.89; H, 4.79; N, 15.71.

2-(3-Carboxy-1-methylindole)acetamides, **5**.

N-Phenyl-2-(3-carboxy-1-methylindole)acetamide, **5a**.

A mixture of **2a,b** or **c** (2 mmoles), aniline (0.36 g, 4 mmoles) and xylene (30 ml) was boiled for 2 hours. By cooling, compound **5** crystallized, mp 232-233° (ethanol), white cottony crystals, yield 75%; ir: 3290 (NH), 2400-3100 (COOH), 1650 (broad, C=O), 690, 735, 750 (aromatic mono and 1,2-disubstitutions); ^{1}H-nmr (DMSO-d_6, 37°): 3.80 (s, CH_3, 3H), 4.52 (s, CH_2, 2H), 7.00-7.65 (m, C_6H_5, $H_{5,6,7}$ of indole and CONH, 9H), 7.95-8.10 (m, H_4, 1H), 10.25 (s, COOH, 1H). The signals for CONH and COOH disappear by addition of deuterium oxide.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.02; H, 5.13; N, 9.02.

N-[2-(3-Carboxy-1-methylindole)acetyl]morpholine, **5b**.

A mixture of **2a** or **c** (2 mmoles), morpholine (0.17 g, 2 mmoles) and xylene (30 ml) was boiled for 2 hours. On cooling **5b** crystallized, mp 227-228° (ethanol), white cottony crystals, yield 80%; ir: 2400-3200 (COOH), 1660 (broad, C=O), 750, 850 (aromatic 1,2- and 1,4-disubstitutions); ^{1}H-nmr (DMSO-d_6, 35°): 3.20-3.80 (m, morpholine, 8H), 3.68 (s, CH_3, 3H), 4.46 (m, CH_2, 2H), 7.00-7.60 (m, $H_{5,7,8}$, 3H), 7.80-8.10 (m, $1H_4$, 1H), 12.00 (bs, COOH, 1H).

Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.27; H, 6.13; N, 9.11.

4-Carboxamido-2-(4-chlorophenyl)-5-methyl-5*H*-pyridazino[4,5-*b*]indoles, **6**.

A mixture of **2b** (0.7 g, 2 mmoles), the corresponding amine (morpholine, piperidine) (2 mmoles) and xylene (30 ml) was boiled for 2 hours. On cooling the respective **6** crystallized. In this way the following compounds were obtained:

4-Morpholinocarboxamido-2-(4-chlorophenyl)-5-methyl-5*H*-pyridazino-[4,5-*b*]indole, **6a**.

Compound **6a** was obtained from morpholine, mp 287° (ethanol/*N,N*-DMF), yield 45%, cottony orange crystals; ir: 1650, 1680 (C=O), 730, 840 (aromatic 1,2- and 1,4-disubstitutions); ^{1}H-nmr (DMSO-d_6): 3.60 (s, CH_2N, 4H), 3.74 (s, N-CH_3, 3H), 3.92 (s, CH_2-O, 4H), 7.20-7.90 (m, $H_{6,7,8}$ and ClC_6H_4, 7H), 8.10-8.30 (m, H_9, 1H).

Anal. Calcd. for $C_{22}H_{19}ClN_4O_3$: C, 62.48; H, 4.73; N, 13.25. Found: C, 62.10; H, 4.34; N, 13.51.

4-Piperidinocarboxamido-2-(4-chlorophenyl)-5-methyl-5*H*-pyridazino-[4,5-*b*]indole, **6b**.

Compound **6b** was obtained from piperidine, mp 230° (ethanol), yield 55%, white needles; ir: 1640, 1680 (C=O), 730, 840 (aromatic 1,2- and 1,4-disubstitutions); ^{1}H-nmr (DMSO-d_6): 1.30-1.75 (m, C-$(CH_2)_3$-C, 6H), 3.40-3.85 (m, CH_2-N-CH_2, 4H), 3.98 (s, CH_3-N, 3H), 7.35-7.95 (m, $H_{6,7,8}$ and ClC_6H_4, 7H), 8.20-8.40 (m, H_9, 1H).

Anal. Calcd. for $C_{23}H_{21}ClN_4O_2$: C, 65.63; H, 4.99; N, 13.32. Found: C, 65.80; H, 4.84; N, 13.16.

2-(3-Carboxy-1-methylindolyl)acetic Acid, **7**.

A mixture of **2b** (10 mmoles) and 5% sodium hydroxide (50 ml) was boiled for 1 hour. The cold solution was acidified with hydrochloric acid and the precipitate was collected, washed with water and recrystallized, mp 261° (ethanol), reported [1] 261°, [2] 262°, yield 80%; ir: 2200-3300 (COOH), 1650, 1700 (C=O), 750 (aromatic 1,2-disubstitution); ^{1}H-nmr (DMSO-d_6): 3.70 (s, N-CH_3, 3H), 4.40 (s, CH_2, 2H), 6.90-7.60 (m, $H_{5,6,7}$, 3H), 7.90-8.10 (m, H_4, 1H).

2-(3-Carboxy-1-methylindolyl)-2-(4-chlorophenylhydrazono)acetic Acid, **8**.

A mixture of **2b** (10 mmoles) and 5% sodium hydroxide (50 ml) was smoothly warmed until total dissolution of the product (1 hour 40°). The dark red coloured solution was filtered and acidified with hydrochloric acid. The precipitate was collected, extracted with 2% sodium bicarbonate solution and the mixture filtered again.

The solution was acidified with diluted hydrochloric acid and the precipitate collected, washed with water, dried at ir and washed with cold methylene chloride. The ir and the ^{1}H-nmr (DMSO-d_6) spectra of the obtained yellow coloured product (2.60 g), mp 155-157° showed it was a mixture of about 70% of **8** and 30% of **7**. All attempted purification of **8** was fruitless. By attempted recrystallization from ethanol, **8** discomposed to give **7**.

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