SHORT PAPER

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Synthesis and crystal structure of 3-[4-diarylmethyl-1-oxophthalazin-2(1*H*)-yl]propanenitriles

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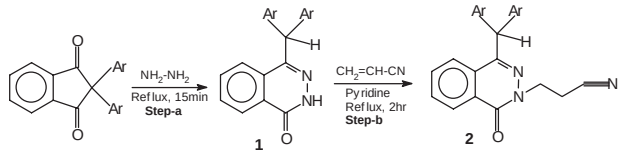
3-[4-Diarylmethyl-1-oxophthalazin-2(1*H*)-yl]propanenitriles were prepared from 4-diarylmethyl-1-(2*H*)phthalazinones by Michael addition and structures were elucidated by X-ray analysis.

Keywords: 3-[4-diarylmethyl-1-oxophthalazin-2(*1H*)-yl]propanenitriles

Various functional derivatives of 4-substituted alkyl-1-(2*H*)phthalazinone-2-acetates such as corresponding acids, amides and hydrazides, have been reported to possess a variety of biological activities like hypnotic,[1] anticonvulsive,[1] antibacterial,[2] antifungal,[2] antianaphilactic,[3] nootropic[3] and inhibition of the aldose reductase,[4] *etc.* Very few reports are available for the synthesis of 4-phenyl- and 4-substituted-1-(2*H*)phthalazinones and their 2-acetate derivatives.[5–11] This increases the necessity of developing suitable and efficient routes to prepare such potentially bio-active compounds from readily available starting materials. Recently we have reported[12] a facile synthesis of 4-diarymethyl-1-(2*H*)phthalazinones **1a–c** (Scheme 1) by condensation of 2,2-diaryl-1,3-indanediones with hydrazine hydrate(Scheme 1, Step-a).



1 and **2**
a : Ar = *p*-ClC_6H_4
b : Ar = *p*-BrC_6H_4
c : Ar = *p*-$OMeC_6H_4$

Scheme 1

As 2(*N*)-substituted phthalazinones are biologically important molecules, we tried to functionalise the N–H group of the phthalazinones **1a–c**. It was observed that under refluxing conditions 4-diarymethyl-1-(2*H*)phthalazinoes **1a–c** react with acrylonitrile in the presence of pyridine to produce the Michael addition products 3-[4-diarylmethyl-1-oxophthalazin-2(1*H*)-yl]propanenitriles **2a–c**, in high yields (Scheme 1, Step-b). From a synthetic point of view the phthalazinones **2a–c** are important as the nitrile group can be suitably functionalised further. Since **2a–c** are potentially bio-active, the molecular structures of **2b** and **2c** have been determined by X-ray crystallography to gain an insight into the three dimensional geometry of the molecules.

The angle C4–C7–C14 in **2b** is 113.3(3)° while in **2c** it is 112.4(1)°. The torsion angle N16–C25–C26–C27 in **2c** is 60.4(3)° while the corresponding angle in **2b** is a comparable one of –61.2(6).

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

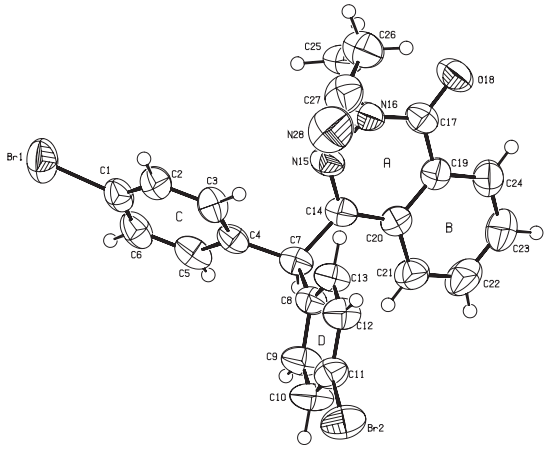
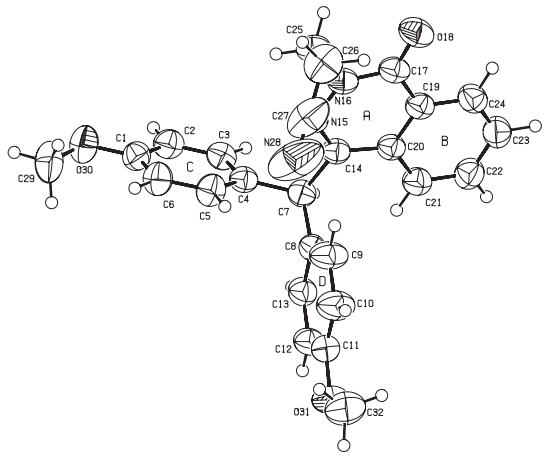


Fig. 1 An ORTEP representation of the molecular structures of **2b** and **2c**, in the solid state. The thermal ellipsoids are shown to the 50% probability level.



There is an angle of 70.9(1)° between the planes **C** and **D** in **2b** but an angle of 86.6(1)° in case of **2c**. The planes **C** and **AB** are at an angle of 58.1(1)° in **2b** while the corresponding angle in **2c** is 78.6(5)°. The planes **D** and **AB** are at an angle of 77.7(1)° in **2b** but at an angle of 89.7(4)° in **2c**.

Experimental

General procedure for preparation of **2a–c:** The appropriate substrate **1a–c** (1.4 mmol) was added to a mixture of 10 ml acrylonitrile and 3 ml of pyridine and the reaction mixture was refluxed for about 2h. The cooled reaction mixture was acidified with 6 N HCl to pH 6.

The mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water and dried over Na_2SO_4. After removal of the solvent under reduced pressure, column chromatography with haxane-EtOAc afforded **2a–c** as solid. The solid products were crystallised from $CHCl_3$-light-petroleum.

3-[4-[Bis (4-chlorophenyl)methyl]-1-oxophthalazin-2(1H)-yl] propanenitrile (**2a**): Yield ~ 89%; m.p. 167°C; IR (KBr): 2250, 1656 cm^{-1} ^1H (300.13MHz) NMR in $CDCl_3$: δ_H 8.47–8.44 (1H, m), 7.76–7.70 (3H, m), 7.28 (4H, apparent d, J = 8.6Hz), 7.13 (4H, apparent d, J = 8.6Hz), 5.90 (1H, s), 4.36 (2H, t, J = 6.6Hz), 2.79 (2H, t, J = 6.6Hz), ^{13}C (75.47MHz) NMR in $CDCl_3$: δ_C 158.8, 146.7, 138.9, 133.4, 133.0, 131.6, 130.5, 130.1, 128.7, 128.6, 127.4, 124.7, 117.1, 52.1, 46.5, 16.5.

3-[4-[Bis (4-bromophenyl)methyl]-1-oxophthalazin-2(1H)-yl] propanenitrile (**2b**): Yield ~ 90%; m.p. 178°C; IR (KBr): 2246, 1649 cm^{-1} ^1H and ^{13}C NMR spectrum of **2b** are similar to that of **2a**.

3-[4-[Bis (4-methoxyphenyl)methyl]-1-oxophthalazin-1(2H)-yl] propanenitrile (**2c**): Yield ~ 90%; m.p. 144°C; IR (KBr): 2248, 1651 cm^{-1} ^1H (300.13MHz) NMR in $CDCl_3$: δ_H 8.46–8.43 (1H, m), 7.80–7.69 (3H, m), 7.15 (4H, d, J = 8.6Hz), 6.84 (4H, d, J = 8.6Hz), 5.85 (1H, s), 4.38 (2H, t, J = 6.6Hz), 3.77 (6H, s), 2.78 (2H, t, J = 6.6Hz). ^{13}C (75.47MHz) NMR in $CDCl_3$: δ_C 159.0, 158.5, 148.1, 133.4, 133.2, 131.2, 130.2, 129.4, 128.0, 127.3, 125.1, 117.2, 114.0, 55.2, 52.0, 49.2, 16.5.

Crystal data: **2b(2c):** $C_{24}H_{17}Br_2N_3O(C_{26}H_{23}N_3O_3)$; Z=4(4); P21/c (P21/c); a=9.6180(1) (15.5711(3)) Å; b= 21.8139(3) (9.2185(2)) Å; c= 10.3660(2) (17.1610(3)) Å; $\alpha = \gamma$ = 90.00°; β= 94.1180(6) (115.6321(2))°; M_r= 523.23(425.47); V=2169.24(6)(2220.91(8)) $Å^3$; μ= 3.758 (0.085) mm^{-1}, F (000)=1040(896), 4948(9685) reflections measured, 4948(5031) unique reflections, R_{int} =0.039(0.024).

X-ray data were collected at room temperature on a Nonius Kappa CCD single crystal diffractometer with Mo-Kα radiation (λ= 0.71070 Å) and ϕ-ω scan [$0 \le h \le 12$, $0 \le k \le 28$, $-13 \le l \le 13$ ($-20 \le h \le 20$, $0 \le k \le 11$, $-22 \le l \le 22$)]. The structures were solved by direct methods with SHELXS-97 and refined by full-matrix least squares on F^2 using SHELXL-97.[13] All non-hydrogen atoms were refined anisotropically and hydrogens were located by refinement. The final R-value was 0.0528(0.0481) for 3626(3710) Fo > 4σ (Fo), wR2 = 0.1367(0.1430), S = 1.156(1.086) using 331(381) parameters and no restraints. The weighting scheme, $w=1 / [\sigma^2(F_o^2) + (0.0466 * P)^2 + 2.66 * P]$ where $P = (Max (F_o^2, 0) + 2 * F_c^2) / 3$ ($w = 1 / [\sigma^2(F_o^2) + (0.0617 * P)^2 + 0.42 * P]$ where $P = (Max (Fo^2, 0) + 2 * Fc^2) / 3$) gave satisfactory analysis of the variance.

Full crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 209484 and CCDC 209485.

Data collection: COLLECT (Nonius, 1997); [14] cell refinement: DENZO-SMN (Otwinowski & Minor, 1997); [15] data reduction: DENZO-SMN; molecular graphics: PLATON (Spek, 1999). [16]

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References

1 H.J. Engelbrecht and D. Lenke, German (East) patent 19629, 1960, *Chem. Abstr.*, 1961, **55**, 22346.
2 B. Abd El-Faltah, M.I. Al-Ashmani, S. El-Feky and E. Roeder, *Egypt. J. Pharm. Sci.*, 1987, **28**, 383.
3 H. Horn, K. Unverferth, G. Laban and D. Lohmann, German (East) patent 286354, 1991, *Chem. Abstr.*, 1991, **115**, 8820.
4 Fujsawa Pharmaceutical Co. Ltd. Japan patent 62252774, 1988, *Chem. Abstr.*, 1988**, 109**, 6531.
5 S. Marcaccini, R. Pepino, C. Polo and M.C. Pozo, *Synthesis*, 2001, **1**, 85
6 J. Epsztajn, Z. Malinowski, J.Z. Brzezinki and M. Karzatka, *Synthesis*, 2001, **14**, 2085.
7 Y. Saito, T. Sakamoto and Y. Kikugawa, *Synthesis*, 2001, **2**, 221.
8 M.M. Abdel-Khalik, M.S. Agamy and M.H. Elnagdi, *Synthesis*, 2001, **12**, 1861.
9 N.R. Patel, In *Condensed pyridazines Including Cinnolines and Phthalazines*, ed R.N. Castle, Wiley-Interscience : New York, 1973; pp. 383-385.
10 H. Horn, K. Unverferth, B. Koerner, D. Lohmann and G. Laban, German(East) Patent 274218**,** 1989, C*hem. Abstr*. 1990, **113**, 23938.
11 H. Horn, E. Morgenstern and K. Univerferth, *Pharmazie***,** 1990, **45**, 724.
12 S.K. Kundu, A. Pramanik and A. Patra, *Synlett*, 2002, **5**, 823.
13 G.M. Sheldrick, SHELXS97 and SHELXL97, University of Göttingen, Germany, 1997.
14 Nonius (1997). COLLECT. Nonius BV, Delft, The Netherlands.
15 Z. Otwinowski and W. Minor, Methods in Enzymology, Macromolecular Crystallography, eds C.W. Carter and R.M. Sweet, Academic Press, London, 1997, Vol. 276, part A, pp. 307-326.
16 A.L. Spek, PLATON. Version of April 1999. Utrecht University, The Netherlands, 1999.