Synthesis of 5*H*-Pyrazolo[5,1-*c*][1,4]benzodiazepine

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The reaction of 2-nitrobenzyl bromide with dimethyl pyrazole-3,5-dicarboxylate gave dimethyl 1-(2-nitrobenzyl)pyrazole-3,5-dicarboxylate which through a few steps procedure afforded the key intermediate 5,10-dihydro-11-oxopyrazolo[5,1-*c*][1,4]benzodiazepine. The latter was reduced and dehydrogenated to yield the new tricyclic system 5*H*-pyrazolo[5,1-*c*][1,4]benzodiazepine.

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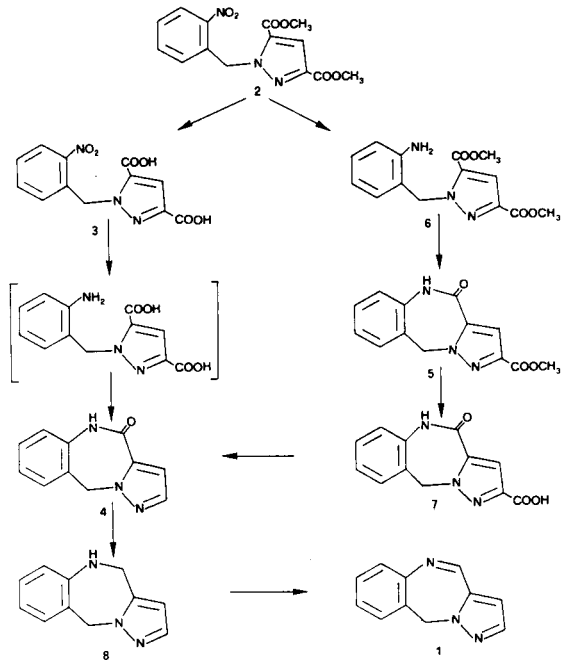
Antramycin, tomaymycin and sibiromycin [1] are antitumor antibiotics containing as common feature the 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine tricyclic ring system. In a search for synthetic tumor inhibitors [2-4] related to the cited antibiotics we now describe the synthesis of 5*H*-pyrazolo[5,1-*c*][1,4]benzodiazepine **1**, an isosteric analog of 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine [5,6]. This work might represent a useful contribution to a synthesis of a variety of pyrazolo[5,1-*c*][1,4]benzodiazepine derivatives.

Dimethyl 1-(2-nitrobenzyl)pyrazolo-3,5-dicarboxylate **2** was obtained (Scheme 1) in good yield by treating, in anhydrous tetrahydrofuran, 2-nitrobenzyl bromide with dimethyl pyrazole-3,5-dicarboxylate as *N*-potassium salt. Acidic hydrolysis of **2** gave the corresponding acid **3**. The direct conversion of **3** to 5,10-dihydro-11-oxopyrazolo-[5,1-*c*][1,4]benzodiazepine (**4**) was carried out by catalytic reduction of the nitro group and by heating the resulting product under reduced pressure. These reactions proceeded in low yields and it was not possible to isolate 1-(2-aminobenzyl)pyrazole-3,5-dicarboxylic acid in the pure state. Therefore an alternative profitable procedure, even if longer, was chosen: **2** was transformed into methyl 5,10-dihydro-11-oxopyrazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylate **5** *via* the amino derivative **6**. Acidic hydrolysis of **5** gave the corresponding acid **7** which, heated in vacuum, provided **4** in good yield. Reduction of the key intermediate **4** with lithium aluminium hydride afforded 10,11-dihydro-5*H*-pyrazolo[5,1-*c*][1,4]benzodiazepine **8** which was dehydrogenated to the expected 5*H*-pyrazolo[5,1-*c*][1,4]-benzodiazepine **1**.

Attempts to obtain the pyrazolo[5,1-*c*][1,4]benzodiazepine ring system by condensation of 2-nitrobenzyl bromide with methyl pyrazole-3(5)-carboxylate (**9**) was unsuccessful. Compound **9** was prepared starting from hydrazine and ethoxymethylenepyruvate [7] unlike the procedure described by Reimlinger [8]. When **9** was allowed to react with 2-nitrobenzyl bromide (Scheme 2) only one product, **10** or **11**, was isolated. Application of the chemistry in Scheme 1 to this product failed to produce the lactam **4**. Accordingly we assigned it the structure of methyl 1-(2-nitrobenzyl)pyrazole-3-carboxylate (**10**) rather than **11**. Assignment of the 1,3-disubstituted structure to **10** is consistent even with the literature data [9,10].

SCHEME 1



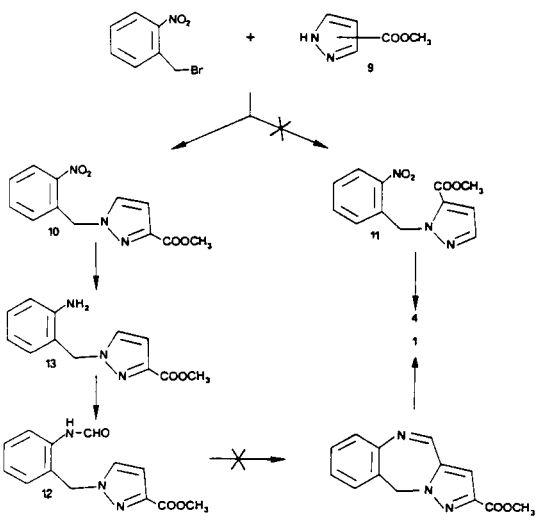
We tried then to prepare **1** from **10** *via* methyl 1-(2-formylaminobenzyl)pyrazole-3-carboxylate **12**, following the procedure described by Artico [6] to synthetize 5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepine. Thus **10** was reduced to the corresponding amino derivative **13**, which, with 99% formic acid, gave **12**. We were unable to cyclize **12** to methyl 5*H*-pyrazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylate using phosphorus oxychloride, polyphosphoric acid and other agents. In any case there was no evidence for ring closure.

All the synthetized compounds were characterized by elemental analysis, ir and pmr spectra. Furthermore the structure of **1** and **8** were confirmed by mass spectra.

EXPERIMENTAL

All melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. The ir spectra were taken in nujol

SCHEME 2



mull with a Perkin-Elmer 337 spectrophotometer. The pmr spectra were recorded with a Varian EM-360 instrument: chemical shifts are reported in δ (ppm) downfield from internal TMS. Mass spectra were run on a Perkin-Elmer 270 mass spectrometer and samples were introduced by direct inlet. Operating conditions: electron beam 70 eV, ion accelerating voltage 2.5 kV and ion source temperature 180°.

Dimethyl 1-(2-Nitrobenzyl)pyrazole-3,5-dicarboxylate (**2**).

A suspension of 1.84 g (10 mmoles) of dimethyl pyrazole-3,5-dicarboxylate and 0.31 g (8 mmoles) of potassium in 20 ml of anhydrous tetrahydrofuran was refluxed for 12 hours. After cooling, 1.72 g (8 mmoles) of 2-nitrobenzyl bromide was added and the mixture was refluxed for 8 hours. The reaction was carried out under a flow of nitrogen. The precipitate was filtered off and the solution was evaporated to give a yellow residue which was recrystallized from ethanol giving 2.1 g (82%) of white crystals, mp 166-168°; ir: 1740 and 1720 (CO), 1530 and 1340 (NO_2) cm^{-1}; pmr (deuteriochloroform): 3.83 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 6.26 (s, 2H, CH_2), 6.5-6.8 (m, 1H, benzenic proton), 7.2-7.7 (m, 3H, 2 benzenic protons and 1 pyrazolic proton), 8.0-8.3 (m, 1H, benzenic proton).

Anal. Calcd. for $C_{14}H_{13}N_3O_6$: C, 52.67; H, 4.10; N, 13.16. Found: C, 52.92; H, 4.29; N, 13.29.

1-(2-Nitrobenzyl)pyrazole-3,5-dicarboxylic Acid (**3**).

A solution of 1.5 g (4.7 mmoles) of **2** in 50 ml of 6 *N* hydrochloric acid was refluxed for 9 hours. Upon standing a solid was obtained which was recrystallized from water giving 0.89 g (65%) of white crystals, mp 245-248° dec; ir: 3300-2200 (COOH), 1700 (CO), 1530 and 1340 (NO_2) cm^{-1}; pmr (DMSO-d_6): 6.18 (s, 2H, CH_2), 6.7-7.1 (m, 1H, benzenic proton), 7.35 (s, 1H, pyrazolic proton), 7.4-7.9 (m, 2H, benzenic protons), 8.0-8.4 (m, 1H, benzenic proton).

Anal. Calcd. for $C_{12}H_9N_3O_6$: C, 49.49; H, 3.12; N, 14.43. Found: C, 49.39; H, 3.13; N, 14.70.

5,10-Dihydro-11-oxopyrazolo[5,1-*c*][1,4]benzodiazepine (**4**).

A) To a solution of 1.1 g (3.8 mmoles) of **3** in 400 ml of ethyl acetate 0.6 g of 10% Pd/C was added. The mixture was hydrogenated in a Parr apparatus at 50 psi for 5 hours. Removal of the catalyst and evaporation of the solvent afforded a crude material which was heated in vacuum (20 mm Hg) at 300-320° for 10 minutes. The sublimate was recrystallized from ethanol giving 0.13 g (18%) of the title compound.

B) Compound **7** (0.97 g, 4 mmoles) was heated in vacuum (20 mm Hg) at 300-320° for 10 minutes. The sublimate was recrystallized from ethanol giving 0.53 g (73%) of white crystals, mp 260°; ir: 3180 (NH), 1670 (CO) cm^{-1}; pmr (DMSO-d_6): 5.43 (s, 2H, CH_2), 6.80 (d, 1H, pyrazolic proton, $J_{1,2}$ = 2 Hz), 7.0-7.7 (m, 5H, 4 benzenic protons and 1 pyrazolic proton), 10.7 (br, 1H, NH, it exchanges with deuterium oxide).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.02; H, 4.49; N, 21.13.

Dimethyl 1-(2-Aminobenzyl)pyrazole-3,5-dicarboxylate (**6**).

To a solution of 1.0 g (3.1 mmoles) of **2** in 150 ml of ethyl acetate 0.5 g of 10% Pd/C was added. The mixture was hydrogenated in a Parr apparatus at 50 psi for 5 hours. Removal of the catalyst and evaporation of the solvent afforded a solid residue which was recrystallized from ethanol giving 0.77 g (85%) of white crystals, mp 118-120°; ir: 3440 and 3350 (NH_2), 1720 (CO) cm^{-1}; pmr (deuteriochloroform): 3.90 (s, 6H, 2 CH_3), 4.6 (br, 2H, NH_2, it exchanges with deuterium oxide), 5.75 (s, 2H, CH_2), 6.5-7.5 (m, 5H, 4 benzenic protons and 1 pyrazolic proton).

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.09; H, 5.47; N, 14.87.

The picrate was obtained as yellow crystals, mp 170-172° (from ethanol).

Anal. Calcd. for $C_{20}H_{18}N_6O_{11}$: C, 46.34; H, 3.50; N, 16.21. Found: C, 46.35; H, 3.52; N, 15.95.

Methyl 5,10-Dihydro-11-oxopyrazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylate (**5**).

One g (3.5 mmoles) of **6** was heated at 180-200°. The cooled solid was treated with 10 ml of methanol and filtered. The residue was recrystallized from acetic acid/water giving 0.74 g (84%) of white crystals, mp 300°; ir: 3170 (NH), 1750 (CO ester), 1670 (CO lactam) cm^{-1}; pmr (DMSO-d_6): 3.85 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 7.1-7.7 (m, 5H, 4 benzenic protons and 1 pyrazolic proton), 10.9 (br, 1H, NH, it exchanges with deuterium oxide).

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.34. Found: C, 60.40; H, 4.29; N, 16.61.

5,10-Dihydro-11-oxopyrazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylic Acid (**7**).

A solution of 1.0 g (3.9 mmoles) of **5** in 22 ml of glacial acetic acid and 14 ml of 6 *N*-hydrochloric acid was refluxed for 35 minutes. After cooling a solid was obtained which was recrystallized from glacial acetic acid giving 0.70 g (75%) of white crystals, mp >310°; ir: 3180 (NH), 3100-2300 (COOH), 1700 (CO acid), 1650 (CO lactam) cm^{-1}.

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 58.94; H, 3.92; N, 17.06.

10,11-Dihydro-5*H*-pyrazolo[5,1-*c*][1,4]benzodiazepine (**8**).

To a suspension of 1.0 g of lithium aluminium hydride in 100 ml of anhydrous tetrahydrofuran a solution of 1.0 g (5.5 mmoles) of **4** in 50 ml of anhydrous tetrahydrofuran was added dropwise. The mixture was refluxed for 12 hours and set aside overnight. Addition of crushed ice, filtration and evaporation of the clear solution yielded crude **8** which was recrystallized from water giving 0.5 g (50%) of white crystals, mp 135-137°; ir: 3380 (NH) cm^{-1}; pmr (deuteriochloroform): 4.0 (br, 1H, NH, it exchanges with deuterium oxide), 4.2-4.6 (br s, 2H, 11-CH_2, when treated with deuterium oxide it becomes a singlet at 4.45), 5.45 (s, 2H, 5-CH_2), 6.08 (d, 1H, pyrazolic proton, $J_{1,2}$ = 2 Hz), 6.4-7.3 (m, 4H, benzenic protons), 7.37 (d, 1H, pyrazolic proton, $J_{1,2}$ = 2 Hz); ms: (m/z) 185 (36) $M^{+\cdot}$, 184 (100), 169 (20).

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.24; H, 5.93; N, 22.66.

5*H*-Pyrazolo[5,1-*c*][1,4]benzodiazepine (**1**).

An homogeneous mixture of 0.2 g (1.1 mmoles) of **8** and 1.0 g of 10% Pd/C was heated at 180° under vacuum (10^{-1} mm Hg) for 1 hour. The mixture was extracted with hot chloroform, filtered and evaporated to give a reddish residue which was recrystallized from water giving 0.06 g (30%) of white crystals, mp 105-109°; ir: 3080 (w), 3050 (w), 1610 (m), 1590 (m), 825 (s), 775-765 (vs) cm^{-1}; pmr (deuteriochloroform): 5.27 (s, 2H, CH_2), 6.58 (d, 1H, pyrazolic proton, $J_{1,2}$ = 2 Hz), 7.1-7.7 (m, 5H, 4 benzenic protons and 1 pyrazolic proton), 8.60 (s, 1H, 11-CH); ms: (m/z)

183 (100) $M^{+\cdot}$, 182 (50), 156 (10), 155 (14), 130 (14), 129 (14), 128 (14), 104 (7), 89 (14), 77 (14).

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.93. Found: C, 72.20; H, 5.00; N, 22.91.

Methyl Pyrazole-3(5)-carboxylate (**9**).

A solution of 4.9 g (31 mmoles) of methyl ethoxymethylenepyruvate [7] and 2 ml of 85% hydrazine hydrate in 100 ml of methanol was refluxed for 30 minutes. Evaporation of the solvent gave a yellow residue which was recrystallized from water giving 1.6 g (40%) of white crystals, mp 136-138° (lit 142° [8], 139-140° [11]); ir: 3120 and 3000-2300 (NH), 1740 (CO) cm^{-1}; pmr (deuteriochloroform): 3.95 (s, 3H, CH_3), 6.84 (d, 1H, J = 2 Hz), 7.85 (d, 1H, J = 2 Hz), 14.3 (br, 1H, NH, it exchanges with deuterium oxide).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.93; H, 4.78; N, 22.49.

Methyl 1-(2-Nitrobenzyl)pyrazole-3-carboxylate (**10**).

A mixture of 2.8 g (22 mmoles) of **9** and 0.7 g (18 mmoles) of potassium in 400 ml of anhydrous tetrahydrofuran was refluxed for 5 hours. After cooling 3.9 g (18 mmoles) of 2-nitrobenzyl bromide was added and the mixture was refluxed for 5 hours. The reaction was carried out under a flow of nitrogen. The precipitate was filtered off and the solution was evaporated to give a residue which was recrystallized from ethanol giving 2.8 g (60%) of white crystals, mp 105-107°; ir: 1730 (CO), 1540 and 1340 (NO_2) cm^{-1}; pmr (deuteriochloroform): 3.93 (s, 3H, CH_3), 5.48 (s, 2H, CH_2), 6.7-7.8 (m, 5H, 3 benzenic protons and 2 pyrazolic protons), 8.12 (m, 1H, benzenic proton).

Anal. Calcd. for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.08. Found: C, 55.10; H, 4.27; N, 16.16.

Methyl 1-(2-Aminobenzyl)pyrazole-3-carboxylate (**13**).

To a suspension of 3.3 g (12.6 mmoles) of **10** in 200 ml of ethyl acetate 1.7 g of 10% Pd/C was added. The mixture was hydrogenated in a Parr apparatus at 50 psi for 6 hours. Removal of the catalyst and evaporation in vacuum of the solvent gave a residue which was recrystallized from diethyl ether/hexane giving 2.3 g (79%) of white crystals, mp 97-99°; ir: 3420 and 3320 (NH_2), 1730 (CO) cm^{-1}; pmr (deuteriochloroform): 3.92 (s, 3H, CH_3), 4.3 (br, 2H, NH_2, ir exchanges with deuterium oxide), 5.30 (s, 2H, CH_2), 6.5-7.5 (m, 6H, 4 benzenic protons and 2 pyrazolic protons).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.01; H, 5.71; N, 17.95.

Methyl 1-(2-Formylaminobenzyl)pyrazole-3-carboxylate (**12**).

Compound **13** (2.3 g, 10 mmoles) in 20 ml of 99% formic acid was refluxed for 30 minutes. After cooling the solution was poured into crushed ice to give a white residue which was recrystallized from benzene/cyclohexane giving 0.8 g (30%) of white crystals, mp 120-121°; ir: 3230 (NH), 1730 (CO ester), 1650 (CO formyl) cm^{-1}; pmr (deuteriochloroform): 3.92 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 6.78 (d, 1H, pyrazolic proton, $J_{4,5}$ = 2 Hz), 7.0-8.2 (m, 5H, 4 benzenic protons and 1 pyrazolic proton), 8.5 (br s, 1H, formyl proton), 9.3 (br, 1H, NH, ir exchanges with deuterium oxide).

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.16; H, 4.71; N, 15.89.

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