Synthesis of Pyrazolo[4,5-*d*]- and Pyrazolo[4,5-*c*][1]benzazepine Derivatives. IV

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Following our reports on synthetic tricyclic analogues of antitumor anthramycin the synthesis of some isomers pyrazolo[4,5-*d*]- and pyrazolo[4,5-*c*][1]benzazepine derivatives is reported.

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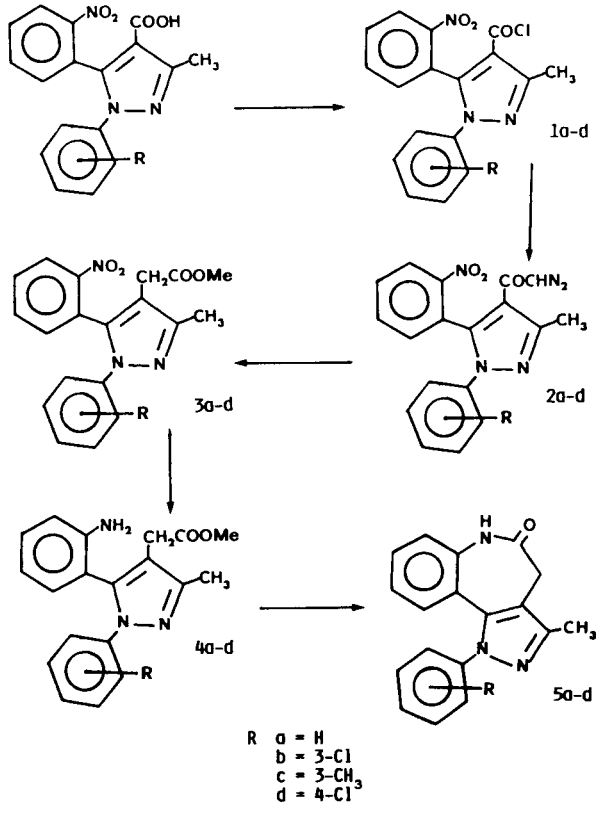
A number of antibiotics possesses the capacity to inhibit the proliferation of neoplasms by interfering with their nuclear events. Like other antitumor drugs these antitumor antibiotics lack of specify, that is they interfer also with the host's nucleic acids.

Structural modifications of these natural products represent a very challenging area to the medicinal chemist, who hopes to find the ideal specific antitumor agent.

The 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine is the common feature of three antitumor antibiotics: anthramycin, tomaymycin and sibiromycin. In two recent papers we reported the synthesis of the new tricyclic ring system 5*H*-pyrazolo[5,1-*c*][1,4]benzodiazepine [1] and of some of its derivatives [2] related to the above cited antibiotics.

Scheme 1



Furthermore more recently we have synthesized some pyrazolo[4,5-*c*]- and pyrazolo[4,3-*c*][1]benzazepines [3] as potential antitumor agents.

Following our study on tricyclic ring systems and with the aim that chemical modifications of the natural antitumor antibiotics will lead to products of biological interest we are now reporting the synthesis of some isomers pyrazolo[4,5-*d*]- and pyrazolo[4,5-*c*][1]benzazepine derivatives.

The synthesis of the pyrazolo[4,5-*d*][1]benzazepine derivatives **5a-d** was carried out as shown in Scheme 1. The recently reported by us 1-aryl-3-methyl-5-(2-nitrophenyl)-pyrazole-4-carboxylic acids [4-5] were converted into the carbonyl chloride **1a-d** by refluxing them in thionyl chloride. Allowing compounds **1a-d** to react with an excess of an ethereal solution of diazomethane the diazoketones **2a-d** were isolated. The latter were submitted to a modified Wolff rearrangement [6-7]. Namely a solution of compounds **2a-d** in methanol was treated at room

Scheme 2

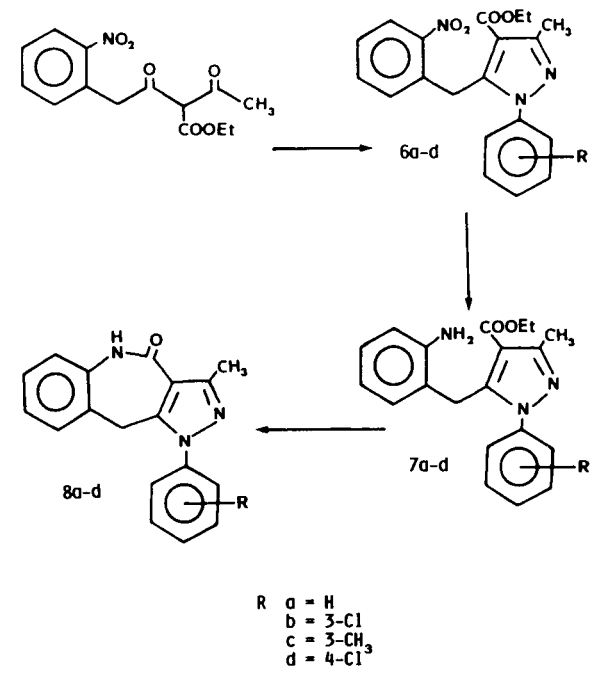


Table I

Physical and ^1H NMR Spectral Data of Compounds **1-5a-d**

Compound	Mp °C	Yield %	Molecular Formula	Analyses % Calcd. (Found) C	H	N	^1H NMR (deuteriochloroform)
1a	103-104	93	$C_{17}H_{12}ClN_3O_3$	59.75 (59.94	3.54 3.60	12.30 12.62)	8.3-8.1 (m, 1H, aromatic), 7.7-7.2 (m, 8H, aromatics), 2.64 (s, 3H, CH_3)
1b	176-178	80	$C_{17}H_{11}Cl_2N_3O_3$	54.28 (54.41	2.95 3.02	11.17 11.34)	8.3-8.1 (m, 1H, aromatic), 7.8-7.0 (m, 7H, aromatics), 2.63 (s, 3H, CH_3)
1c	144-146	92	$C_{18}H_{14}ClN_3O_3$	60.77 (61.00	3.97 4.03	11.81 11.92)	8.3-8.0 (m, 1H, aromatic), 7.7-6.9 (m, 7H, aromatics), 2.64 (s, 3H, CH_3), 2.26 (s, 3H, CH_3)
1d	132-134	90	$C_{17}H_{11}Cl_2N_3O_3$	54.28 (54.37	2.95 3.12	11.17 11.24)	8.3-8.1 (m, 1H, aromatic), 7.8-7.2 (m, 7H, aromatics), 2.64 (s, 3H, CH_3)
2a	113-115	85	$C_{18}H_{13}N_5O_3$	62.25 (62.17	3.77 3.61	20.16 19.98)	8.2-7.9 (m, 1H, aromatic), 7.7-7.2 (m, 8H, aromatics), 5.25 (s, 1H, CH), 2.60 (s, 3H, CH_3)
2b	139-141	78	$C_{18}H_{12}ClN_5O_3$	56.63 (56.48	3.17 3.12	18.34 18.23)	8.3-8.0 (m, 1H, aromatic), 7.7-7.0 (m, 7H, aromatics), 5.26 (s, 1H, CH), 2.56 (s, 3H, CH_3)
2c	139-141	85	$C_{19}H_{15}N_5O_3$	63.15 (62.97	4.18 4.09	19.38 19.21)	8.2-8.0 (m, 1H, aromatic), 7.7-6.8 (m, 7H, aromatics), 5.25 (s, 1H, CH), 2.58 (s, 3H, CH_3), 2.25 (s, 3H, CH_3)
2d	153-155	81	$C_{18}H_{12}ClN_5O_3$	56.63 (56.51	3.17 3.15	18.34 18.28)	8.2-8.0 (m, 1H, aromatic), 7.7-7.1 (m, 7H, aromatics), 5.26 (s, 1H, CH), 2.58 (s, 3H, CH_3)
3a	72-73	65	$C_{19}H_{17}N_3O_4$	64.95 (65.03	4.88 4.91	11.96 12.01)	8.2-7.9 (m, 1H, aromatic), 7.7-7.1 (m, 8H, aromatics), 3.62 (s, 3H, CH_3 ester), 3.30 (s, 2H, CH_2), 2.36 (s, 3H, CH_3)
3b	74-76	35	$C_{19}H_{16}ClN_3O_4$	59.15 (59.32	4.18 4.20	10.89 11.00)	8.2-7.9 (m, 1H, aromatic), 7.8-7.0 (m, 7H, aromatics), 3.62 (s, 3H, CH_3 ester), 3.28 (s, 2H, CH_2), 2.33 (s, 3H, CH_3)
3c	66-67	48	$C_{20}H_{19}N_3O_4$	65.74 (65.81	5.24 5.29	11.50 11.63)	8.1-7.9 (m, 1H, aromatic), 77-6.8 (m, 7H, aromatics), 3.63 (s, 3H, CH_3 ester), 3.30 (s, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.23 (s, 3H, CH_3)
3d	118-120	53	$C_{19}H_{16}ClN_3O_4$	59.15 (59.40	4.18 4.22	10.89 11.10)	8.2-7.9 (m, 1H, aromatic), 7.8-7.2 (m, 7H, aromatics), 3.63 (s, 3H, CH_3 ester), 3.30 (s, 2H, CH_2), 2.37 (s, 3H, CH_3)
4a	132-133	83	$C_{19}H_{19}N_3O_2$	71.01 (71.18	5.96 5.98	13.07 13.18)	7.4-6.6 (m, 9H, aromatics), 3.67 (s, 3H, CH_3 ester), 3.5 (br s, 2H, NH_2), 2.37 (s, 2H, CH_2), 2.32 (s, 3H, CH_3)
4b	118-120	58	$C_{19}H_{18}ClN_3O_2$	64.14 (64.01	5.10 5.08	11.81 11.73)	7.6-6.6 (m, 8H, aromatics), 3.67 (s, 3H, CH_3 ester), 3.5 (br s, 2H, NH_2), 3.37 (s, 2H, CH_2), 2.32 (s, 3H, CH_3)
4c	119-121	91	$C_{20}H_{21}N_3O_2$	71.62 (71.36	6.31 6.28	12.53 12.50)	7.3-6.5 (m, 8H, aromatics), 3.66 (s, 3H, CH_3 ester), 3.5 (br s, 2H, NH_2), 3.37 (s, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.25 (s, 3H, CH_3)
4d	73-75	60	$C_{19}H_{18}ClN_3O_2$	64.14 (64.34	5.10 5.14	11.81 11.98)	7.3-6.5 (m, 8H, aromatics), 3.66 (s, 3H, CH_3 ester), 3.5 (br s, 2H, NH_2), 3.37 (s, 2H, CH_2), 2.32 (s, 3H, CH_3)
5a	237-238	95	$C_{18}H_{15}N_3O$	74.72 (74.78	5.23 5.26	14.52 14.62)	9.1 (br s, 1H, NH), 7.5-6.9 (m, 9H, aromatics), 3.41 (s, 2H, CH_2), 2.40 (s, 3H, CH_3)
5b	203-204	90	$C_{18}H_{14}ClN_3O$	66.77 (66.89	4.36 4.40	12.98 13.16)	9.1 (br s, 1H, NH), 7.5-6.9 (m, 8H, aromatics), 3.40 (s, 2H, CH_2), 2.40 (s, 3H, CH_3)
5c	238-240	95	$C_{19}H_{17}N_3O$	75.23 (75.08	5.65 5.59	13.85 13.72)	9.1 (br s, 1H, NH), 7.4-6.9 (m, 8H, aromatics), 3.40 (s, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.32 (s, 3H, CH_3)
5d	265-267	93	$C_{18}H_{14}ClN_3O$	66.77 (66.86	4.36 4.38	12.98 13.11)	8.8(br s, 1H, NH), 7.4-6.9 (m, 8H, aromatics), 3.37 (s, 2H, CH_2), 2.37 (s, 3H, CH_3)

temperature with a solution of silver benzoate in triethylamine to yield the methyl [1-aryl-3-methyl-5-(2-nitrophenyl)pyrazol-4-yl]acetate **3a-d**. The nitro group was catalytically reduced to give the amino derivatives **4a-d** which by ring closure in sodium methoxide provided the target compounds **5a-d**.

The preparation of the isomers pyrazolo[4,5-*c*][1]benzazepine derivatives **8a-d** was achieved using the synthetic sequence illustrated in Scheme 2. Allowing ethyl 2-acetyl-3-oxo-4-(2-nitrophenyl)butanoate [8] to react with the suitable arylhydrazine the 1-aryl-5-(2-nitrobenzyl)pyrazole derivatives **6a-d** were isolated. Subsequent catalytic hydrogenation and cyclization afforded compounds **8a-d**.

Table II

Physical and ^1H NMR Spectral Data of Compounds **6-8a-d**

Compound	Mp °C	Yield %	Molecular Formula	Analyses % Calcd. (Found) C	H	N	^1H NMR: [a] deuteriochloroform, [b] dimethylsulfoxide-d_6
6a	147-148	30	$C_{20}H_{19}N_3O_4$	65.74 (65.87	5.24 5.31	11.50 11.73)	[a] 8.1-7.8 (m, 1H, aromatic), 7.6-6.9 (m, 8H, aromatics), 4.67 (s, 2H, CH_2), 4.20 (q, 2H, CH_2), 2.60 (s, 3H, CH_3), 1.13 (t, 3H, CH_3)
6b	133-134	27	$C_{20}H_{18}ClN_3O_4$	60.08 (60.31	4.54 4.62	10.51 10.79)	[a] 8.1-7.9 (m, 1H, aromatic), 7.6-6.9 (m, 7H, aromatics), 4.67 (s, 2H, CH_2), 4.18 (q, 2H, CH_2), 2.56 (s, 3H, CH_3), 1.13 (t, 3H, CH_3)
6c	111-112	20	$C_{21}H_{21}N_3O_4$	66.48 (66.21	5.58 5.50	11.07 10.94)	[a] 8.1-7.8 (m, 1H, aromatic), 7.6-6.9 (m, 7H, aromatics), 4.67 (s, 2H, CH_2), 4.20 (q, 2H, CH_2), 2.58 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.13 (t, 3H, CH_3)
6d	103-105	30	$C_{20}H_{18}ClN_3O_4$	60.08 (60.22	4.54 4.56	10.51 10.63)	[a] 8.1-7.8 (m, 1H, aromatic), 7.6-6.9 (m, 7H, aromatics), 4.67 (s, 2H, CH_2), 4.19 (q, 2H, CH_2), 2.58 (s, 3H, CH_3), 1.13 (t, 3H, CH_3)
7a	95-96	85	$C_{20}H_{21}N_3O_2$	71.62 (71.78	6.31 6.33	12.53 12.64)	[a] 7.5-6.3 (m, 9H, aromatics), 4.27 (q, 2H, CH_2), 4.15 (s, 2H, CH_2), 3.3 (br s, 2H, NH_2), 2.53 (s, 3H, CH_3), 1.25 (t, 3H, CH_3)
7b	78-80	78	$C_{20}H_{20}ClN_3O_2$	64.95 (65.03	5.45 5.47	11.36 11.41)	[a] 7.5-6.3 (m, 8H, aromatics), 4.28 (q, 2H, CH_2), 4.15 (s, 2H, CH_2), 3.6 (br s, 2H, NH_2), 2.52 (s, 3H, CH_3), 1.25 (t, 3H, CH_3)
7c	103-105	79	$C_{21}H_{23}N_3O_2$	72.18 (72.31	6.63 6.68	12.03 12.24)	[a] 7.4-6.3 (m, 8H, aromatics), 4.28 (q, 2H, CH_2), 4.13 (s, 2H, CH_2), 3.8 (br s, 2H, NH_2), 2.54 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.25 (t, 3H, CH_3)
7d	132-135	83	$C_{20}H_{20}ClN_3O_2$	64.95 (65.10	5.45 5.51	11.36 11.53)	[a] 7.5-6.4 (m, 8H, aromatics), 4.28 (q, 2H, CH_2), 413 (s, 2H, CH_2), 3.3 (br s, 2H, NH_2), 2.55 (s, 3H, CH_3), 1.25 (t, 3H, CH_3)
8a	253-254	75	$C_{18}H_{15}N_3O$	74.72 (74.58	5.23 5.20	14.52 14.23)	[b] 9.9 (br s, 1H, NH), 7.52 (''s'', 5H, aromatics), 7.3-7.0 (m, 4H, aromatics), 4.00 (s, 2H, CH_2), 2.42 (s, 3H, CH_3)
8b	275-276	65	$C_{18}H_{14}ClN_3O$	66.77 (66.89	4.36 4.38	12.98 13.08)	[b] 10.0 (br s, 1H, NH), 7.8-7.5 (m, 4H, aromatics), 7.4-7.0 (m, 4H, aromatics), 4.08 (s, 2H, CH_2), 2.38 (s, 3H, CH_3)
8c	218-220	68	$C_{19}H_{17}N_3O$	75.23 (74.98	5.65 5.59	13.85 13.51)	[b] 9.9 (br s, 1H, NH), 7.5-7.0 (m, 8H, aromatics), 4.02 (s, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.38 (s, 3H, CH_3)
8d	>300	68	$C_{18}H_{14}ClN_3O$	66.77 (66.91	4.36 4.41	12.98 13.10)	[b] 9.8 (br s, 1H, NH), 7.7-7.4 (m, 4H, aromatics), 7.3-7.0 (m, 4H, aromatics), 4.00 (s, 2H, CH_2), 2.40 (s, 3H, CH_3)

EXPERIMENTAL

All melting points were determined on a Buchi 510 capillary melting point apparatus and are uncorrected. The ^1H nmr spectra were recorded with a Varian EM-360 instrument: chemical shifts are reported in δ (ppm) downfield from internal tetramethylsilane. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck; 70-230 mesh) were used for analytical and column chromatography respectively.

Synthesis of 1-Aryl-3-methyl-5-(2-nitrophenyl)pyrazole-4-carbonyl Chlorides (**1a-d**).

A solution of 1-aryl-3-methyl-5-(2-nitrophenyl)pyrazole-4-carboxylic acid [4-5] (9.3 mmoles) in thionyl chloride (93 mmoles) was refluxed in water bath for 3 hours. The excess of thionyl chloride was distilled under vacuum. The resulting glassy residue was recrystallized from cyclohexane giving white crystals. Physical and ^1H nmr spectral data of compounds **1a-d** are listed in Table 1.

Synthesis of 1-Aryl-3-methyl-4-ω-diazoacetyl-5-(2-nitrophenyl)pyrazoles **2a-d**.

To a suspension of compound **1a-d** (3.0 mmoles in diethyl ether (200 ml) an ethereal solution of diazomethane, prepared from 10 g of *N*-methyl-*N*-(tolyl-4-sulfonyl)nitrosamide, was slowly added. The reaction was carried out at room temperature. The mixture was allowed to stand overnight. Evaporation of the solvent afforded a crude residue which was recrystallized from diethyl ether giving yellow crystals. Physical and ^1H nmr data of compounds **1a-d** are listed in Table 1.

Synthesis of Methyl [1-Aryl-3-methyl-5-(2-nitrophenyl)pyrazol-4-yl]acetates **3a-d**.

A solution of silver benzoate in triethylamine (ratio 1:10) was prepared and filtered to remove the precipitate. This solution was slowly added, at room temperature and under stirring, to a solution of compound **2a-d** (3.0 mmoles) in methanol (100 ml) until the evolution of nitrogen was ended. The mixture was then stirred for 1 hour and successively refluxed for a few minutes after the addition of charcoal. The filtered clear solution was taken to dryness under vacuum. The resulting residue was dissolved in diethyl ether and washed with a 0.1 *N* solution of sodium bicarbonate (20 ml). Evaporation of the solvent afforded a crude residue which was purified by column chromatography (eluting system: chloroform). The crude product which ensues from the evaporation of the solvent, was recrystallized from methanol/water giving yellow crystals. Physical and ^1H nmr spectral data of compounds **3a-d** are listed in Table 1.

Synthesis of Methyl [1-Aryl-3-methyl-5-(2-aminophenyl)pyrazol-4-yl]acetates **4a-d** and Ethyl 1-aryl-3-methyl-5-(2-aminobenzyl)pyrazole-4-carboxylates **7a-d**.

To a solution of the nitro derivative **3a-d** or **6a-d** (2.0 mmoles) in ethyl acetate (100 ml) 10% Pd/C (0.2 g) was added. The mixture was hydrogenated in a Parr apparatus at 50 psi for 10 hours. Removal of the catalyst and evaporation of the solvent afforded a crude product which was purified by crystallization. Namely compounds **4a-d** were recrystallized from cyclohexane while compounds **7a-d** were recrystalliz-

ed from ethanol/water both giving white crystals. Physical and ^{1}H nmr spectral data of compounds **4a-d** and **7a-d** are listed in Table 1 and Table 2 respectively.

Synthesis of 1-Aryl-3-methyl-5,6-dihydro-4*H*-pyrazolo[4,5-*d*][1]benzazepin-5-ones **5a-d** and 1-Methyl-3-aryl-9,10-dihydro-4*H*-pyrazolo[4,5-c][1]-benzazepin-10-ones **8a-d**.

To a solution of sodium methoxide (0.1 g) of sodium in 50 ml of methanol) the amino derivative **4a-d** or **7a-d** (3.0 mmoles) was added. The mixture was refluxed overnight. Evaporation of the solvent afforded a residue which was purified by crystallization. Namely compounds **5a-d** were recrystallized from methanol while compounds **8a-d** were recrystallized from ethanol/water both giving white crystals. Physical and ^{1}H nmr spectral data of compounds **5a-d** and **8a-d** are listed in Table 1 and Table 2 respectively.

Ethyl 1-Aryl-3-methyl-5-(2-nitrobenzyl)pyrazole-4-carboxylates **6a-d**.

To a solution of ethyl 2-acetyl-3-oxo-4-(2-nitrophenyl)butanoate (3.1 mmoles) [8] in absolute ethanol (25 ml) an equimolecular amount of arylhydrazine hydrochloride was added. After addition of triethylamine (0.43) the mixture was refluxed for 5 hours. Upon cooling a precipitate was recovered. Recrystallization from ethanol gave the title compounds as white crystals.

Physical and ^{1}H nmr spectral data of compounds **6a-d** are listed in Table 2.

REFERENCES AND NOTES

[1] L. Cecchi and G. Filacchioni, *J. Heterocyclic Chem.*, **20**, 871 (1983).

[2] F. Melani, L. Cecchi and G. Filacchioni, *ibid.*, **21**, 813 (1984).

[3] F. Melani, L. Cecchi, G. Palazzino and G. Filacchioni, *ibid.*, **22**, 1109 (1985).

[4] L. Cecchi, F. Melani, G. Palazzino, G. Filacchioni and G. C. Porretta, *Farmaco, E. Sci.*, **39**, 888 (1984).

[5] L. Cecchi, F. Melani, G. Palazzino and G. Filacchioni, *ibid.*, **39**, 953 (1984).

[6] M. S. Newman and P. F. Beal III, *J. Am. Chem. Soc.*, **72**, 5163 (1950).

[7] H. R. Snyder, F. Verbanac and D. B. Bright, *ibid.*, **74**, 3243 (1952).

[8] F. Arndt, B. Eistert and W. Partale, *Chem. Ber.*, **61**, 1107 (1928).