Synthesis of 5*H*-10,11-Dihydropyrazolo[5,1-*c*]-[1,4]benzodiazepinederivatives. II [2]

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Ethyl 3(5)-formylpyrazole-5(3)-carboxylate, 2-nitrobenzyl bromide or 2-nitrobenzoyl chloride are the starting basic materials to prepare with a few reaction steps, pyrazolo[5,1-*c*][1,4]benzodiazepines bearing at position 2 a substituted propionic chain (**7-9**) or bearing at position 5 a carbonyl group (**12**). Compounds **7-9**, **12** are to be considered aza analogs of the antitumor antibiotic antramycin.

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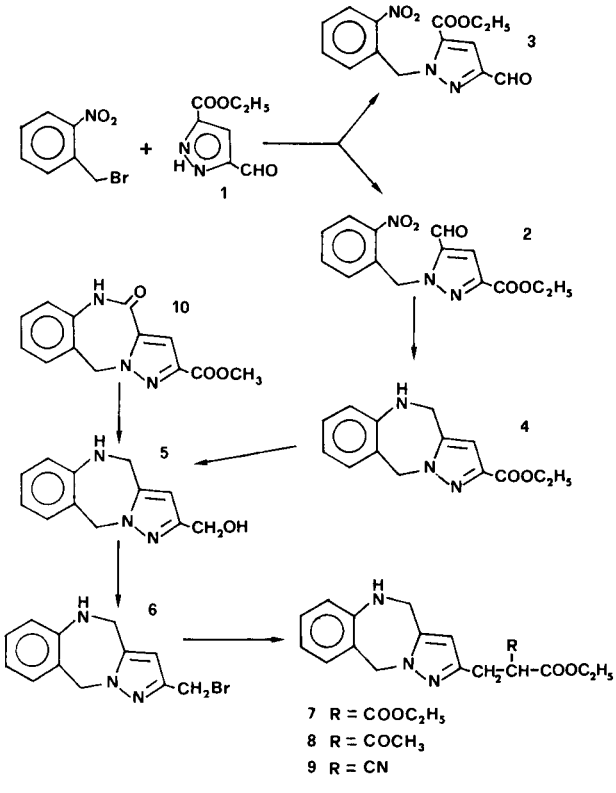
Antramycin, tomaymycin and sibiromycin [1] are antitumor antibiotics containing as common feature the 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine tricyclic ring system. Recently we reported [2] the synthesis of 5*H*-pyrazolo[5,-1-*c*][1,4]benzodiazepine an isosteric analog of 5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepine. In this paper we are reporting the synthesis of some pyrazolo[5,1-*c*][1,4]benzodiazepines bearing at position 2 a substituted propionic chain or bearing at position 5 a carbonyl group. These derivatives are related to the above cited antibiotics.

Allowing 2-nitrobenzyl bromide to react with ethyl 3(5)-formylpyrazole-5(3)-carboxylate (**1**) [3] the main product of the reaction was ethyl 1-(2-nitrobenzyl)-5-formylpyrazole-3-carboxylate (**2**) (Scheme 1). From the reaction mixture a small amount of the isomer ethyl 1-(2-nitrobenzyl)-3-formylpyrazole-5-carboxylate (**3**) was even isolated. Catalytic reduction of **2** yielded ethyl 5*H*-10,11-dihydropyrazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylate (**4**) which structure is supported by ir and pmr spectra. The pmr spectrum of **4** shows, among the others, a signal of an exchangeable proton and two signals at δ 4.45 and 5.52 which, in the literature data [2], could be attributed to the C_{11} and C_5 protons respectively. The ir spectrum shows absorption bands of the NH and the CO ester at 3330 and 1735 cm^{-1} respectively. Compound **4** was treated with lithium aluminium hydride to afford the 2-hydroxymethyl-5*H*-10,11-dihydropyrazolo[5,1-*c*][1,4]benzodiazepine (**5**). The latter was transformed into the corresponding 2-bromomethyl derivative **6** using phosphorus tribromide. When diethyl malonate was allowed to react with **6** it gave rise to the ethyl 3-(5*H*-10,11-dihydropyrazolo[5,1-*c*][1,4]benzodiazepin-2-yl)-2-carbethoxypropionate (**7**). Likewise were prepared compounds **8** and **9** reacting **6** with ethyl acetoacetate or ethyl cyanoacetate respectively.

SCHEME 1

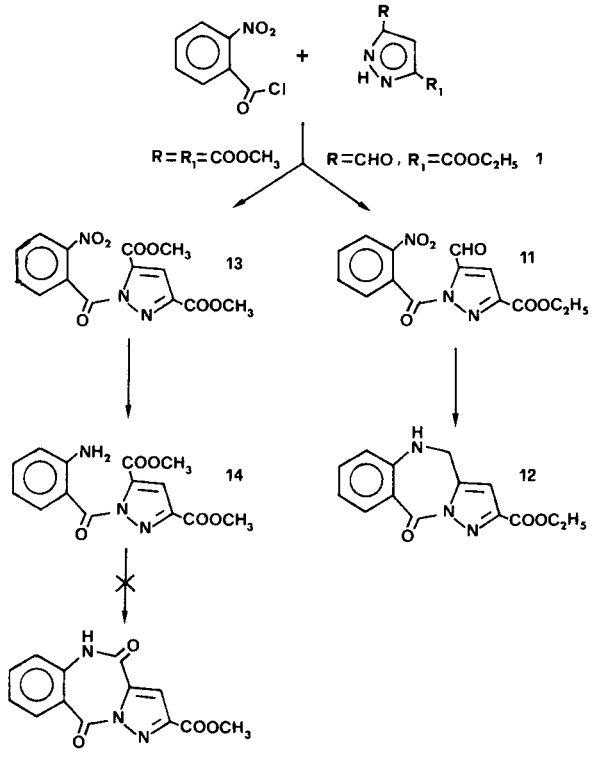


This pathway is facile and convenient and allowed us to reach our aim with a few reaction steps. Moreover, compound **5** was first prepared reacting with lithium aluminium hydride, methyl 5,10-dihydro-11-oxopyrazolo-[5,1-*c*][1,4]benzodiazepine-2-carboxylate (**10**) [2]. However the reduction of compound **10** proceeded with very poor yields and hence we do not suggest the use of this procedure.

The synthesis of the pyrazolobenzodiazepine bearing a carbonyl group at position 5 was achieved by reacting 2-nitrobenzoyl chloride with **1** (Scheme 2). From the reaction mixture only the isomer ethyl 1-(2-nitrobenzoyl)-5-formylpyrazole-3-carboxylate (**11**) was isolated. Compound **11** was catalytically reduced to give rise to the ethyl 10,11-dihydro-5-oxopyrazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylate (**12**). The pmr spectrum of **12** shows, among the others, two protons at the C_{11} (δ 4.42), one exchangeable proton and a C_6 proton at low fields (δ 8.3-8.5). The high δ value of the C_6 proton is due to the presence of the near carbonyl group. The characteristic absorption bands of the NH, CO ester and CO amide at 3350, 1730 and 1680 cm^{-1} re-

spectively are present in the ir spectrum.

SCHEME 2



In an attempt to prepare methyl 10*H*-5,11-dioxopyrazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylate we reacted 2-nitrobenzoyl chloride with dimethyl pyrazole-3,5-dicarboxylate. Catalytic reduction of the resulting nitro derivative **13** gave rise to the dimethyl 1-(2-aminobenzoyl)pyrazole-3,5-dicarboxylate (**14**). Unfortunally we were unable to cyclize the amino derivative **14** by heating it at room or at reduced pressure or by using cyclizing agents. In every case the cleavage of the aroyl group ensued, the starting dimethyl pyrazole-3,5-dicarboxylate being recovered.

All the compounds synthesized are characterized by elemental analysis, ir and pmr spectra. Furthermore the structure of compound **12** was confirmed by the mass spectrum.

EXPERIMENTAL

All melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. The ir spectra were taken in nujol 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 (70 eV ionizing voltage). Column chromatography was run on silica gel 60 (Merck), 70-230 mesh (gravity flow). Preparative thin layer chromatography was performed on precoated silica gel 60 Merck F_{254} plates (layer thickness 2 mm).

Ethyl 1-(2-Nitrobenzyl)-5-formylpyrazole-3-carboxylate (**2**) and Ethyl 1-(2-Nitrobenzyl)-3-formylpyrazole-5-carboxylate (**3**).

A suspension of 3.0 g (17.8 mmoles) of **1** and 0.7 g (17.8 mmoles) of potassium in 150 ml of anhydrous tetrahydrofuran was refluxed for 3 hours. After cooling 3.9 g (17.8 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 taken to dryness to give a mixture of compound **2** and **3**. Recrystallization from ethanol gave only compound **2** (3.7 g, 69%), white needles, mp 144-146°: ir: 3120 (w), 1730 (vs), 1680 (vs), 1535 (vs), 1350 (s), 1245 (vs), 1160 (m), 1105 (m), 1035 (m), 860 (m), 765 (s), 725 (s) cm^{-1}; pmr (deuteriochloroform): 1.42 (t, 3H, CH_3), 4.42 (q, 2H, CH_2), 6.22 (s, 2H, CH_2), 6.5-6.8 (m, 1H, benzene proton), 7.3-7.6 (m, 3H, 2 benzene protons and 1 pyrazole proton), 8.0-8.3 (m, 1H, benzene proton), 9.83 (s, 1H, formyl proton).

Anal. Calcd. for $C_{14}H_{13}N_3O_5$: C, 55.45; H, 4.32; N, 13.86. Found: C, 55.27; H, 4.46; N, 13.67.

The mother liquor containing compounds **2** and **3** was taken to dryness and the two isomers were separated by column chromatography (eluting system: benzene/ethyl acetate 9:1). The first running band afforded compound **3** (0.5 g, 10%) as white needles, mp 65-67° (from ethyl ether/light petroleum); ir: 3120 (s), 1730 (vs), 1700 (vs), 1530 (vs), 1350 (vs), 1280 (vs), 1205 (s), 1140 (s), 1105 (s), 1020 (m), 790 (m), 775 (m), 765 (m), 725 (vs) cm^{-1}; pmr (deuteriochloroform): 1.28 (t, 3H, CH_3), 4.28 (q, 2H, CH_2), 6.25 (s, 2H, CH_2), 6.6-6.8 (m, 1H, benzene proton), 7.3-7.6 (m, 3H, 2 benzene protons and 1 pyrazole proton), 8.0-8.3 (m, 1H, benzene proton), 10.00 (s, 1H, formyl proton).

Anal. Calcd. for $C_{14}H_{13}N_3O_5$: C, 55.45; H, 4.32; N, 13.86. Found: C, 55.48; H, 4.37; N, 14.22.

The second running band consisted in a second crop of compound **2** (0.6 g, overall yield 80%).

Ethyl 5*H*-10,11-Dihydropyrazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylate (**4**).

To a solution of 1.5 g (5.0 mmoles) of **2** in 200 ml of ethyl acetate 0.7 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 of the solvent afforded a solid residue which was recrystallized from ethanol giving 0.85 g (67%) of compound **4**. White crystals, mp 169-171°; ir: 3330 (m), 1735 (vs), 1500 (m), 1230 (vs), 1190 (m), 1140 (m), 1105 (m), 1030 (m), 730 (m) cm^{-1}; pmr (deuteriochloroform): 1.37 (t, 3H, CH_3), 3.8-4.6 (m, 5H, CH_2ester, 11-CH_2 and NH, the latter exchanges with deuterium oxide), 5.52 (s, 2H, 5-CH_2), 6.5-7.3 (m, 5H, 4 benzene protons and 1 pyrazole proton).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.49; H, 5.91; N, 16.54.

2-Hydroxymethyl-5*H*-10,11-dihydropyrazolo[5,1-*c*][1,4]benzodiazepine (**5**).

A) To a suspension of 0.6 g of lithium aluminium hydride in 200 ml of anhydrous tetrahydrofuran a solution of 1.3 g (5.0 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 solvent yielded crude **5** which was recrystallized from benzene giving 0.8 g (73%).

B) Methyl 5,10-dihydro-11-oxopyrazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylate (**10**) (1.0 g, 3.9 mmoles) and lithium aluminium hydride (1.0 g) were allowed to react as above described to give 0.2 g (20%) of compound **5**, white crystals, mp 141-143° (from benzene); ir: 3340 (m), 3400-2300 (br), 1500 (m), 1620 (w), 1350 (m), 1320 (m), 1040 (s), 1000 (vs), 735 (vs) cm^{-1}; pmr (DMSO-d_6): 4.2-4.6 (m, 4H, CH_2OH and 11-CH_2, when treated with deuterium oxide it becomes a broad singlet at 4.42), 4.90 (t, 1H, OH, J_{CH_2OH} = 5.5 Hz, it exchanges with deuterium oxide), 5.40 (s, 2H, 5-CH_2), 5.8-6.2 (br s, 2H, 1 pyrazole proton and NH, it becomes a singlet at 6.12 when treated with deuterium oxide), 6.3-7.2 (m, 4H, 4 benzene protons).

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.64; H, 6.03; N, 19.30.

5H-10,11-Dihydro-2-bromomethylpyrazolo[5,1-*c*][1,4]benzodiazepine (**6**).

A solution of 1.0 g (4.6 mmoles) of **5** in 5 ml of phosphorus tribromide was heated under stirring at 70° for 6 hours. After cooling crushed ice, ethyl acetate and 6 *N* sodium hydroxyde (*p*H 9) were added. The organic layer was separated and dried (sodium sulfate). After evaporation of the solvent the residue was recrystallized from ethyl acetate giving 0.9 g (68%), white needles, mp > 300°; ir: 3280 (vs), 1610 (s), 1500 (s), 1340 (m), 1315 (m), 1265 (m), 1210 (s), 1145 (m), 1100 (m), 1020 (m), 805 (m), 750 (s), 575 (s) cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}BrN_3$: C, 51.82; H, 4.35; N, 15.11. Found: C, 51.55; H, 4.24; N, 15.32.

Ethyl 3-(5*H*-10,11-Dihydropyrazolo[5,1-*c*][1,4]benzodiazepin-2-yl)-2-carbethoxypropionate (**7**).

A suspension of 0.28 g (1.8 mmoles) of diethyl malonate and 0.07 g (1.8 mmoles) of potassium in 60 ml of anhydrous benzene was refluxed for 4 hours. After cooling 0.5 g (1.8 mmoles) of compound **6** was added and the mixture was refluxed for 3 hours. The precipitate was filtered off and the solution was taken to dryness. The residue was purified through a column chromatography (eluting system: benzene/ethyl acetate 1:1) giving 0.4 g (62%), white crystals, mp 58-60° (from cyclohexane); ir: 3260 (s), 1730 (vs), 1610 (w), 1500 (w), 1300 (m), 1270 (s), 1240 (s), 1195 (m), 1150 (w), 1030 (m), 740 (m) cm^{-1}; pmr (deuteriochloroform): 1.21 (t, 6H, $2CH_3$), 3.20 (d, 2H, CH_2CH, $J_{CH_2,CH}$ = 8 Hz), 3.6-4.5 (m, 8H, $2CH_2$-CH_3, 11-CH_2, CH-CH_2 and NH, the latter exchanges with deuterium oxide), 5.38 (s, 2H, 5-CH_2), 5.90 (s, 1H, pyrazole proton), 6.5-7.3 (m, 4H, 4 benzene protons).

Anal. Calcd. for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.49; N, 11.76. Found: C, 64.00; H, 6.21; N, 11.98.

Ethyl 3-(5*H*-10,11-Dihydropyrazolo[5,1-*c*][1,4]benzodiazepin-2-yl)-2-acetylpropionate (**8**).

Compound **6** (0.5 g, 1.8 mmoles), potassium (0.07 g, 1.8 mmoles) and ethyl acetoacetate (0.23 g, 1.8 mmoles) were reacted as described above to obtain compound **7**. The crude material was purified through a column chromatography (eluting system: chloroform/acetonitrile 9:1) giving 0.35 g (59%) of a white oil; ir: 3400 (s), 1740 (vs), 1720 (vs), 1610 (s), 1500 (s), 1320 (m), 1265 (s), 1150 (m), 1020 (m), 750 (s) cm^{-1}; pmr (deuteriochloroform): 1.21 (t, 3H, CH_3-CH_2), 2.24 (s, 3H, CH_3-CO), 3.13 (d, 2H, CH_2CH, $J_{CH_2,CH}$ = 8 Hz), 3.3-3.6 (br s, 1H, NH, it exchanges with deuterium oxide), 3.8-4.5 (m, 5H, CH-CH_2, CH_2-CH_3 and 11-CH_2), 5.32 (s, 2H, 5-CH_2), 5.88 (s, 1H, pyrazole proton), 6.5-7.3 (m, 4H, 4 benzene protons).

The picrate was obtained as yellow crystals, mp 136-138° (from ethyl ether).

Anal. Calcd. for $C_{24}H_{24}N_6O_{10}$: C, 51.80; H, 4.35; N, 15.10. Found: C, 51.67; H, 4.40; N, 15.12.

Ethyl 3-(5*H*-10,11-Dihydropyrazolo[5,1-*c*][1,4]benzodiazepin-2-yl)-2-cyanopropionate (**9**).

Compound **6** (0.5 g, 1.8 mmoles), potassium (0.07 g, 1.8 mmoles) and ethyl cyanoacetate (0.2 g, 1.8 mmoles) were reacted as above described to obtain compound **7**. The crude material was purified through a column chromatography (eluting system: chloroform/acetonitrile 9:1) giving 0.4 g (71%) of compound **9**, white needles, mp 94-96° (from cyclohexane); ir: 3310 (s), 2250 (w), 1730 (vs), 1620 (m), 1510 (s), 1400 (m), 1320 (m), 1280 (s), 1165 (w), 1070 (w), 1025 (m), 860 (w), 745 (s), 730 (w) cm^{-1}; pmr (deuteriochloroform): 1.28 (t, 3H, CH_3), 3.20 (m, 2H, AB part of an ABX system, CH_2-CH), 3.7-4.5 (m, 6H, CH_2-CH_3, 11-CH_2, CH-CH_2 and NH, the latter exchanges with deuterium oxide), 5.40 (s, 2H, 5-CH_2), 6.05 (s, 1H, pyrazole proton), 6.5-7.3 (m, 4H, 4 benzene protons).

Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C, 65.78; H, 5.84; N, 18.05. Found: C, 65.66; H, 6.01; N, 18.30.

Ethyl 1-(2-Nitrobenzoyl)-5-formylpyrazole-3-carboxylate (**11**).

A suspension of 1.72 g (10.3 mmoles) of **1** and 0.4 g (10.3 mmoles) of potassium in 50 ml of anhydrous tetrahydrofuran was refluxed for 6 hours. After cooling 1.9 g (10.3 mmoles) of 2-nitrobenzoyl chloride was added. The mixture was left aside overnight. The reaction was carried out under a flow of nitrogen. The precipitate was filtered off and the solution was taken to dryness to give a crude which was recrystallized from ethyl acetate giving 1.3 g (40%), white crystals, mp 146-147°; ir: 1760 (vs), 1740 (vs), 1690 (s), 1540 (vs), 1360 (vs), 1330 (vs), 1255 (vs), 1210 (vs), 1145 (m), 1030 (m), 930 (s), 860 (m), 785 (m), 735 (m), 710 (s) cm^{-1}; pmr (deuteriochloroform): 1.33 (t, 3H, CH_3), 4.33 (q, 2H, CH_2), 7.55 (s, 1H, pyrazole proton), 7.7-8.0 (m, 3H, 3 benzene protons), 8.1-8.5 (m, 1H, C_6 benzene proton), 10.70 (s, 1H, formyl proton).

Anal. Calcd. for $C_{14}H_{11}N_3O_6$: C, 53.00; H, 3.49; N, 13.24. Found: C, 53.17; H, 3.39; N, 13.27.

Ethyl 10,11-Dihydro-5-oxopyrazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylate (**12**).

To a solution of 0.7 g (2.2 mmoles) of **11** in 100 ml of ethyl acetate 0.3 g of 10% Pc/C was added. The mixture was hydrogenated in a Parr apparatus at 50 psi for 8 hours. Removal of the catalyst and evaporation of the solvent afforded a crude material which was purified by preparative tlc (eluting system: chloroform/acetonitrile 8:2), second running band, giving 0.2 g (33%) of compound **12**, yellow crystals, mp 189-191°; ir: 3350 (s), 1730 (s), 1680 (vs), 1620 (m), 1530 (m), 1360 (m), 1310 (m), 1235 (s), 1165 (m), 1145 (m), 1105 (m), 1030 (m), 995 (m), 975 (m), 945 (m), 745 (s) cm^{-1}; pmr (deuteriochloroform): 1.36 (t, 3H, CH_3), 4.2-4.6 (m, 4H, CH_2-CH_3 and 11-CH_2), 5.4 (br s, 1H, NH, it exchanges with deuterium oxide), 6.7-7.6 (m, 4H, 3 benzene protons and 1 pyrazole proton), 8.3-8.5 (m, 1H, C_6 benzene proton).

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.84; H, 4.94; N, 15.15.

Dimethyl 1-(2-Nitrobenzoyl)pyrazole-3,5-dicarboxylate (**13**).

A suspension of 1.8 g (10.2 mmoles) of dimethyl pyrazole-3,5-dicarboxylate and 0.31 g (8.0 mmoles) of potassium in 100 ml of anhydrous tetrahydrofuran was refluxed for 3 hours. After cooling 1.5 g (8.0 mmoles) of 2-nitrobenzoyl chloride was added and the mixture was refluxed for 2 hours. The reaction was carried out under a nitrogen flow. The precipitate was filtered off and the solution was taken to dryness to give a residue which was recrystallized from ethanol giving 2.3 g (86%) of **13**, white crystals, mp 137-139°; ir: 1770 (vs), 1750 (vs), 1720 (vs), 1540 (vs), 1350 (vs), 1300 (vs), 1270 (vs), 1235 (vs), 1205 (vs), 1125 (m), 1090 (m), 995 (m), 910 (vs), 855 (m), 825 (m), 710 (vs) cm^{-1}; pmr (deuteriochloroform): 3.84 (s, 3H, CH_3), 4.00 (s, 3H, CH_3), 7.23 (s, 1H, pyrazole proton), 7.6-7.9 (m, 3H, 3 benzene protons), 8.1-8.4 (m, 1H, C_6 benzene proton).

Anal. Calcd. for $C_{14}H_{11}N_3O_7$: C, 50.46; H, 3.33; N, 12.61. Found: C, 50.10; H, 3.26; N, 12.56.

Dimethyl 1-(2-Aminobenzoyl)pyrazole-3,5-dicarboxylate (**14**).

To a solution of 2.0 g (6.0 mmoles) of **13** in 100 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 6 hours. Removal of the catalyst and evaporation of the solvent afforded a solid residue which was recrystallized from ethanol giving 1.4 g (77%) of compound **14**, yellow crystals, mp 162-165°; ir: 3470 (vs), 3370 (vs), 3140 (w), 1740 (vs), 1720 (vs), 1690 (vs), 1630 (vs), 1560 (s), 1300 (s), 1280 (s), 1235 (vs), 1205 (s), 1175 (m) 1110 (m), 1100 (m), 1015 (m), 915 (s), 760 (vs), 685 (m) cm^{-1}; pmr (deuteriochloroform): 3.86 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 6.15 (br s, 2H, NH_2 they exchange with deuterium oxide), 6.4-7.5 (m, 5H, 4 benzene protons and 1 pyrazole proton).

Anal. Calcd. for $C_{14}H_{13}N_3O_5$: C, 55.45; H, 4.32; N, 13.86. Found: C, 55.15; H, 4.45; N, 14.00.

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[3] R. Hüttel, *Chem. Ber.*, **74**, 1680 (1941).