Indian Journal of Chemistry
Vol. 37B, July 1998, pp. 651 - 656

Studies in anthraquinones: Preparation of 2-substituted-pyrimido anthraquinones and related fused 1,2,4-triazolo, tetrazolo and pyrazolino derivatives

C O Kangani & H E Master*
Nadkarny-Sacasa Research Laboratory, St. Xavier's College, Mumbai 400001

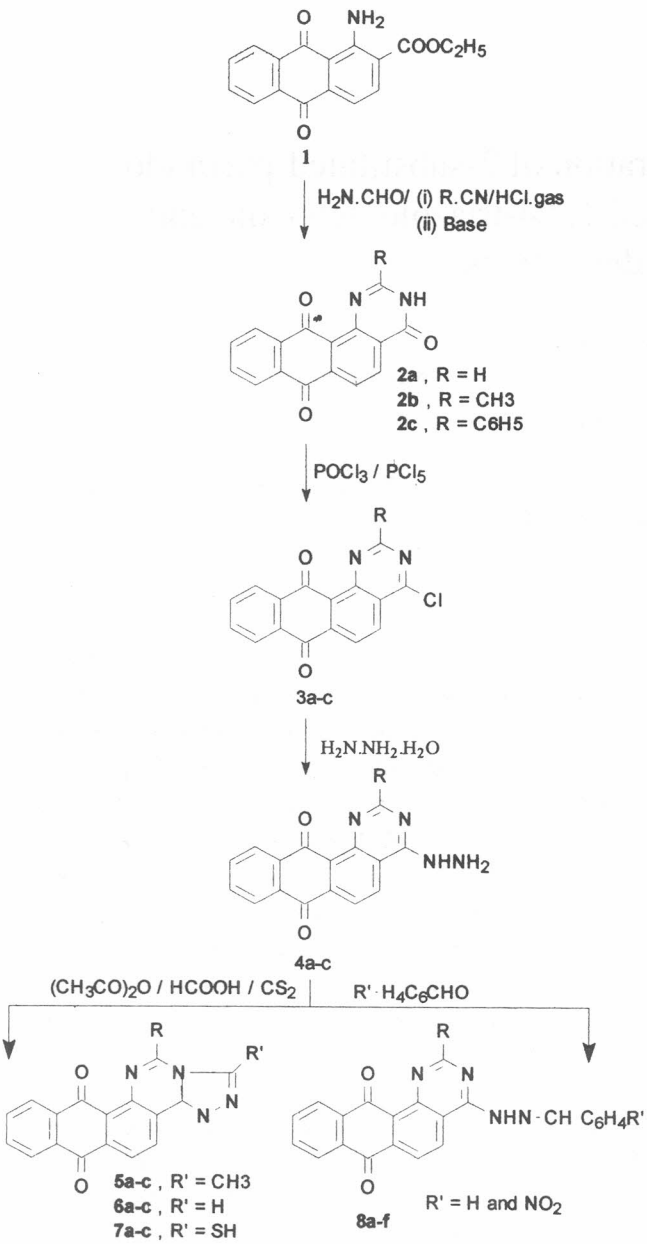
Received 12 March 1997; accepted 17 October 1997

Syntheses of 2-substituted-4(3*H*)-oxopyrimido[4,5-*a*]anthraquinones **3**, 4-hydrazino-2-substituted-pyrimido[4,5-*a*]anthraquinones **4**, 5-substituted-1,2,4-triazolo[4,3-*c*]pyrimido[4,5-*a*]anthraquinones **5-7**, tetrazolo[4,5-*c*]pyrimido[4,5-*a*]anthraquinones **10**, and pyrazolyl/pyrazolinylpyrimido[4,5-*a*]anthraquinones derivatives **11** and **12** have been reported.

The presence of a pyrimidine ring in anti-hypertensive drugs, sedatives, anti-inflammatory agents, diuretics, hypocholesteroiemics, anti-allergic and anti-tussive drugs[1-7] is well-known. On the other hand, condensed 1,2,4-triazoloes are biologically important compounds[8-10]. This prompted us to take up synthetic routes leading to 2-substituted-4(3*H*)-oxopyrimido[4, 5-*a*]anthraquinone and as well as 5-substituted-1,2,4-triazolo[4,3-*c*]pyrimido[4,5-*a*]anthraquinone using with a series of such compounds could be made. Amino esters serve as a good synthon for the formation of a pyrimidine ring[11]. The synthesis of a pyrimidine ring could be achieved by reaction of enamino esters with formamide[12] and reaction of enamino esters with nitriles in the presence of acid followed by base catalyzed cyclisation[13].

Herein, we report the synthesis of 2-substituted-pyrimido[4,5-*a*]anthraquinones and 4-hydrazino-2-substituted pyrimido[4,5-*a*]anthraquinones followed by the preparation of fused triazolo[14-17], tetrazolo and pyrazolinopyrimido derivatives. 4(3*H*)-Oxopyrimido[4,5-*a*]anthraquinone **2a** was obtained by direct reaction of the enamino ester **1** with formamide which on treatment with acetonitrile and phenyl nitriles in the presence of dry hydrogen chloride gas[18-19] followed by base treatment furnished 2-methyl/2-phenyl-4(3*H*)-oxopyrimido-[4,5-*a*] anthraquinones **2b,c.** Compounds **2a-c** on treatment with $POCl_3$ and PCl_5 gave 4-chloro-2-substituted-pyrimido[4,5-*a*]anthraquinones **3a-c**, which on reaction with hydrazine hydrate afforded 4-hydrazino-2-substituted-pyrimido[4, 5-*a*]anthraquinones **4a-c**. Compounds **4a-c**, when treated with acetic anhydride and formic acid respectively gave, 3-methyl-5-substituted-1, 2, 4-triazolo[4,3-*c*]pyrimido[4,5-*a*]anthraquinones **5a-c** and 5-substituted-1,2,4-triazolo[4, 3-*c*]pyrimido[4, 5-*a*]anthraquinones **6a-c**. Also, **4a-c** on refluxing with carbon disulphide yielded 3-mercapto-5-substiuted-1,2,4-triazolo[4,3-*c*] pyrimido[4,5-*a*]anthra quinones **7a-c** (Scheme I, Table I). Further, **4a-c** on treatment with aromatic aldehydes in ethanol and/or glacial acetic acid gives both 4-(arylidenehydrazone)-pyrimido[4, 5-*a*]anthraquinones **8a-f** (Scheme I), and 3-aryl-5-substituted-1,2,4-triazolo[4,3-*c*]pyrimido[4,5-*a*]anthraquinones **9a-f**, respectively. **4a-c** when treated with sodium nitrite in concentrated ortho-phosphoric acid, the tetrazolo derivatives **10a-c** were obtained. The IR spectra of these compounds do not show any characteristic band for the azido group at about 2000-2200 cm^{-1}, it seems that in the solid state **10a-c** have essentially the tetrazole structure represented without any demonstrable contribution of the possible azido form.

Finally, **4a-c** when refluxed with acetyl acetone, or/and ethyl acetoacetate afforded the pyrazolino derivatives, 2-substituted-4-(3′,5′-dimethylpyrazol-1′-yl)pyrimido[4,5-*a*]anthraquinones **11a-c**, and 2-substituted-4-(3′-methyl-5′- oxo-2′-pyrazolin-1′-



Scheme I

yl)pyrimido [4,5-*a*]anthraquinones **12a-c** (Scheme II, Table I).

Experimental Section

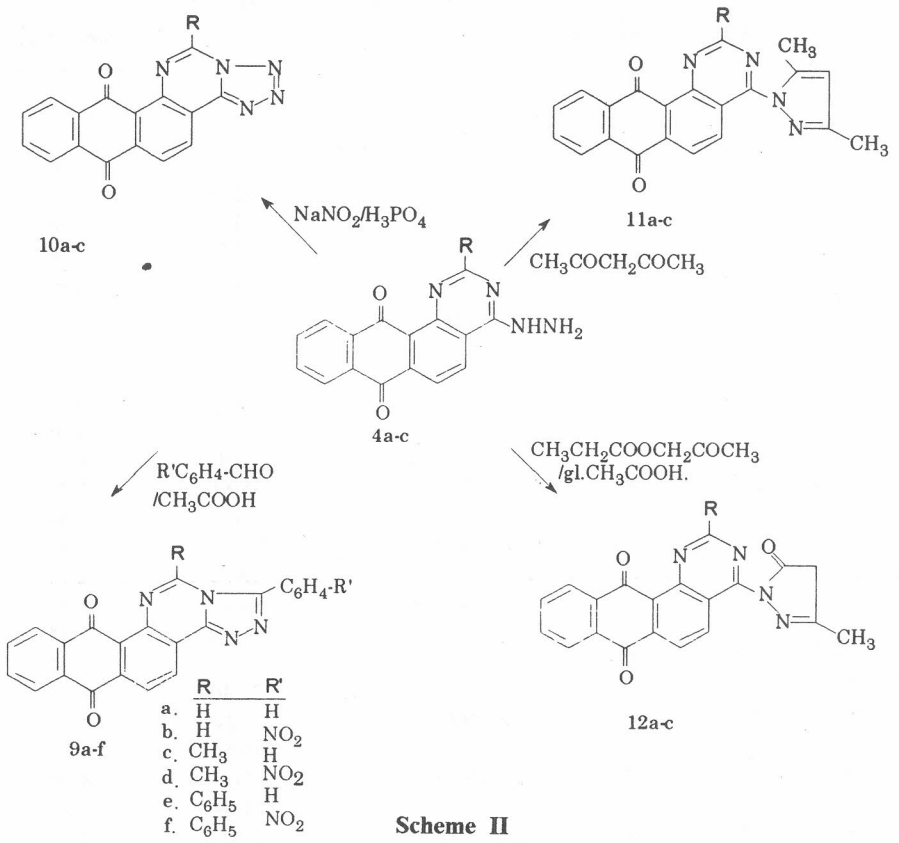
All melting points are uncorrected. The IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer using potassium bromide. The ^{1}HNMR spectra in DMSO-d_6 on a Varian Gemini 300 MHz spectrophotometer (chemical shifts in δ, ppm downfield from TMS as internal standard); mass spectra were scanned on Kartos MS 80 RFA mass spectrometer at 70ev. Satisfactory C, H, N analysis were obtained.

4(3*H*)-Oxopyrimido[4,5-*a*]anthraquinone 2a. To ethyl 1-aminoanthraquinone-2-carboxylate **1** (0.591 g, 0.002 mole) was added formamide (25 mL). The reaction mixture was refluxed in an oil-bath (160-80°) for 14 hr. It was concentrated, cooled and poured into ice-water. The solid separated out was filtered, dried and crystallised from aqueous N,N-dimethylformamide (95:5), m.p.>330°, yield 80% (Found: C, 69.60; H, 2.84; N, 10.10. $C_{16}H_8N_2O_3$ requires C, 69.56; H, 2.89; N, 10.14%). IR (KBr): 3429, and 3290 (NH), 1667(C=O) and 1593 (C=N); ^{1}HNMR (DMSO-d_6); 7.6-8.5 (m, 6H, Ar-H), 8.7(s, 1H, CH); mass: m\z 276, 246, 232, 203.

2-Methyl-4(3*H*)-oxopyrimido[4, 5-*a*]anthraquinone 2b. To compound **1** (0.591 g, 0.002 mole) was added acetonitrile (5 mL, excess) in 10 mL dioxane and dry hydrogen chloride gas was passed through the solution for 24 hr at room temperature. The reaction mixture was then left overnight. The solid obtained was filtered, dissolved in water and basified with sodium carbonate. The solid that precipitated was filtered, washed with water and dried. This intermediate was dissolved in ethanol (20 mL) and 6% aqueous sodium hydroxide (5 mL). The reaction mixture was then refluxed for 6 hr. The solvent was evaporated and the product was dissolved in water and acidified with glacial acetic acid. The solid that precipitated was filtered and crystallised from N,N-dimethylformamide: ethanol (80:20), m.p.290°, yield 50% (Found: C, 70.56; H, 3.40; N, 9.50. $C_{17}H_{10}N_2O_3$ requires C, 70.34; H, 3.47; N, 9.65%). IR (KBr): 3200 (NH), 1670 (C=O), ^{1}HNMR (DMSO-d_6): 2.5(s, 3H, CH_3), 7.4-8.3 (m, 6H, Ar-H), 9.0-9.4(s, 1H, NH).

The procedure for the 2-methyl derivative described above was repeated, using 0.206 g (0.002 mole) phenyl nitrile instead of acetonitrile, m.p. 278° and yield 73% (Found: C, 75.12; H, 3.36; N, 7.87 $C_{22}H_{12}N_2O_3$ requires C, 74.99; H, 3.43; N, 7.95%). ^{1}H NMR (DMSO-d_6): 7.3-8.2(m, 11H, Ar-H), 9.0 (bs,1H, NH).

4-Chloro-2-substituted-pyrimido[4, 5-*a*]anthraquinone 3a. A mixture of **2a** (0.002 mole), $POCl_3$ (100 mL), PCl_5 (2 g) was heated under reflux in an oil-bath (110-20°) for 18 hr. Excess phosphorous oxychloride was distilled off under



Scheme II

Table I—Physical data of the compounds 3-12

Compd	R	R'	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.) C	H	N
3a	H	-	189	50	$C_{16}H_7N_2O_2Cl$	65.07 (65.21	2.23 2.39	9.29 9.51)
3b	CH_3	-	187	53	$C_{17}H_9N_2O_2Cl$	66.36 (66.14	2.70 2.94	8.93 9.07)
3c	C_6H_5	-	180	57	$C_{22}H_{11}N_2O_2Cl$	71.02 (71.26	2.63 2.99	7.42 7.55)
4a	H	-	227	52	$C_{16}H_{10}N_4O_2$	66.26 (66.20	3.40 3.47	19.48 19.30)
4b	CH_3	-	224	61	$C_{17}H_{12}N_4O_2$	67.02 (67.10	3.86 3.97	18.58 18.41)
4c	C_6H_5	-	224	64	$C_{22}H_{14}N_4O_2$	71.90 (72.12	3.67 3.85	15.42 15.29)
5a	H	CH_3	>330	65	$C_{18}H_{10}N_4O_2$	68.81 (68.79	3.20 3.21	18.03 17.83)
5b	CH_3	CH_3	>330	70	$C_{19}H_{12}N_4O_2$	69.79 (69.51	3.50 3.68	17.00 17.06)
5c	C_6H_5	CH_3	>330	70	$C_{24}H_{14}N_4O_2$	73.90 (73.84	3.43 3.61	14.40 14.35)
6a	H	H	>330	76	$C_{17}H_8N_4O_2$	68.11 (68.00	2.67 2.69	18.35 18.66)
6b	CH_3	H	>330	72	$C_{18}H_{10}N_4O_2$	68.95 (68.79	3.03 3.21	17.75 17.83)
6c	C_6H_5	H	>330	70	$C_{24}H_{14}N_4O_2$	73.90 (73.84	3.43 3.61	14.40 14.35)

Table I — Physical data of the compounds **3-12**

Compd	R	R'	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)		
						C	H	N
7a	H	SH	>330	74	$C_{17}H_8N_4O_2S$	61.31 (61.44	2.35 2.43	17.03 16.86)
7b	CH_3	SH	>330	73	$C_{18}H_{10}N_4O_2S$	62.19 (62.42	3.31 2.91	16.00 16.18)
7c	C_6H_5	SH	>330	61	$C_{23}H_{12}N_4O_2S$	67.57 (67.64	2.90 2.96	13.85 13.72)
8a	H	H	248	55	$C_{23}H_{14}N_4O_2$	72.85 (73.01	3.61 3.73	14.57 14.81)
8b	H	NO_2	274	71	$C_{23}H_{13}N_5O_4$	65.20 (65.25	2.85 3.09	16.30 16.54)
8c	CH_3	H	256	77	$C_{24}H_{16}N_4O_2$	73.37 (73.46	4.08 4.11	14.15 14.28)
8d	CH_3	NO_2	287	80	$C_{24}H_{15}N_5O_4$	65.81 (65.90	3.23 3.46	15.93 16.01)
8e	C_6H_5	H	250	74	$C_{29}H_{18}N_4O_2$	76.58 (76.64	3.93 3.99	12.20 12.33)
8f	C_6H_5	NO_2	270	61	$C_{29}H_{17}N_5O_2$	69.49 (69.74	3.35 3.43	13.89 14.02)
9a	H	H	>330	62	$C_{23}H_{12}N_4O_2$	73.19 (73.40	3.01 3.21	14.96 14.89)
9b	H	NO_2	>330	73	$C_{23}H_{11}N_5O_4$	65.24 (65.56	2.57 2.63	16.54 16.62)
9c	CH_3	H	>330	79	$C_{24}H_{14}N_4O_2$	73.67 (73.84	3.70 3.61	14.54 14.35)
9d	CH_3	NO_2	>330	65	$C_{24}H_{13}N_5O_4$	66.15 (66.21	2.88 3.01	16.23 16.08)
9e	C_6H_5	H	>330	74	$C_{29}H_{16}N_4O_2$	76.82 (76.98	3.37 3.56	12.30 12.38)
9f	C_6H_5	NO_2	>330	75	$C_{29}H_{15}N_5O_4$	69.82 (70.02	3.00 3.04	14.17 14.08)
10a	H	-	>330	78	$C_{16}H_7N_5O_2$	63.54 (63.79	2.49 2.34	23.08 23.25)
10b	CH_3	-	>330	73	$C_{17}H_9N_5O_2$	63.50 (64.76	2.79 2.88	22.15 22.21)
10c	C_6H_5	-	>330	83	$C_{22}H_{11}N_5O_2$	69.86 (70.02	2.83 2.94	18.49 18.56)
11a	H	-	253	54	$C_{21}H_{14}N_4O_2$	71.15 (71.18	4.14 3.98	15.75 15.81)
11b	CH_3		247	59	$C_{22}H_{16}N_4O_2$	71.58 (71.73	4.29 4.38	15.20 15.21)
11c	C_6H_5	-	>330	70	$C_{27}H_{18}N_4O_2$	75.17 (75.34	4.08 4.21	12.85 13.02)
12a	H	-	276	61	$C_{20}H_{12}N_4O_3$	67.68 (67.41	3.19 3.39	15.68 15.72)
12b	CH_3	-	270	67	$C_{21}H_{14}N_4O_3$	68.25 (68.10	3.40 3.81	14.86 15.13)
12c	C_6H_5	-	268	60	$C_{26}H_{16}N_4O_3$	72.38 (72.22	3.44 3.73	12.99 12.96)

vacuum. The reaction mixture was cooled and poured into a mixture of ice, water and sodium bicarbonate. The solid was filtered, dried and crystallised from dioxane.IR (KBr): 1669 (C=O), 1625 (C=N); ^{1}HNMR: 7.6-8.2(m, 6H, Ar-H), 8.9 (s, 1H, CH).

Similarly **3b,c** were synthesised and the physical data of **3a-c** are recorded in Table I.

4-Hydrazinopyrimido[4, 5-*a*]anthraquinone 4a. To **3a** (0.001 mole), dissolved in hot ethanol (100 mL) was added excess hydrazine hydrate (98%, 0.004 mole). The reaction mixture was heated under reflux on a water-bath for 12 hr. The product obtained was concentrated and cooled. The solid was filtered, dried and crystallised from benzene-pet. ether(60-80°) (95:5%) to give **4a**. IR (KBr): 3428, 3310 (NH), 1664 (C=O), 1637 (C=N); ^{1}H NMR: 5.5 (s, 2H, NH_2), 7.2-8.4 (m, 6H, Ar-H), 8.8 (s,1H, CH), 9.1 (bs, 1H, NH).

4-Hydrazino-2-methylpyrimido[4, 5-*a*]anthraquinone **4b** was prepared similarly ^{1}HNMR: 2.35(s, 3H, CH_3), 7.4-8.0 (m, 6H, Ar-H), 9.0(bs, 1H, NH).

The physical data of **3a-c** are recorded in Table I.

3-Methyl-1,2,4-triazolo[4,3-*c*]pyimido[4, 5-*a*]-anthraquinone 5a. To **4a** (0.002 mole) was added excess acetic anhydride (15 mL) and catalytic amounts of 4-toluenesulphonic acid. The reaction mixture was heated at reflux temperature for 9 hr. The product was cooled and poured into cold water and neutralized with a solution of sodium carbonate and kept overnight at room temperature. It was filtered, washed with water, dried and crystallised from aqueous N,N-dimethylformamide to give **5a** ^{1}HNMR: 2.9(s, 3H,CH_3), 7.8-8.2 (m, 6H, Ar-H), 8.5 (s, 1H, Ar-H).

The ^{1}HNMR spectrum of **5c**: 2.6 (s, 3H, CH_3), 7.5-7.7 (m, 6H, Ar-H), 7.9 (m, 2H, Ar-H), 8.1 (2 d, 2H, Ar-H), 8.3(d, 1H, Ar-H).

The physical data of **5a-c** are recorded in Table I.

1, 2, 4-Triazolo[4,3-*c*]pyrimido[4, 5-*a*]anthra quinone 6a. To **4a** (0.002 mole) was added excess formic acid (10 mL) in the presence of catalytic amounts of 4-toluenesulphonic acid. The reaction mixture was then refluxed for 7 hr and excess of formic acid was distilled off under the vacuum. The residue was cooled and to it was added 100 mL ice cold water and the mixture shaken. It was filtered and the precipitate obtained was washed with sodium bicarbonate to remove excess formic acid. The triazole **6a** obtained was crystallised from N,N-dimethylformamide. ^{1}HNMR: 7.2-8.3(m, 6H, Ar-H), 9.6 (s, 1H, CH=N), 10.4, (s, 1H, CH).

Similarly, **6b** and **6c** were synthesised and their physical data are recorded in Table I.

3-Mercapto-1,2,4-triazolo[4,3-*c*]pyrimido[4,5-*a*]anthraquinone 7a. To **4a** (0.002 mole) dissolved in warm pyridine (2 mL) was added excess carbon disulphide (30 mL). The mixture was then refluxed on a water bath for 7 hr. At the end of the reaction, excess of carbon disulphide was removed by distillation and the residue poured into cold water containing hydrochloric acid. The precipitate obtained was filtered, washed with water, dried and crystallised from N,N-dimethylformamide to give **7a**. IR (KBr): 3319 (NH); ^{1}HNMR: 7.6-8.4 (m,6H, Ar-H), 8.9 (s, 1H, CH), 13.1 (bs, 1H, SH).

Similarly **7b** and **7c** were synthesised and their physical data are recorded in Table I.

4-(Benzylidenehydrazono)pyrimido[4, 5-*a*]anthraquinone 8a.To 4a (0.001 mole) dissolved in absolute ethanol (50 mL) was added benzaldehyde (0.001 mole). The reaction mixture was refluxed on a water bath for 6 hr. The solid which separated on cooling was filtered and crystallised from N,N-dimethylformamide to give **8a**. IR (KBr): 3180, 3430 (NH); 1686 (C=O) 1620 (C=N); ^{1}HNMR: 7.2 (s, 5H, Ar-H), 7.6-8.1 (m, 6H, Ar-H), 8.4 (s,1H, =CH-Ph), 8.7 (s,1H, CH), 9.1 (bs, 1H, NH).

Similarly **8b-f** were synthesised and their physical data are recorded in Table I.

3-Phenyl-1, 2, 4-triazolo[4, 3-*c*]pyrimido[4, 5-*a*]anthraquinone 9a. To **4a** (0.001 mole) in gl. acetic acid (20 mL) was added benzaldehyde (0.001 mole). The mixture was refluxed on an oil-bath for 16 hr. After cooling the separated solid was crystallised from N,N-dimethylformamide to give **9a**. IR (KBr): 1680 (C=O), 1620 (C=N), no absorption band in the region of NH_2.

Similarly **9b-9f** were synthesised and their physical data are recorded in Table I.

1,2,3,4-Tetrazolo[4,5-*c*]pyrimido[4, 5-*a*]anthraquinone 10a. Compound **4a** (0.001 mole) was dissolved in conc. orthophosphoric acid (15 mL) and the mixture was cooled to 0-5° in an ice-bath and 12 mL of 2*N* sodium nitrite gradually added to the hydrazine while stirring over a period of 7 hr. After the addition of sodium nitrite was complete, the temperature was allowed to rise to room temperature. It was then stirred for a further period of 24 hr. As the reaction proceeded the product started separating. The mixture was poured into 50 mL cold water, dried and crystallised from

N,N-dimethylformamide to yield **10a**. ^{1}HNMR: 7.6-8.4(m, 6H, Ar-H), 10.4(s, 1H, Ar-H).

Similarly, **10b,c** were synthesised and their physical data are recorded in Table I.

4-(3′,5′-Dimethylpyrazol-1′-yl)pyrimido[4, 5-*a*] anthraquinone 11a. To **4a** (0.001 mole) dissolved in hot ethanol (50 mL) was added acetyl acetone (0.0015 mole) and a few drops gl. acetic acid. The reaction mixture was then heated under reflux for 6 hr, and then cooled. The product that precipitated was filtered, washed with 10 mL cold methanol, dried and crystallised from aqueous N,N-dimethylformamide to give **11a**. ^{1}HNMR: 2.15 (s, 3H, CH_3) 2.30 (s, 3H, CH_3), 6.18 (s, 1H, pyrazoline H), 7.4-8.0 (m, 6H, Ar-H), 8.9 (bs, 1H, CH).

Similarly **11b,c** were synthesised and their physical data are recorded in Table I.

4-(3'-Methyl-5′-oxo-2′- pyrazolin-1′-yl)pyrimido[4,5-*a*]anthraquinone 12a. To **4a** (0.001 mole) dissolved in hot ethanol (50 mL) was added ethyl acetoacetate (0.0015 mole) and a few drops gl. acetic acid. The reaction mixture was then heated under reflux for 10 hr. On cooling, the solid that separated was filtered, washed with cold methanol, dried and crystallised from aqueous N,N-dimethylformamide to yield **11a**. ^{1}HNMR: 2.3 (s, 3H, CH_3), 5.4 (s, 1H, pyrazoline H), 7.4-7.9 (m, 6H, Ar-H), 9.1 (s,1H, CH), 12.1 (b, 1H, OH).

Similarly **12b,c** were synthesised and their physical data are recorded in Table I.

References:

1 Castaner J, *Drugs of the Future*. Vol 11, **1977,** 383.
2 Manhas M B, Sharma S D & Amin S G, *J Med Chem*, 15, **1972,** 106.
3 Devani M B, Shishoo C J, Pathak M S, Parik S H & Padhya A C, *J Pharm Sci*, 65, **1976**, 660.
4 *German Pat,* 2,264,222 **1973**; *Chem Abstr*, 79, **1973**, 78837d.
5 *Belgian Pat* 769,844 **1972**; *Chem Abstr*, 77, **1972**, 5512.
6 Thomas K, *British Pat* 1,057,612 **1967**; *Chem Abstr*, 67, **1967,** 100149.
7 Sauter F, *German Pat,* 2,210,503 **1972**; *Chem Abstr*, 77, **1972**, 164752.
8 Wade J J, *US Pat* 4,528,288 **1985**; *Chem Abstr*, 104, **1986,** 5889x.
9 Francis J E & Gelotte K O, *US Pat* 4,713,383 **1987**; *Chem Abstr*, 109, **1988,** 129041.
10 Kottke K, Kuhmstedt H, Hagen V, Renner H & Schnitzler S, *German(E) Pat*, 139,715 **1983**; *Chem Abstr*, 99, **1983,** 70757.
11 Wamhoff H , *Lectures in Heterocyclic Chemistry*, Vol V, **1980** S.61, and the references cited therein.
12 Magidon O Yu & Glushkov R.B, *Chem Abstr*, 64, **1966,** 196334g.
13 Dave K G, Shishoo C J, & Devani M B, *J Heterocycl Chem*, 17, **1980,** 1497.
14 Polya J B, *Comprehensive Heterocylic Chemistry*, Vol 5, edited by A R Katritzky and C W Rees (Pergamon Press, Oxford), **1984,** 762.
15 EL-Sherif , Ahmed H, Mohamad M A & Ahmad E A, *Bull Chem Soc Japan*, 57, **1984,** 1138, *Chem Abstr*, 101, **1984,** 55051b.
16 Wammof H & Lichtenthalor L, *Chem Ber*, 111, **1978**, 2297.
17 Wilfred T, Westwood R & Alun D, *Eur Pat*, 76199 **1981**; *Chem Abstr*, 99, **1983,** 194989s.
18 Ulrich H ,*The Chemistry of Imidoyl Halides*, (Plenum Press New York, NY), **1968**, Chapter 3.
19 Jonson F & Madronero R , *Advance In Heterocyclic Chemistry*, Vol 6, edited by A R Katritzky (Academic Press, New York, NY), **1966**, P 95.