Tetrahedron Letters,Vol.28,No.43,pp 5165-5168,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

THE CORRECT SYNTHESIS OF 2,3-DIHYDRO-2-ARYL-4-R-[1]BENZOPYRANO[4,3-c]PYRAZOLE-3-ONES.

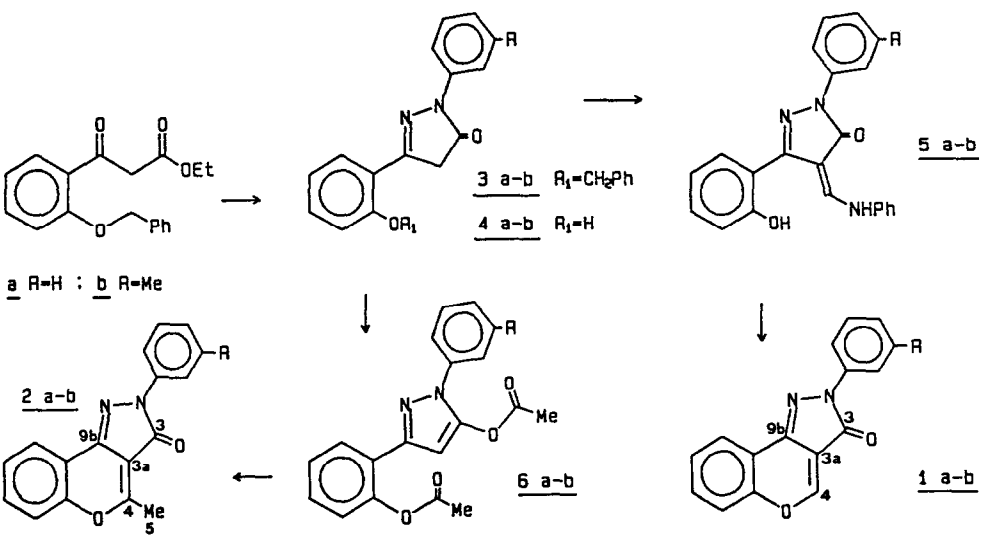
Vittoria Colotta, Lucia Cecchi*, Fabrizio Melani, Giovanna Palazzino and Guido Filacchioni

Dipartimento di Scienze Farmaceutiche, Via G. Capponi, 9, 50121 Firenze, Italy

Summary: The correct synthesis of the title compounds 1a-b and 2a-b is described. The claimed synthesis of 2a from 2-methyl-3-chromonecarbonitrile is shown not to lead to 2a, as previously reported but to 1,4-dihydro-1-phenyl-3-methyl[1]benzopyrano[3,4-d]pyrazole-4-one 10a.

Following our former researches on pyrazolo-quinoline derivatives [1-4] we decided to synthesize 2-aryl-[1]benzopyrano[4,3-c]pyrazole-3-ones 1a-b and its 4-methyl derivatives 2a-b, which are isosters of pyrazolo-quinolin-3-ones (CGS series[5]).

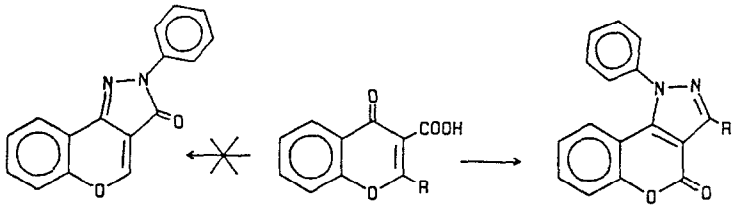
On heating a mixture of equimolar amounts of ethyl 3-(1-benzyloxyphenyl)-3-oxopropanoate[6] and arylhydrazine at 100-120°C, 1-aryl-3-(2-benzyloxyphenyl)pyrazole-5-ones 3a-b were isolated. Catalytic hydrogenation (10% Pd/C) of the latter gave rise to compounds 4a-b which, refluxed in dry ethanol with ethyl orthoformate and aniline, were converted into 5a-b. The heating of a 5% solution of NaOH of 5b followed by acidification with HCl yielded compound 1b. In the case of 5a a mixture of 1a and 1-phenyl-3-(2-hydroxyphenyl)-4-formylpyrazole-5-one was recovered.



Cyclization ensued when the mixture was treated with a few drops of conc. H_2SO_4. From the reaction of 4a-b with Ac_2O and AcONa we obtained 6a-b, which when dissolved in ethanol, added to an equimolar amount of piperidine, and refluxed for 15', in turn yielded 2a-b.

Evidence of the structures 1 and 2 was obtained from the physical and spectral data listed in Table 1. Additional support to the attributed structures was given by the ^{13}C-NMR spectra (see Table 2).

However the synthesis of 1a and 2a has already been reported[7-8]. The synthesis of 1a was subsequently disproved by Chantegrel et al.[9] who demonstrated that by reacting 3-chromonecarboxylic acid 7 with phenylhydrazine, the well-known nucleophilic rearrangement took place, leading to 1,4-dihydro-1-phenyl[1]benzopyrano[3,4-d]pyrazole-4-one 8. Likewise from 2-methyl-3-chromonecarboxylic acid 9, 10a was prepared[9].



1a

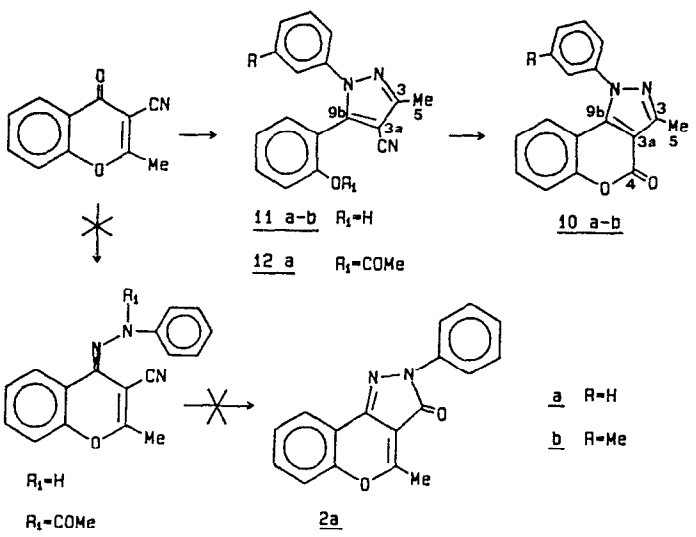
7 R=H

9 R=Me

8 R=H

10a R=Me

Rather surprisingly, compound 2a was claimed to be prepared by reacting 2-methyl-chromonecarbonitrile with phenylhydrazine[8], and the change in the reaction course accounted for by the presence of the 2-methyl substituent. However, in our hands 2-methyl-chromonecarbonitrile[10] and arylhydrazine yielded 11a-b which, refluxed in ethylene glycol, led to 10a-b. Thus, the claimed intermediates 4-phenylhydrazone and its N-acetyl derivative are implausible, and are instead 1-phenyl-3-methyl-4-cyano-5-(2-hydroxyphenyl)pyrazole 11a and its acetate 12a.



11 a-b R_1=H

12 a R_1=COMe

10 a-b

R_1=H

R_1=COMe

2a

a R=H

b R=Me

The structure of 10a was confirmed by comparison with an authentic sample prepared following the synthetic pathway described by Chantegrel et al.[9]. The structures of 10b, 11a-b and 12a are supported by their physical and spectral data (see Tables 1 and 2).

In conclusion, to date nobody has ever actually synthesized the title compounds, since the reported synthesis of 2a is to be ruled out just as that of its 4-H derivative 1a has already been[9].

Table 1. Physical and spectral data of new compounds.

Compd.[a]	R	Yield % (cryst.solv.)	M.p. (°C)	I.R. cm^{-1} (nujol)	^{1}H-NMR (ppm) ($CDCl_3$)
1a	H	75(D)	169-70	1225,1665,1670	7.0-7.7(m,6H ar); 7.9-8.3(m,3H ar); 8.42(s,1H H_4).
1b	Me	40(D)	175-6	1240,1660,1685	2.42(s,3H Me);6.9-7.7(m,5H ar);7.8-8.1(m,2H ar);8.1-8.3(m,1H ar);8.40 (s,1H H_4).
2a	H	60(A)	165-7	1255,1660,1680	2.80(s,3H Me);7.1-7.7(m,6H ar);8.0-8.3(m,3H ar).
2b	Me	55(A)	160-1	1255,1650,1690	2.40(s,3H Me);2.8(s,3H Me);6.9-7.6 (m,5H ar); 7.8-8.2(m,3H ar).
3a	H	56(A)	149-51	1700	3.87(s,2H CH_2);5.07(s,2H CH_2-Ph); 6.9-7.7(m,11H ar);7.9-8.2(m,3H ar).
3b	Me	52(A)	121-2	1620	2.40(s,3H Me);3.90(s,2H CH_2);5.10 (s,2H CH_2-Ph); 6.8-8.3(m,13H ar).
4a	H	65(D)	130-2	1710	3.80(s,2H CH_2);6.8-7.8(m,7H ar);7.8-8.0(m,2H ar).
4b	Me	78(D)	124-5	1700	2.40(s,3HMe); 3.86(s,2H CH_2);6.8-7.7(m,8H ar); 10.8(s,1H OH).
5a	H	65(A)	142-3	1635,1660	6.8-7.6(m,13H, ar + NH);7.8-8.1(m,2H ar);8.4(br.s,1H =CH-N);10.45(s,1H OH).
5b	Me	72(A)	135-6	1625,1660	2.40(s,3H Me);6.8-7.6(m,12H, ar + NH); 7.8-8.0(m,2H ar);8.4(br.s,1H =CH-N); 10.56(s,1H OH).
6a	H	88(D)	93-5	1765,1790	2.21(s,3H Me);2.26(s,3H Me);6.64(s,1H pyr);7.0-7.7(m,8H ar);7.8-8.0(m,1H ar).
6b	Me	60(D)	85-6	1750,1800	2.24(s,3H Me);2.28(s,3H Me);2.40(s,3H Me);6.64(s,1H pyr);7.0-7.7(m,7H ar); 7.8-8,8(m,1H ar).
10b	Me	60(A)	196-7	1750	2.50(s,3H Me);2.70(s,3H Me-pyr);6.9-7.7(m,8H ar).
11a	H	75(B)	197-9[8]	2235,3120	2.48(s,3H Me); 6.8-7.3(m,9H ar).
11b	Me	30(B)	144-6	2220,3270	2.26(s,3H Me);2.48(s,3H Me-pyr);6.6-7.5(m,8H ar).
12a	H	64(C)	118-20[8]	1770,2220	2.11(s,3H Me);2.50(s,3H Me-pyr);7.0-7.7(m,9H ar).

[a] All products gave satisfactory microanalyses.(A) EtOH,(B) MeOH,(C) AcOEt,(D) C_6H_{12}/AcOEt

Table 2. Selected ^{13}C-NMR (ppm, $CDCl_3$) spectral data of some significant compounds

Compd.	C-3	C-3a	C-4	C-9b	C-5
1a	160.79	113.38	153.17	140.01	
1b	160.66	113.37	152.92	139.80	
2a	161.66	109.04	167.76	140.07	16.41
2b	161.67	108.93	168.51	140.20	16.56
10b	150.57	106.18	157.81	141.51	12.70
11a [a]	151.42	94.27		145.91	12.32

[a] solvent DMSO-d_6

The carbon shifts were assigned from multiplicity in the off-resonance decoupled spectra and examination of the coupled spectra.

References

1. L.Cecchi, F.Melani, G.Palazzino, G.Filacchioni, C.Martini, E.Pennacchi and A.Lucacchini, Farmaco, Ed. Sci., 40, 509 (1985)
2. F.Melani, L.Cecchi, G.Palazzino, G.Filacchioni, C.Martini, E.Pennacchi and A.Lucacchini, J. Med. Chem., 29, 291 (1986)
3. F.Melani, L.Cecchi, G.Palazzino, G.Filacchioni, C.Martini, E.Pennacchi and A.Lucacchini, J. Pharm. Sci., 75, 1175 (1986)
4. G.Palazzino, L.Cecchi, F.Melani, V.Colotta, G.Filacchioni, C.Martini and A.Lucacchini, J. Med. Chem., in press.
5. N.Yokoyama, B.Ritter and A.D.Neubert, J. Med. Chem., 25, 337 (1982)
6. J.L.Charlton, G.Lypka and V.Sayeed, J. Heterocyclic Chem., 17, 593 (1980)
7. C.K.Ghosh and K.K.Mukhopadhyay, Synthesis, 779 (1978)
8. C.K.Ghosh and C.Pal, Indian J. Chem., 24B, 1288 (1985)
9. B.Chantegrel, A.I.Nadi and S.Gelin, Tetrahedron Lett., 24, 381 (1984)
10. Z.Jerzmanowska and W.Basinski, Rocz. Chem., 51, 2283 (1977)

(Received in UK 22 May 1987)