PYRAZOLO[1',5':1,6]PYRIMIDO[4,5-*d*]PYRIDAZIN-7(8*H*)-ONE: A NEW HETEROCYCLIC RING SYSTEM FROM ISOXAZOLOPYRIDAZINONES

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Abstract - Treatment of isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones (1a-d) with hydrazine afforded the pyrazole derivatives (3a-d) which were converted in high yields into the new pyrazolo[1',5':1,6]pyrimido[4,5-*d*]pyridazin-7(8*H*)-ones (4a-d) by ring-closure with acetic anhydride.

In the course of our studies on the reactivity of isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones, we have recently shown that compounds of type 1 react in alkaline medium to give the tetrahydrodiazepinones 2 through an initial nucleophilic attack of the hydroxide ion on the lactamic linkage.[1] Because hetero-condensed pyrazoles are interesting compounds from the pharmacological viewpoint,[2-7] we decided to investigate the reactivity of isoxazoles 1a-d towards hydrazine in order to ascertain the potentiality of these compounds to be converted into substituted pyrazoles which in turn may be considered as useful starting materials for new heterocyclic ring-systems.

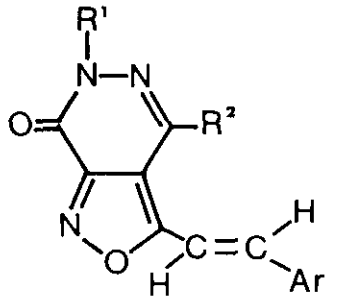
Thus, treatment of compounds 1a-d with ethanolic hydrazine afforded in very good yields (Table 1) the pyrazoles 3a-d whose structures were determined on the basis of chemical and spectroscopic evidence and by elemental analysis data.

In particular, their ^{1}H-nmr spectra showed signals (Table 2) due to NH_2 and NH groups.

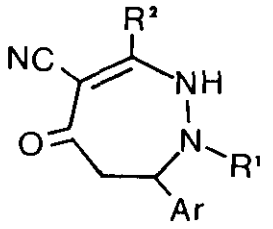
Following the reaction of 2-*o*-aminophenylbenzimidazoles with acetic acid which

led to benzimidazo[1,2-*c*]quinazolines,[8] we carried out the same condensation with compounds 3a-d in order to obtain pyrazolo-condensed systems.

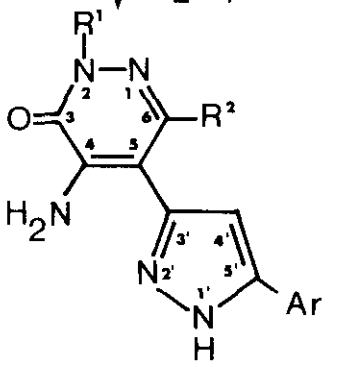
Therefore 3a-d refluxed with acetic anhydride for 15 min gave in excellent yields colourless solids which were recognized as the pyrazolo[1',5':1,6]pyrimido[4,5-*d*]pyridazines 4a-d. The spectral data of the new compounds (Experimental and Table 2) agreed well with the assigned structures.



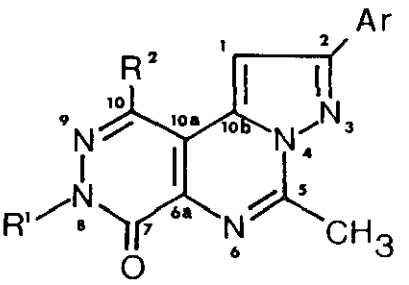
1a-d



2a-b



3a-d



4a-d

	Ar	R¹	R²
a	Ph	H	Ph
b	Ph	CH_3	Ph
c	p-Cl C_6H_4	H	CH_3
d	p-Cl C_6H_4	CH_3	CH_3

As regards the ^{13}C-nmr spectra of compounds 3a-d and 6 (Table 3), the complete assignment was based on chemical shifts and substituent effect considerations

Table 1. Yields and physical data of compounds **3a-d** and **4a-d**

Compd	Yield,%	mp(°C)	Cryst.Solvent	Compd	Yield,%	mp(°C)	Cryst.Solvent
3a	86	275-76	EtOH	4a	80	>345	AcOH
3b	66	294	EtOH	4b	59	320	AcOH
3c	71	300-02	EtOH	4c	70	>340	AcOH
3d	93	269-71	EtOH	4d	71	300	AcOH

as well as on coupled spectra. In particular, the distinction between pyrazolic C-3' and C-5' was accomplished on the basis of coupled spectra of **3a-d** registered in the presence of CF_3COOH; the former appear as doublets [^2J(C-3',H-4')=6.1-6.3 Hz], whereas the latter are multiplets.

The model compound **6**, useful for confirming the assignments of the pyridazine moiety was prepared following the method reported for similar compounds.[9]

Table 2. ^{1}H-nmr data of compounds **3a-d** and **4a-d**

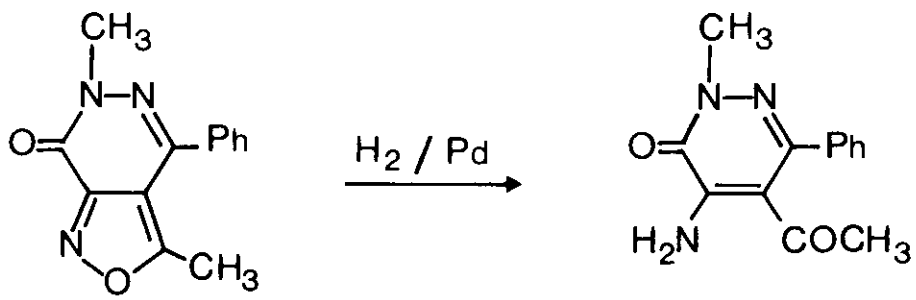
Compd	^{1}H-nmr (δ,ppm,DMSOd$_6$)
3a	5.62(s,1H,4'-H), 7.1(exch s,2H,NH_2),7.4 (m,10H,2xPh), 12.8(exch s,1H, 2-NH),13.5(exch vbr s,1H,1'-NH)
3b	3.72(s,3H,N-CH_3),5.78(s,1H,4'-H),7.1(exch vbr s,2H,NH_2),7.3-7.7(m,10H, 2xPh),13.3(exch vbr s,1H,1'-NH)
3c	2.15(s,3H,6-CH_3),6.4(s,2H,NH_2),6.95(s,1H,4'-H),7.72(m AA'BB',4H,ArH_4), 12.4(exch br s,1H,2-NH),13.3(exch vbr s,1'-NH)
3d	2.21(s,3H,6-CH_3),3.66(s,3H,N-CH_3),6.57(exch s,2H,NH_2),6.98(s,1H,4'-H), 7.72(m AA'BB',4H,ArH_4),13.3(exch vbr s,1H,1'-NH)
4a	3.05(s,3H,5-CH_3),5.80(s,1H,1-H),7.20-7.60(m,10H,2xPh),13.35(exch br s, 1H,8-NH)
4b[a]	3.20(s,3H,5-CH_3),4.00(s,3H,8-CH_3),6.00(s,1H,1-H),7.20-7.90(m,10H,2xPh)
4c	2.78(s,3H,10-CH_3),3.03(s,3H,5-CH_3),7.25(s,1H,1-H),7.90(m AA'BB',4H,ArH_4) 12.80(exch br s,1H,8-NH)
4d[a]	2.78(s,3H,10-CH_3),3.18(s,3H,5-CH_3),3.91(s,3H,NCH_3),7.29(S,1H,1-H),7.80 (m AA'BB',4H,ArH_4)

[a]Spectra recorded in $CDCl_3$

Table 3. ^{13}C-nmr chemical shifts of compounds 3a-d and 6 (δ, ppm, DMSOd_6)

Compd	C-3'	C-4'[a]	C-5'	C=O	C-4	C-5	C-6	Others
3a	143.5	103.5	147.8	156.2	142.0	105.2	145.2	137.2(s),129.6(s),129.0(d), 128.9(d),128.4(d),128.2(d), 128.0(d),125.1(d)
3b	143.25	103.4	146.7	155.1	141.5	104.2	145.4	137.8(s),129.6(s),129.0(d), 128.9(d),128.1(d),127.8(d), 125.0(d),39.5(q)
3c	142.6	103.75	144.7	156.0	141.8	106.2	145.3[b]	132.6(s),129.5(s),128.9(d), 127.0(d),20.5(q)
3d	142.9	103.6	144.7	155.0	141.4	104.9	143.7[b]	132.4(s),129.6(s),128.8(d), 126.95(d),39.0(q),21.1(q)
6	-	-	-	155.1	144.0	109.3	146.3	200.1(s),137.9(s),128.9(d), 128.5(d),128.4(d),39.45(q), 31.0(q)

[a] $^1J(C\text{-}4', H\text{-}4') = 176.3\text{-}176.5$ Hz. [b] $^2J(C\text{-}6, CH_3) = 6.4$ Hz



5 6

This procedure may represent a useful route for other tricyclic pyrazolo heterocycles with potential pharmacological activity; investigation in this field are now in progress.

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Unless otherwise stated, ir spectra were measured for nujol mulls

with a Perkin-Elmer 337 spectrometer. ^{1}H-nmr spectra were recorded with either a Varian EM-360 or a Perkin-Elmer R32 spectrometers and ^{13}C-nmr spectra with a Varian FT-80A instrument: chemical shift are reported in ppm from internal tetramethylsilane, coupling constants in Hz. Mass spectral data were taken with a LKB 2091 mass spectrometer. Silica-gel plates (Merck F_{254}) were used for analytical tlc.

Compounds 1a-d were prepared as reported in the literature.[1,10] All the new compounds gave satisfactory microanalytical data.

General Procedure for the Synthesis of Compounds 3a-d

Hydrazine hydrate (5 ml) in ethanol (10 ml) was added to a solution of compounds 1a-d (1.5 g) in the same solvent (10 ml) and the solution was refluxed for 15 min. After cooling, dilution of the reaction mixture with water (10 ml) afforded white solids which were filtered-off,dried, and crystallized (Table 1).

4-Amino-6-phenyl-5-(5'-phenyl-1*H*-pyrazol-3-yl)pyridazin-3(2*H*)-one (3a): ir (KBr) 3500-3000 br (NH_2 and 2xNH) and 1645 cm^{-1} (CO); MS: m/e (%) 329 (100) M^+ and 328 (63) M^+-1. Anal. Calcd for $C_{19}H_{15}N_5O$: C, 69.27; H, 4.59; N, 21.26. Found: C, 69.48; H, 4.71; N, 21.15.

4-Amino-2-methyl-6-phenyl-5-(5'-phenyl-1*H*-pyrazol-3-yl)pyridazin-3(2*H*)-one (3b): ir 3500-3000 br (*NH_2 and NH*) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{20}H_{17}N_5O$: C, 69.94; H, 4.99; N, 20.39. Found: C, 69.65; H, 5.15; N, 20.50.

4-Amino-5-[5'-(4-chlorophenyl)-1*H*-pyrazol-3-yl]-6-methylpyridazin-3(2*H*)-one (3c): ir 3500-3000 br (NH_2 and 2xNH) and 1660 cm^{-1} (CO). Anal. Calcd for $C_{14}H_{12}ClN_5O$: C, 55.73; H, 4.01; N, 23.20. Found: C, 55.69; H, 4.15; N, 23.35.

4-Amino-5-[5'-(4-chlorophenyl)-1*H*-pyrazol-3-yl]-2,6-dimethylpyridazin-3(2*H*)-one (3d): ir 3500-3000 br (NH_2 and NH) and 1700 cm^{-1} (CO); MS: m/e (%) 315 (100) M^+ and 317 (53) M^++2. Anal. Calcd for $C_{15}H_{14}ClN_5O$: C, 57.05; H, 4.46; N, 22.17. Found: C, 57.25; H, 4.52; N, 22.01.

5-Acetyl-4-amino-2-methyl-6-phenylpyridazin-3(2*H*)-one (6)

Palladium on activated carbon (0.5 g) was added to a suspension of 3,6-dimethyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one (5)[11] (1.2 g) in ethanol (220 ml) and the mixture was hydrogenated in the Parr apparatus for 15 h. After filtration and several washings with the same solvent, compound 6 separated from the ethanolic solution as white crystals. (1.1 g, yield 91%), mp 199-200°C (from EtOH); ir 3420 and 3320 (NH_2), 1680 (CH_3CO),and 1635 cm^{-1}(CO); ^{1}H-nmr (DMSOd_6) δ 1.71(s,3H,$COCH_3$),3.69(s,3H,N-CH_3),7.45(m,5H,Ph),7.80(exch br s,2H,NH_2). Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.16; H, 5.39; N, 17.28. Found: C, 64.23; H, 5.49; N, 16.98.

General Procedure for the Synthesis of Compounds 4a-d

A suspension of compounds 3a-d (0.5 g) in acetic anhydride (8 ml) was refluxed under stirring for 15 min. After cooling, the solid which separated was filtered, washed with water, and crystallized (Table 1).

5-Methyl-2,10-diphenylpyrazolo[1',5':1,6]pyrimido[4,5-*d*]pyridazin-7(8*H*)-one (4a): ir 3300-3000 (NH) and 1680 cm^{-1}(CO). Anal. Calcd for $C_{21}H_{15}N_5O$: C, 71.38; H, 4.28; N, 19.82. Found: C, 71.21; H, 4.02; N, 19.71.

5,8-Dimethyl-2,10-diphenylpyrazolo[1',5':1,6]pyrimido[4,5-*d*]pyridazin-7(8*H*)-one (4b): ir 1690 cm^{-1} (CO); ^{13}C-nmr ($CDCl_3$) δ 157.8(s),155.8(s),153.9(s),143.1(s), 136.6(s),135.35(s),135.1(s),131.1(s),129.75(d),129.5(d),128.9(d),128.8(d),128.7 (d),126.6(d),117.4(s),100.0(d,C-1),40.45(q),20.4(q). Anal. Calcd for $C_{22}H_{17}N_5O$: C, 71.92; H, 4.66; N, 19.06. Found: C, 71.78; H, 4.59; N, 19.26.

2-(4'-Chlorophenyl)-5,10-dimethylpyrazolo[1',5':1,6]pyrimido[4,5-*d*]-pyridazin-7(8*H*)-one (4c): ir 3300-3000 (NH) and 1680 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{12}ClN_5O$: C, 58.99; H, 3.68; N, 21.49. Found: C, 59.01; H, 3.99; N, 21.29.

2-(4'-Chlorophenyl)-5,8,10-trimethylpyrazolo[1',5':1,6]pyrimido[4,5-*d*]pyridazin-7(8*H*)-one (4d): ir 1690 cm^{-1} (CO); ^{13}C-nmr ($CDCl_3$) δ 157.8(s),155.2(s),153.6(s), 139.7(s),137.0(s),135.8(s),135.2(s),129.8(s),129.2(d),128.1(d),117.9(s),99.5(d, C-1),40.2(q),21.9(q),20.4(q). Anal. Calcd for $C_{17}H_{14}ClN_5O$: C, 60.09; H, 4.15; N, 20.61. Found: C, 60.29; H, 4.36; N, 20.47.

REFERENCES

1. V.Dal Piaz, G.Ciciani, A.Costanzo, G.Auzzi, and S.Chimichi, *Heterocyles*, 1984, 22, 1741.
2. R.E.Orth, *J.Pharm.Sci.*, 1968, 57, 537 and references cited therein.
3. W.E.Kirkpatrick, T.Okabe, I.W.Hillyard, R.K.Robins, A.T.Dren, and T.Novinson, *J.Med.Chem.*, 1977, 20, 386.
4. V.C.Dewey and G.W.Kidder, *Can.J.Biochem.*, 1977, 55, 110.
5. S.W.Schneller and D.R.Moore, *J.Heterocycl.Chem.*, 1978, 15, 319.
6. T.Higashino, Y.Iwai, and E.Hayashi, *Chem.Pharm.Bull.*, 1976, 24, 3120.
7. T.Higashino, Y.Iwai, and E.Hayashi, *ibid.*, 1977, 25, 535.
8. M.Davis, *J.Chem.Soc.*, 1962, 945.
9. V.Sprio, E.Aiello, and A.Mazza, *Ann.Chim.*, 1967, 57, 836.
10. V.Dal Piaz, S.Pinzauti, and P.Lacrimini, *J.Heterocycl.Chem.*, 1976, 13,409.
11. G.Renzi and S.Pinzauti, *Farmaco,Ed.Sci.*, 1969, 24, 885.

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